

**Hoffmann - Rockstroh - Kamps**

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# **HIV Medicine 2006**

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**Flying Publisher**

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## Preface 2006

As in previous years, all chapters of the 14<sup>th</sup> edition have been thoroughly revised, and new chapters have been added (HIV and Renal Disease, Sexual Dysfunction in HIV/AIDS). Again, the book is freely available on the Internet. That is the way, we firmly believe, that medical textbooks should be handled in the 21<sup>st</sup> century.

HIV Medicine is now available in Spanish, German, Russian, and Portuguese ([www.hivmedicine.com/textbook/lang.htm](http://www.hivmedicine.com/textbook/lang.htm)), and we expect translations into further languages. This is clearly a challenge for the future, and the authors of HIV Medicine are ready to take the challenge. As a matter of fact, the 2007 edition is already under way.

The philosophy which governs the publication of HIV Medicine 2006 has been published at [www.freemedicalinformation.com](http://www.freemedicalinformation.com).

Christian Hoffmann

Jürgen K. Rockstroh

Bernd Sebastian Kamps

Hamburg, Bonn, Paris – August 2006

## Preface 2003

Hardly any field of medicine has ever undergone a similar stormy development to that of the therapy of HIV infection. Little more than 10 years passed, between the discovery of the pathogen and the first effective treatment! However, there is also hardly a field that is subjected to so many fast- and short-lived trends. What today seems to be statute, is tomorrow often already surpassed. Nevertheless, therapeutical freedom must not be confused with freedom of choice. This book presents the medical knowledge that is actual today: from December 2002 to January 2003.

Because HIV medicine changes so fast, HIV Medicine 2003 will be updated every year. Additional chapters about opportunistic infections, malignancies and hepatitis are freely available at our Web site [www.HIVMedicine.com](http://www.HIVMedicine.com).

Under certain conditions, the editors and the authors of this book might agree to remove the copyright on HIV Medicine for all languages except English and German. You could therefore translate the content of HIV Medicine 2003 into any language and publish it under your own name – without paying a license fee. For more details, please see <http://hivmedicine.com/textbook/cr.htm>.

Christian Hoffmann and Bernd Sebastian Kamps  
Hamburg/Kiel and Paris/Cagliari, January 2003

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## Content

<b>1. Introduction.....</b>	<b>23</b>
Transmission routes .....	23
Natural history .....	25
CDC classification system.....	26
Epidemiology .....	28
Conclusion.....	29
References .....	29
<b>2. Acute HIV-1 Infection.....</b>	<b>33</b>
Introduction .....	33
Immunological and virological events during acute HIV-1 infection .....	33
Signs and symptoms .....	35
Diagnosis .....	35
Treatment.....	37
References .....	37
<b>3. HIV Testing .....</b>	<b>41</b>
How to test.....	41
HIV antibody diagnosis .....	42
When to test.....	49
Problem: The "diagnostic window".....	50
Direct detection of HIV .....	51
Test results.....	52
Special case: Babies born to HIV-infected mothers .....	53
Special case: Needlestick injury or other occupational HIV exposure .....	54
Special case: Screening of blood donations.....	55
What is relevant in practice? .....	56
Useful Internet sources relating to HIV testing .....	57
References .....	58
<b>4. Pathogenesis of HIV-1 Infection .....</b>	<b>61</b>
1. The structure of HIV-1 .....	62
2. The HIV replication cycle .....	66
3. HIV and the immune system .....	74
References .....	82
<b>5. ART 2006 .....</b>	<b>89</b>
1. Perspective.....	89
2. Overview of antiretroviral agents .....	94
3. ART 2006/2007: The horizon and beyond .....	130
4. Goals and principles of therapy .....	162

## 14 Content

5. When to start HAART .....	184
6. Which HAART to start with? .....	199
7. When to change HAART .....	224
8. How to change HAART .....	231
9. Salvage therapy .....	238
10. When to stop HAART .....	253
11. Monitoring .....	267
<b>6. Management of Side Effects .....</b>	<b>279</b>
Gastrointestinal side effects .....	279
Hepatotoxicity .....	281
Pancreatitis .....	284
Renal problems .....	284
CNS disorders .....	286
Peripheral polyneuropathy .....	287
Haematological changes .....	288
Allergic reactions .....	289
Lactic acidosis .....	290
Avascular necrosis .....	292
Osteopenia/osteoporosis .....	292
Increased bleeding episodes in hemophiliacs .....	293
Specific side effects .....	293
References .....	294
<b>7. Lipodystrophy Syndrome .....</b>	<b>301</b>
Background .....	301
Clinical manifestation .....	301
HAART, lipodystrophy syndrome and cardiovascular risk .....	303
Pathogenesis .....	304
Diagnosis .....	307
Therapy .....	309
References .....	313
<b>8. Mitochondrial Toxicity of Nucleoside Analogs .....</b>	<b>317</b>
Introduction .....	317
Pathogenesis of mitochondrial toxicity .....	317
Clinical manifestations .....	318
Monitoring and diagnosis .....	322
Treatment and prophylaxis of mitochondrial toxicity .....	323
References .....	326

<b>9. HIV Resistance Testing.....</b>	<b>331</b>
Assays for resistance testing.....	331
Background .....	333
Interpretation of genotypic resistance profiles.....	336
Summary .....	344
Resistance tables.....	346
References .....	349
<b>10. Pregnancy and HIV .....</b>	<b>357</b>
HIV therapy in pregnancy .....	357
References .....	370
<b>11. Antiretroviral Therapy in Children .....</b>	<b>375</b>
Characteristics of HIV infection in childhood .....	375
Diagnosis of HIV infection < 18 months of age.....	379
Diagnosis of HIV infection > 18 months of age.....	379
When to initiate antiretroviral therapy.....	379
General considerations for treatment of HIV-infected children .....	382
Strategy.....	383
Classes of antiretrovirals .....	384
Drug interaction.....	388
Monitoring of therapy efficacy and therapy failure.....	388
Change of therapy.....	388
Supportive therapy and prophylaxis .....	389
Conclusion.....	389
References .....	390
<b>12. Opportunistic Infections (OIs).....</b>	<b>395</b>
OIs in the HAART era.....	395
Pneumocystis pneumonia (PCP).....	398
Cerebral toxoplasmosis.....	406
CMV retinitis.....	412
Candidiasis .....	418
Tuberculosis .....	422
Interaction of HIV and MTB.....	422
Clinical manifestations .....	423
Diagnosis.....	424
Therapy.....	426
Atypical mycobacteriosis (MAC).....	436
Herpes simplex .....	440
Herpes zoster .....	443
Progressive multifocal leukoencephalopathy .....	446

16 Content

Bacterial pneumonia .....	450
Cryptosporidiosis.....	453
Cryptococcosis .....	456
Salmonella septicemia .....	460
Immune reconstitution inflammatory syndrome (IRIS) .....	462
Wasting syndrome .....	468
Rare OIs.....	471
<b>13. Kaposi's Sarcoma.....</b>	<b>481</b>
Signs, symptoms and diagnosis .....	481
Prognosis and staging .....	483
Treatment.....	484
Local therapy .....	484
Chemotherapy.....	485
Immunotherapy.....	487
Monitoring and follow-up care .....	487
References .....	488
<b>14. Malignant Lymphomas.....</b>	<b>491</b>
Systemic non-Hodgkin lymphomas (NHL).....	492
Primary CNS lymphoma .....	503
Hodgkin's disease (HD) .....	506
Multicentric Castleman's Disease (MCD) .....	508
<b>15. The New HIV Patient.....</b>	<b>515</b>
The initial interview .....	515
The laboratory .....	516
The examination .....	517
<b>16. Vaccinations and HIV.....</b>	<b>519</b>
General considerations .....	519
Vaccinations in HIV-infected children .....	520
Postexposure prophylaxis .....	521
Practical approach to vaccinations.....	521
Details on individual vaccines .....	522
<b>17. Traveling with HIV .....</b>	<b>533</b>
Travel preparations .....	533
Antiretroviral therapy (ART).....	533
General precautions .....	534
Vaccinations .....	534
Malaria prophylaxis.....	535
Entry regulations and travel insurance .....	535
Special risks.....	536



Medical problems after traveling.....	539
References .....	539
Links.....	540
<b>18. HIV and HBV/HCV Coinfections.....</b>	<b>541</b>
HIV and HCV Coinfection .....	541
HIV and HBV coinfection .....	554
<b>19. GBV-C Infection .....</b>	<b>565</b>
Is GBV-C a friendly virus?.....	565
Does the knowledge about GBV-C have any practical use? .....	567
Proposed pathomechanisms.....	568
References .....	569
<b>20. HIV and Renal Function .....</b>	<b>571</b>
Clinical manifestation/diagnosis of nephropathy .....	571
Routine tests for renal impairment .....	572
HIV-associated nephropathy (HIV-AN).....	572
Post-infectious glomerulonephritis.....	573
Principles of therapy of glomerulonephritis .....	573
Renal safety of antiretroviral therapy .....	574
Nephroprotection.....	577
Estimating the GFR.....	578
Dosage of antiretrovirals in renal insufficiency.....	578
OIs and renal insufficiency.....	579
References .....	581
<b>21. HIV-associated Skin and Mucocutaneous Diseases.....</b>	<b>585</b>
Introduction .....	585
Dermatological examination and therapy in HIV-infected patients .....	587
HAART: Influence on (muco-) cutaneous diseases.....	589
Conclusions .....	590
Most frequent HIV-associated skin diseases .....	591
Skin and mucocutaneous disease related to antiretroviral drugs .....	601
References .....	603
<b>22. HIV and Sexually Transmitted Diseases.....</b>	<b>611</b>
Syphilis.....	611
Gonorrhea.....	613
Chlamydia infection .....	615
Chancroid .....	616
Condylomata acuminata .....	617

<b>23. HIV and Cardiac Diseases.....</b>	<b>619</b>
Coronary artery disease (CHD).....	619
Congestive heart failure.....	621
Pericardial effusion.....	623
Cardiac arrhythmias.....	623
Valvular heart disease.....	624
Further cardiac manifestations.....	624
References.....	625
<b>24. HIV-associated Pulmonary Hypertension.....</b>	<b>629</b>
Etiology, pathogenesis, classification.....	629
Diagnosis.....	630
Therapy.....	631
Conclusion for clinicians.....	636
References and Internet addresses.....	636
<b>25. HIV and Pulmonary Diseases.....</b>	<b>639</b>
Anamnesis.....	640
Pulmonary complications.....	642
References.....	645
<b>26. HIV-1 associated Encephalopathy and Myelopathy.....</b>	<b>647</b>
HIV encephalopathy.....	647
HIV-associated myelopathy.....	651
References.....	652
<b>27. Neuromuscular Diseases.....</b>	<b>655</b>
Polyneuropathy and polyradiculopathy.....	655
Myopathy.....	663
<b>28. HIV and Psychiatric Disorders.....</b>	<b>667</b>
Major depression.....	667
Psychotic disorders.....	673
Acute treatment in psychiatric emergency.....	676
References.....	677
<b>29. Sexual Dysfunction in HIV/AIDS.....</b>	<b>679</b>
Introduction.....	679
Definitions.....	679
Etiology of sexual dysfunction in HIV/AIDS.....	679
Ongoing research.....	681
Diagnosis of sexual dysfunction.....	681
Therapy for sexual dysfunction.....	682
<b>30. HIV and Wish for Parenthood.....</b>	<b>687</b>
Introduction.....	687

Pre-conceptual counseling.....	689
Male HIV infection.....	689
Female HIV infection.....	690
HIV infection of both partners.....	691
Psychosocial aspects.....	692
The future.....	692
References.....	694
<b>31. Post-Exposure Prophylaxis (PEP) .....</b>	<b>697</b>
Transmission.....	697
Transmission risk.....	697
Effectiveness and limitations of PEP.....	698
When is PEP indicated?.....	699
Potential risks of PEP.....	699
Initial interventions.....	700
Initiation of PEP.....	701
Management of PEP.....	703
References.....	703
<b>32. Drug Profiles.....</b>	<b>706</b>
3TC – Lamivudine.....	706
Abacavir (ABC).....	707
Acyclovir.....	709
Amphotericin B.....	709
Amprenavir.....	711
Atazanavir.....	712
Atovaquone.....	713
Azithromycin.....	714
AZT – Zidovudine.....	715
Cidofovir.....	717
Clarithromycin.....	718
Clindamycin.....	719
Combivir™.....	719
Co-trimoxazole.....	720
d4T – Stavudine.....	721
Dapsone.....	722
Daunorubicin, liposomal.....	723
ddC – Zalcitabine.....	724
ddI – Didanosine.....	725
Delavirdine.....	726
Doxorubicin (liposomal).....	727

Efavirenz .....	728
Emtricitabine (FTC) .....	730
Erythropoietin .....	731
Ethambutol .....	731
Fluconazole .....	733
Fosamprenavir .....	734
Foscarnet .....	735
Ganciclovir .....	736
G-CSF .....	737
Indinavir .....	738
Interferon alfa 2a/2b .....	739
Interleukin-2 .....	740
Isoniazid (INH) .....	741
Itraconazole .....	742
Kivexa™ (USA: Epzicom™) .....	743
Lopinavir .....	744
Nelfinavir .....	745
Nevirapine .....	746
Pentamidine .....	748
Pyrimethamine .....	749
Ribavirin .....	750
Rifabutin .....	752
Rifampin (or rifampicin) .....	753
Ritonavir .....	754
Saquinavir .....	756
Sulfadiazine .....	757
T-20 (Enfuvirtide) .....	758
Tenofovir .....	759
Tipranavir .....	761
Trizivir™ .....	762
Truvada™ .....	763
Valganciclovir .....	764
Voriconazole .....	765
<b>33. Drug-Drug Interactions .....</b>	<b>767</b>

Part 1

# Basics



# 1. Introduction

Bernd Sebastian Kamps and Christian Hoffmann

The first reports of homosexual patients suffering from previously rare diseases such as pneumocystis pneumonia and Kaposi's sarcoma were published in May 1981 (Centers for Disease Control 1981a, 1981b, 1981c). It soon became clear that the new disease affected other population groups as well, when the first cases were reported in injecting drug users. However, it took almost two years until, in 1983, the human immunodeficiency virus type I (HIV-1) was defined as the primary cause of the acquired immunodeficiency syndrome (Barré-Sinoussi 1983, Broder 1984, Gallo 1984).

Almost 25 years have now elapsed. Twenty-five years, in which HIV infection has changed from a fatal condition to a manageable chronic illness. Twenty-five years, in which the development of antiretroviral therapy (ART) has been one of the dramatic advances in the history of medicine. However, for the vast majority of people living with HIV/AIDS, ART is still light years away – largely inaccessible in resource-poor countries where HIV continues to devastate families, communities and societies, especially the poor and the socially marginalized.

In the following 800 pages, we present a comprehensive overview of the treatment of HIV infection and its complications. As in previous years, all chapters have been thoroughly revised, and most parts of the book were available on the Internet ([www.HIVMedicine.com](http://www.HIVMedicine.com)) months before they were printed here. The philosophy that governs the publication of HIV Medicine 2006 has recently been published at [www.freemedicalinformation.com](http://www.freemedicalinformation.com). We firmly believe that that is the way medical textbooks should be handled in the 21<sup>st</sup> century.

## Transmission routes

There are several ways in which someone can become infected with HIV. These transmission routes are well defined (see also Chapter “Post-Exposure Prophylaxis”). HIV infection can be transmitted through:

- unprotected sexual intercourse with an infected partner;
- injection or transfusion of contaminated blood or blood products (infection through artificial insemination, skin grafts and organ transplants is also possible);
- sharing unsterilized injection equipment that has been previously used by someone who is infected;
- maternofetal transmission (during pregnancy, at birth, and through breastfeeding).

Occupational infections of healthcare or laboratory workers may occur; however, a 1995 study estimated that although 600,000 to 800,000 needlestick injuries occurred among healthcare workers every year in the USA, occupational infection was not frequent. The risk of occupational HIV transmission from contaminated needles to healthcare workers was found to be 0.3 % in case series performed prior to the availability of potent ART.

There are sometimes concerns that there may be alternative routes of HIV transmission. It must be explicitly stated that HIV is **NOT** transmitted by mosquitoes, flies, fleas, bees, or wasps. HIV is **NOT** transmitted through casual every day contact. No case of HIV infection has been documented to arise from contact with non-bloody saliva or tears. Since HIV is not transmitted by saliva, it is not possible to contract it through sharing a glass, a fork, a sandwich, or fruit (Friedland 1986, Castro 1988, Friedland 1990). In the opinion of leading experts, exposure of intact skin to HIV-contaminated body fluids (e.g. blood) is not sufficient to transfer the virus.

### **Sexual intercourse**

Unprotected sexual intercourse is the most important transmission route of HIV infection worldwide. Although receptive anal sex is estimated to produce the highest risk of infection, infection after a single insertive contact has also been described. The presence of other sexually transmitted diseases markedly increases the risk of becoming infected with HIV.

The lower the viral load, the less infectious the patient. A prospective study of 415 HIV-discordant couples in Uganda showed that of 90 new infections occurring over a period of up to 30 months, none was from an infected partner with a viral load below 1,500 copies/ml. The risk of infection increased with every log of viral load by a factor of 2.45 (Quinn 2000). It should be noted that the levels of viral load in blood and other body fluids do not always correlate with one another. Thus, individual risk remains difficult to estimate. In addition, HIV-infected patients are not protected from superinfection with new viral strains.

The higher the viral load, the more infectious the patient. This is especially true for patients during acute HIV infection. During acute HIV-1 infection, the virus replicates extensively in the absence of any detectable adaptive immune response, reaching levels of over 100 million copies of HIV-1 RNA/ml (see Chapter “Acute HIV-1 infection”).

### **Intravenous drug use**

Sharing unsterilized injection equipment that has been previously used by someone who is infected is an important route of HIV transmission in many countries with a high prevalence of intravenous drug users. In contrast to the accidental needlestick injury (see also Chapter “Post-Exposure Prophylaxis”), the risk of transmission through sharing injection equipment is far higher: the intravenous drug user ensures the proper positioning of the needle by aspiration of blood.

### **Maternofetal**

In the absence of any intervention, an estimated 15-30 % of mothers with HIV infection will transmit the infection during pregnancy and delivery. In approximately 75 % of these cases, HIV is transmitted during late pregnancy or during delivery. About 10 % of vertical HIV infections occur before the third trimester, and 10-15 % are caused by breastfeeding.

In Western countries, perinatal (vertical) HIV infection has become rare since the introduction of antiretroviral transmission prophylaxis and elective cesarean section. For more details, see Chapter “Pregnancy and HIV”.



## Injection or transfusion of contaminated blood products

In most Western countries, administration or transfusion of HIV-contaminated blood or blood products has become a rare event. With current testing methods (for details see also Chapter “HIV Testing”), the risk of acquiring HIV from a unit of transfused blood is about 1:1,000,000. However, while Western European countries, the United States, Australia, Canada, and Japan have strict and mandatory screening of donated blood for HIV, not all countries do.

## Natural history

The “natural history” described in the following refers to HIV infection in the absence of HAART.

The acute viral syndrome of “primary” HIV infection (which is defined as the time period from initial infection with HIV to the development of an antibody response) shows symptoms that often resemble those of mononucleosis. These appear within days to weeks following exposure to HIV (see Chapter “Acute HIV-1 Infection”). However, clinical signs and symptoms may not occur in all patients. During acute HIV infection, there is usually a high plasma viremia and frequently a marked decrease in CD4+ T-cells. The CD4+ T-cell count later increases again, normally to levels inferior to the pre-infection values (see Figure 1).

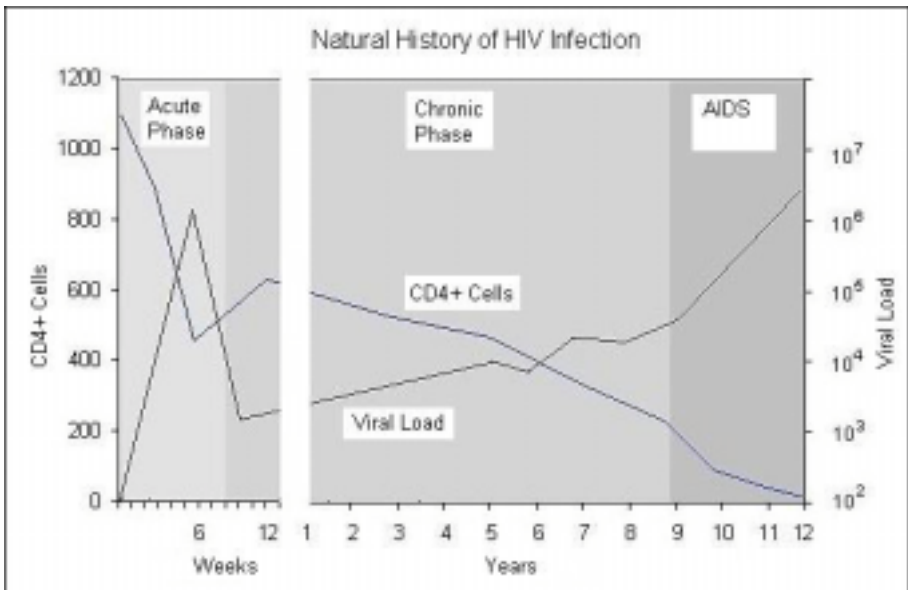


Figure 1: CD4+ T-cell count and viral load during HIV infection.

After the acute infection, equilibrium between viral replication and the host immune response is usually reached, and many infected individuals may have no clinical manifestations of HIV infection for years. Even in the absence of antiretroviral treatment, this period of clinical latency may last 8-10 years or more. However, the

term “latency period” may be misleading, given the incredibly high turnover of the virus and the relentless daily destruction of CD4+ T-cells.

At the end of the “latency period”, a number of symptoms or illnesses may appear which do not fulfill the definition of AIDS. These include slight immunological, dermatological, hematological and neurological signs. Many of them are listed in the Category B of the CDC classification system (see Table 1). Constitutional symptoms, such as fever, weight loss, night sweats, and diarrhea may also develop. In this situation, the level of 200 CD4+ T-cells/ $\mu$ l is an important cut-off, below which the risk of many AIDS-defining illnesses increases, among them several opportunistic infections and certain neoplasms (see Table 1). Above 200 CD4+ T-cells/ $\mu$ l, most AIDS-defining illnesses are rare events (see also Chapter “AIDS”).

However, the course of infection may vary dramatically, and in some cases, the progression to AIDS occurs rapidly. Host factors mainly determine whether or not an HIV-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors, who represent about 5 % of all infected patients (for details, see “Pathogenesis of HIV-1 Infection”).

## CDC classification system

The most widely accepted classification system of HIV infection, initially published by the U.S. Centers for Disease Control and Prevention (CDC) in 1986, is based on certain conditions associated with HIV infection (see Table 1). This classification system was intended for use in conducting public health surveillance and it has been a useful epidemiological tool for many years. In 1993, the CDC classification was revised (CDC 1993b). Since then, the clinical definition of AIDS has been expanded in the USA (not in Europe) to include HIV-infected patients with a CD4+ T-cell count of less than 200 cells/ $\mu$ l or less than 14 % of all lymphocytes, even in the absence of the listed conditions.

Thus, the current CDC classification categorizes persons on the basis of clinical conditions and CD4+ T-lymphocyte counts. There are three clinical categories (A, B, C – see Table 1) and three CD4+ T-lymphocyte categories (1, 2, 3 – see Table 2). For example, a patient with oropharyngeal candidiasis and a CD4+ T-cell count of 250/ $\mu$ l would be classified as B2; someone with asymptomatic infection and a CD4+ T-cell count of 550/ $\mu$ l would be in category A1. Categorization of the CD4+ T-cells should be based on the lowest accurate CD4+ T-cell count (“CD4 nadir”) and not on the most recent one.

For children less than 13 years of age, there is a modified and revised classification system for HIV infection (see chapter “Antiretroviral Therapy in Children”). It should also be noted that, besides the CDC classification, the World Health Organization (WHO) has also published a staging system for HIV infection. The WHO classification is an approach for use in resource-limited settings and is widely used in Africa and Asia.

Table 1. Clinical categories of the CDC classification system in HIV-infected persons

<p><b>Category A</b></p> <p>Asymptomatic HIV infection</p> <p>Acute (primary) HIV infection with accompanying illness or history of acute HIV infection</p> <p>Persistent generalized lymphadenopathy</p> <p><b>Category B</b></p> <p>Symptomatic conditions* that are not included among conditions listed in clinical Category C. Examples include, but are not limited to:</p> <p>Bacillary angiomatosis</p> <p>Candidiasis, oropharyngeal (thrush)</p> <p>Candidiasis, vulvovaginal; persistent, frequent, or poorly responsive to therapy</p> <p>Cervical dysplasia (moderate or severe)/cervical carcinoma in situ</p> <p>Constitutional symptoms, such as fever (38.5° C) or diarrhea lasting longer than 1 month</p> <p>Hairy leukoplakia, oral</p> <p>Herpes zoster (shingles), involving at least two distinct episodes or more than one dermatome</p> <p>Idiopathic thrombocytopenic purpura</p> <p>Listeriosis</p> <p>Pelvic inflammatory disease, particularly if complicated by tubo-ovarian abscess</p> <p>Peripheral neuropathy</p>	<p><b>Category C - AIDS-defining illnesses**</b></p> <p>Candidiasis of bronchi, trachea, or lungs</p> <p>Candidiasis, esophageal</p> <p>Cervical cancer, invasive*</p> <p>Coccidioidomycosis, disseminated or extrapulmonary</p> <p>Cryptococcosis, extrapulmonary</p> <p>Cryptosporidiosis, chronic intestinal (greater than 1 month's duration)</p> <p>Cytomegalovirus disease (other than liver, spleen, or nodes)</p> <p>Cytomegalovirus retinitis (with loss of vision)</p> <p>Encephalopathy, HIV-related</p> <p>Herpes simplex: chronic ulcer(s) (greater than 1 month's duration); or bronchitis, pneumonitis, or esophagitis</p> <p>Histoplasmosis, disseminated or extrapulmonary</p> <p>Isosporiasis, chronic intestinal (greater than 1 month's duration)</p> <p>Kaposi's sarcoma</p> <p>Lymphoma, Burkitt's (or equivalent term)</p> <p>Lymphoma, immunoblastic (or equivalent)</p> <p>Lymphoma, primary, of brain</p> <p>Mycobacterium avium complex or M. kansasii, disseminated or extrapulmonary</p> <p>Mycobacterium tuberculosis, any site (pulmonary or extrapulmonary)</p> <p>Mycobacterium, other species or unidentified species, disseminated or extrapulmonary</p> <p>Pneumocystis pneumonia</p> <p>Pneumonia, recurrent*</p> <p>Progressive multifocal leukoencephalopathy</p> <p>Salmonella septicemia, recurrent</p> <p>Toxoplasmosis of brain</p> <p>Wasting syndrome due to HIV</p>
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\* These conditions must meet at least one of the following criteria: a) the conditions are attributed to HIV infection or are indicative of a defect in cell-mediated immunity; or b) the conditions are considered by physicians to have a clinical course or to require management that is complicated by HIV infection.

\*\* Once a Category C condition has occurred, the person will remain in Category C.

Table 2. The CD4+ T-lymphocyte categories\*

Category 1: >500 CD4+ T-cells/ $\mu$ l
Category 2: 200-499 CD4+ T-cells/ $\mu$ l
Category 3: <200 CD4+ T-cells/ $\mu$ l

\*Categorization is based on the lowest accurate CD4+ T-cell count, not the most recent one

## Epidemiology

This is not the place for a detailed description of the epidemiological situation of the HIV pandemic. The prevalence and incidence of HIV/AIDS vary considerably from continent to continent, from country to country, from region to region. Several countries in sub-Saharan Africa report infection rates of 30 %, especially in urban areas. In other countries, HIV prevalence still remains low. However, low national prevalence rates can be misleading. They often disguise serious epidemics that are initially concentrated in certain localities or among specific population groups and that threaten to spill over into the wider population. The joint United Nations program on HIV/AIDS (UNAIDS) provides by far the best and most comprehensive overview. The annual AIDS epidemic update of UNAIDS reports on the latest developments in the global HIV/AIDS epidemic. With maps and regional summaries, it provides the most recent estimates of the epidemic's scope and explores new trends in the epidemic's evolution. It can be found at the Website <http://www.unaids.org/>. Table 1 provides an overview of the devastating situation of the HIV pandemic.

Table 3: The AIDS epidemic\*\*

	HIV-infected adults and children	HIV prevalence among adults (%)	New infections per day	Daily deaths from AIDS
Subsaharian Africa	25,000,800	7.2	8,700	6,500
South and Southeast Asia	7,400,000	0.7	2,700	1,300
Eastern Europe and Central Asia	1,600,000	0.9	740	170
Latin America	1,800,000	0.6	550	180
East Asia	870,000	0.1	380	110
North Africa and Middle East	510,000	0.2	180	160
North America	1,200,000	0.7	120	50
Caribbean	300,000	1.6	80	70
Western and Central Europe	720,000	0.3	60	30
Australia, New Zealand and Pacific Region	74,000	0.5	20	10
Total	40,300,000	1.1	13,530	8,580

\* Adapted from WHO: AIDS Epidemic Update 2005, <http://hiv.net/link.php?id=227>

## Conclusion

HIV cannot be transmitted as easily as the influenza virus. Compared to other viral diseases, the prevention of HIV infection is therefore easier. In rich countries, individuals who don't want to be infected with HIV may protect themselves and avoid HIV infection. The same people will not be able to avoid the influenza virus of the next pandemic.

HIV infection has become a treatable disease – at least in countries that can afford widespread health coverage. The following chapters describe how patients should be managed in these countries.

Outside these havens of material well-being, things have not changed since the early years of the HIV epidemic 25 years ago. Many people live in a world where no medical progress seems to have been made. This is a shameful situation, and future generations will hopefully do better than we did.

## References

1. Ammann AJ, Cowan MJ, Wara DW, et al. Acquired immunodeficiency in an infant: possible transmission by means of blood products. *Lancet* 1983, 1: 956-8. <http://amedeo.com/lit.php?id=6132270>
2. Andreani T, Modigliani R, le Charpentier Y, et al. Acquired immunodeficiency with intestinal cryptosporidiosis: possible transmission by Haitian whole blood. *Lancet* 1983, 1: 1187-91. <http://amedeo.com/lit.php?id=6133990>
3. Armbruster C, Kriwanek S, Vorbach H. Gender-specific differences in the natural history, clinical features, and socioeconomic status of HIV-infected patients: experience of a treatment centre in Vienna. *Wien Klin Wochenschr* 2000, 112: 754-60. <http://amedeo.com/lit.php?id=11042904>
4. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for AIDS. *Science* 1983, 220: 868-71. <http://amedeo.com/lit.php?id=6189183>
5. Bobat R, Moodley D, Coutsooudis A, Coovadia H, Gouws E. The early natural history of vertically transmitted HIV-1 infection in African children from Durban, South Africa. *Ann Trop Paediatr* 1998,, 18: 187-96. <http://amedeo.com/lit.php?id=9924555>
6. Bowen PA 2nd, Lobel SA, Caruana RJ, et al. Transmission of HIV by transplantation: clinical aspects and time course analysis of viral antigenemia and antibody production. *Ann Intern Med* 1988, 108: 46-8. <http://amedeo.com/lit.php?id=3276264>
7. Broder S, Gallo RC. A pathogenic retrovirus (HTLV-III) linked to AIDS. *N Engl J Med* 1984, 311:1292-7.
8. Burger H, Weiser B, Robinson WS, et al. Transmission of lymphadenopathy-associated virus/human T lymphotropic virus type III in sexual partners. Seropositivity does not predict infectivity in all cases. *Am J Med* 1986, 81: 5-10. <http://amedeo.com/lit.php?id=3014878>
9. Calzavara L, Burchell AN, Major C, et al. Increases in HIV incidence among men who have sex with men undergoing repeat diagnostic HIV testing in Ontario, Canada. *AIDS* 2002, 16: 1655-61. <http://amedeo.com/lit.php?id=12172087>
10. Castro KG, Lieb S, Jaffe HW, et al. Transmission of HIV in Belle Glade, Florida: lessons for other communities in the United States. *Science* 1988, 239: 193-7. <http://amedeo.com/lit.php?id=3336781>
11. Centers for Disease Control (1981c). Follow-up on Kaposi's sarcoma and Pneumocystis pneumonia. *MMWR Morb Mortal Wkly Rep* 1981, 30: 409-10.
12. Centers for Disease Control (1981b). Kaposi's sarcoma and Pneumocystis pneumonia among homosexual men--New York City and California. *MMWR Morb Mortal Wkly Rep* 1981, 30: 305-8.
13. Centers for Disease Control (1981a). Pneumocystis pneumonia--Los Angeles. *MMWR Morb Mortal Wkly Rep* 1981, 30: 250-2. Volltext: <http://hiv.net/link.php?id=144>
14. Centers for Disease Control (1982a). epidemiologic notes and reports persistent, generalized lymphadenopathy among homosexual males. *MMWR Morb Mortal Wkly Rep* 1982, 31: 249. <http://hiv.net/link.php?id=145>
15. Centers for Disease Control (1982b). epidemiologic notes and reports update on kaposi's sarcoma and opportunistic infections in previously healthy persons -- United States. *MMWR Morb Mortal Wkly Rep* 1982, 31: 294. <http://hiv.net/link.php?id=146>

## 30 Introduction

16. Centers for Disease Control (1982c). A Cluster of Kaposi's Sarcoma and Pneumocystis carinii Pneumonia among Homosexual Male Residents of Los Angeles and range Counties, California. *MMWR Morb Mortal Wkly Rep* 1982, 31: 305. <http://hiv.net/link.php?id=147>
17. Centers for Disease Control (1982d). Opportunistic Infections and Kaposi's Sarcoma among Haitians in the United States. *MMWR Morb Mortal Wkly Rep* 1982, 31: 353. <http://hiv.net/link.php?id=148>
18. Centers for Disease Control (1982e). Epidemiologic Notes and Reports Pneumocystis carinii Pneumonia among Persons with Hemophilia A. *MMWR Morb Mortal Wkly Rep* 1982, 31: 365. <http://hiv.net/link.php?id=149>
19. Centers for Disease Control (1982f). Update on Acquired Immune Deficiency Syndrome (AIDS) among Patients with Hemophilia A. *MMWR Morb Mortal Wkly Rep* 1982, 31: 644. <http://hiv.net/link.php?id=151>
20. Centers for Disease Control (1982g). Epidemiologic Notes and Reports Possible Transfusion- Associated Acquired Immune Deficiency Syndrome (AIDS) – California. *MMWR Morb Mortal Wkly Rep* 1982, 31, 652. <http://hiv.net/link.php?id=150>
21. Centers for Disease Control (1982h). Unexplained Immunodeficiency and Opportunistic Infections in Infants – New York, New Jersey, California. *MMWR Morb Mortal Wkly Rep* 1982, 31: 665. <http://hiv.net/link.php?id=152>
22. Centers for Disease Control (1982i). Epidemiologic Notes and Reports Immunodeficiency among Female Sexual Partners of Males with Acquired Immune Deficiency Syndrome (AIDS) -- New York. *MMWR Morb Mortal Wkly Rep* 1982, 31, 697. <http://hiv.net/link.php?id=154>
23. Centers for Disease Control (1982j). Acquired Immune Deficiency Syndrome (AIDS) in Prison Inmates -- New York, New Jersey. *MMWR Morb Mortal Wkly Rep* 1982, 31: 700. <http://hiv.net/link.php?id=153>
24. Centers for Disease Control (1983). Current Trends Acquired Immunodeficiency Syndrome (AIDS) Update. *MMWR Morb Mortal Wkly Rep* 1983, 33: 309-11. Volltext: <http://hiv.net/link.php?id=143>
25. Centers for Disease Control (1985a). Provisional Public Health Service inter-agency recommendations for screening donated blood and plasma for antibody to the virus causing acquired immunodeficiency syndrome. *MMWR Morb Mortal Wkly Rep* 1985, 34: 1-5. <http://hiv.net/link.php?id=157>
26. Centers for Disease Control (1985b). International Notes Update: Acquired Immunodeficiency Syndrome – Europe. *MMWR Morb Mortal Wkly Rep* 1985, 34: 147. <http://hiv.net/link.php?id=156>
27. Centers for Disease Control (1985c). Current Trends Update: Acquired Immunodeficiency Syndrome -- United States. *MMWR Morb Mortal Wkly Rep* 1985, 34: 245. <http://hiv.net/link.php?id=155>
28. Centers for Disease Control (1986). Recommendations for preventing transmission of infection with human T-lymphotropic virus type III/lymphadenopathy-associated virus during invasive procedures. CDC, Department of Health and Human Services. *Ann Intern Med* 1986, 104: 824-5. <http://amedeo.com/lit.php?id=3010783>
29. Centers for Disease Control (1990). Possible transmission of HIV to a patient during an invasive dental procedure. *MMWR* 1990, 39: 489-93. <http://hiv.net/link.php?id=158>
30. Centers for Disease Control (1991a). Current trends preliminary analysis: HIV serosurvey of orthopedic surgeons, 1991. *MMWR Morb Mortal Wkly Rep* 1991, 40: 309-12. <http://hiv.net/link.php?id=168>
31. Centers for Disease Control (1991b). Update: Transmission of HIV infection during invasive dental procedures - Florida. *MMWR* 1991, 40: 377-81. <http://hiv.net/link.php?id=159>
32. Centers for Disease Control (1993a). Investigations of persons treated by HIV-infected health-care workers -- United States. *MMWR Morb Mortal Wkly Rep* 1993, 42: 329-31. <http://hiv.net/link.php?id=169>
33. Centers for Disease Control (1993b). 1993 Revised Classification System for HIV Infection and Expanded Surveillance Case Definition for AIDS Among Adolescents and Adults. *MMWR* 1992, 41(RR-17). <http://hiv.net/link.php?id=184>
34. Centers for Disease Control (1994). HIV transmission in household settings - United States. *MMWR* 1994, 43: 353-6. <http://hiv.net/link.php?id=160>
35. Centers for Disease Control (1995). HIV transmission in a dialysis center. *MMWR* 1995, 44: 404-12. <http://hiv.net/link.php?id=161>
36. Ciesielski C, Marianos D, Ou CY, et al: Transmission of HIV in a dental practice. *Ann Intern Med* 1992, 116: 798 -805. <http://amedeo.com/lit.php?id=1567094>
37. Consensus Statement on Antiretroviral Treatment for AIDS in Poor Countries by Individual Members of the Faculty of Harvard University. 2001. <http://hiv.net/link.php?id=182>
38. Cowan MJ, Hellmann D, Chudwin D, et al. Maternal transmission of AIDS. *Pediatrics* 1984, 73: 382-6. <http://amedeo.com/lit.php?id=6608091>
39. Deschamps MM, Fitzgerald DW, Pape JW, Johnson WD Jr. HIV infection in Haiti: natural history and disease progression. *AIDS* 2000, 14: 2515-21. <http://amedeo.com/lit.php?id=11101063>

40. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to < 400 copies/ml. *AIDS* 2002, 16: 1521-7. <http://amedeo.com/lit.php?id=12131190>
41. European Study Group On Heterosexual Transmission Of HIV Comparison of female to male and male to female transmission of HIV in 563 stable couples. *Br Med J* 1992, 304: 809-13. <http://amedeo.com/lit.php?id=1392708>
42. Friedland G, Kahl P, Saltzman B, et al. Additional evidence for lack of transmission of HIV infection by close interpersonal (casual) contact. *AIDS* 1990, 4: 639-44. <http://amedeo.com/lit.php?id=2118767>
43. Friedland GH, Saltzman BR, Rogers MF, et al. Lack of transmission of HTLV-III/LAV infection to household contacts of patients with AIDS or AIDS-related complex with oral candidiasis. *N Engl J Med* 1986, 314:344-9. <http://amedeo.com/lit.php?id=3456076>
44. Gallo RC, Salahuddin SZ, Popovic M, et al. Frequent detection and isolation of cytopathic retroviruses (HTLV-III) from patients with AIDS and at risk for AIDS. *Science* 1984, 224: 500-3. <http://amedeo.com/lit.php?id=6200936>
45. Gottlieb MS, Schroff R, Schanker HM, et al. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men: evidence of a new acquired cellular immunodeficiency. *N Engl J Med* 1981, 305:1425-31. <http://amedeo.com/lit.php?id=6272109>
46. Groopman JE, Sarngadharan MG, Salahuddin SZ, et al. Apparent transmission of human T-cell leukemia virus type III to a heterosexual woman with the AIDS. *Ann Intern Med* 1985, 102: 63-6. <http://amedeo.com/lit.php?id=2981497>
47. Hammer SM, Turmen T, Varedzlis B, Perriens J. Antiretroviral guidelines for resource-limited settings: The WHO's public health approach. *Nat Med* 2002, 8: 649-50.
48. Harris C, Small CB, Klein RS, et al. Immunodeficiency in female sexual partners of men with the AIDS. *N Engl J Med* 1983, 308: 1181-4. <http://amedeo.com/lit.php?id=6221192>
49. Hubert JB, Burgard M, Dussaix E, et al. Natural history of serum HIV-1 RNA levels in 330 patients with a known date of infection. *AIDS* 2000, 14: 123-31. <http://amedeo.com/lit.php?id=10708282>
50. Jean SS, Pape JW, Verdier RI, et al. The natural history of HIV 1 infection in Haitian infants. *Pediatr Infect Dis J* 1999, 18: 58-63. <http://amedeo.com/lit.php?id=9951982>
51. Kamradt T, Niese D, Brackmann HH, et al. Heterosexual transmission of HIV in hemophiliacs. *Klin Wochenschr* 1990, 68:1203-7. <http://amedeo.com/lit.php?id=1981245>
52. Kreiss JK, Kitchen LW, Prince HE, Kasper CK, Essex M. Antibody to human T-lymphotropic virus type III in wives of hemophiliacs. Evidence for heterosexual transmission. *Ann Intern Med* 1985, 102: 623-6. <http://amedeo.com/lit.php?id=2984972>
53. Kumarasamy N, Solomon S, Flanigan TP, Hemalatha R, Thyagarajan SP, Mayer KH. Natural history of HIV disease in southern India. *Clin Infect Dis* 2003, 36: 79-85. <http://amedeo.com/lit.php?id=12491206>
54. Lackritz EM, Satten GA, Aberle-Grasse J, et al. Estimated risk of transmission of the HIV by screened blood in the United States. *N Engl J Med* 1995, 333: 1721-5. <http://amedeo.com/lit.php?id=7491134>
55. Lee CA. The natural history of HIV disease in haemophilia. *Blood Rev* 1998, 12: 135-44. <http://amedeo.com/lit.php?id=9745883>
56. Lyles RH, Munoz A, Yamashita TE, et al. Natural history of HIV type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. Multicenter AIDS Cohort Study. *J Infect Dis* 2000, 181: 872-80. <http://amedeo.com/lit.php?id=10720507>
57. MacKellar DA, Valleroy LA, Secura GM, et al. Repeat HIV testing, risk behaviors, and HIV seroconversion among young men who have sex with men: a call to monitor and improve the practice of prevention. *J Acquir Immune Defic Syndr* 2002, 29: 76-85. <http://amedeo.com/lit.php?id=11782594>
58. Masur H, Michelis MA, Greene JB, et al. An outbreak of community-acquired Pneumocystis carinii pneumonia: initial manifestation of cellular immune dysfunction. *N Engl J Med* 1981, 305:1431-8. <http://amedeo.com/lit.php?id=6975437>
59. Melbye M, Biggar RJ, Ebbesen P, et al. Seroepidemiology of HTLV-III antibody in Danish homosexual men: prevalence, transmission, and disease outcome. *Br Med J* 1984, 289: 573-5. <http://amedeo.com/lit.php?id=6087972>
60. Melbye M, Njelesani EK, Bayley A, et al. Evidence for heterosexual transmission and clinical manifestations of HIV infection and related conditions in Lusaka, Zambia. *Lancet* 1986, 2:1113-5. <http://amedeo.com/lit.php?id=2877269>
61. Moore RD, Chaisson RE. Natural history of HIV infection in the era of combination antiretroviral therapy. *AIDS* 1999, 13: 1933-42. <http://amedeo.com/lit.php?id=10513653>
62. Murphy DA, Mitchell R, Vermund SH, Futterman D. Factors associated with HIV testing among HIV-positive and HIV-negative high-risk adolescents: the REACH Study. *Pediatrics* 2002, 110: e36. <http://amedeo.com/lit.php?id=12205286>

63. Padian N, Marquis L, Francis DP, et al. Male-to-female transmission of HIV. *JAMA* 1987, 258: 788-90. <http://amedeo.com/lit.php?id=3475478>
64. Paul-Ehrlich-Institut, Bundesamt für Sera und Impfstoffe. Sicherheit der HIV-1-Diagnostika. <http://www.pei.de/themen/hivdiasta.htm>
65. Peterman TA, Stoneburner RL, Allen JR, Jaffe HW, Curran JW. Risk of HIV transmission from heterosexual adults with transfusion-associated infections. *JAMA* 1988, 259: 55-8. <http://amedeo.com/lit.php?id=3334772>
66. Phair JP. Determinants of the natural history of HIV type 1 infection. *J Infect Dis* 1999, 179 Suppl 2: S384-6. <http://amedeo.com/lit.php?id=10081512>
67. Piot P, Quinn TC, Taelman H, et al. AIDS in a heterosexual population in Zaire. *Lancet* 1984, 2: 65-9. <http://amedeo.com/lit.php?id=6146009>
68. Pitchenik AE, Fischl MA, Spira TJ. AIDS in low-risk patients. Evidence for possible transmission by an asymptomatic carrier. *JAMA* 1983, 250: 1310-2. <http://amedeo.com/lit.php?id=6224028>
69. Pitchenik AE: AIDS in low-risk patients. Evidence for possible transmission by an asymptomatic carrier. *JAMA* 1983, 250:1310 -2. <http://amedeo.com/lit.php?id=6224028>
70. Pokrovsky VV, Eramova EU: Nosocomial outbreak of HIV infection in Elista, USSR. V. International Conference on AIDS 1989, Montreal, Abstract W.A.O.5.
71. Quinn TC, Mann JM, Curran JW, Piot P. AIDS in Africa: an epidemiologic paradigm. *Science* 1986, 234: 955-63. <http://amedeo.com/lit.php?id=3022379>
72. Redfield RR, Markham PD, Salahuddin SZ, et al. Frequent transmission of HTLV-III among spouses of patients with AIDS-related complex and AIDS. *JAMA* 1985, 253: 1571-3. <http://amedeo.com/lit.php?id=2983127>
73. Redfield RR, Markham PD, Salahuddin SZ, et al. Heterosexually acquired HTLV-III/LAV disease (AIDS-related complex and AIDS). Epidemiologic evidence for female-to-male transmission. *JAMA* 1985, 254: 2094-6. <http://amedeo.com/lit.php?id=2995695>
74. Redfield RR, Wright DC, Tramont EC. The Walter Reed staging classification for HTLV-III/LAV infection. *N Engl J Med* 1986;314:131-2.
75. Richtlinien zur Gewinnung von Blut und Blutbestandteilen und zur Anwendung von Blutprodukten (Hämotherapie). Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz. Springer-Verlag 2000, 43:555-589. <http://hiv.net/link.php?id=183>
76. Risk factors for AIDS among Haitians residing in the United States. Evidence of heterosexual transmission. The Collaborative Study Group of AIDS in Haitian-Americans. *JAMA* 1987, 257: 635-9. <http://amedeo.com/lit.php?id=3795445>
77. Rogers AS, Froggatt JW, Townsend T, et al. Investigation of potential HIV transmission to the patients of an HIV-infected surgeon. *JAMA* 1993, 269: 1795-1801. <http://amedeo.com/lit.php?id=8459510>
78. Spira R, Lepage P, Msellati P, et al. Natural history of HIV type 1 infection in children: a five-year prospective study in Rwanda. Mother-to-Child HIV-1 Transmission Study Group. *Pediatrics* 1999, 104: e56. <http://amedeo.com/lit.php?id=10545582>
79. Stewart GJ, Tyler JP, Cunningham AL, et al. Transmission of human T-cell lymphotropic virus type III (HTLV-III) by artificial insemination by donor. *Lancet* 1985, 2: 581-5. <http://amedeo.com/lit.php?id=2863597>
80. UNAIDS. AIDS Epidemic Update 2004. <http://hiv.net/link.php?id=227>
81. Vergis EN, Mellors JW. Natural history of HIV-1 infection. *Infect Dis Clin North Am* 2000, 14: 809-25, v-vi. <http://amedeo.com/lit.php?id=11144640>
82. Vogt M, Luthy R, Bircher A, et al. Heterosexual transmission of the acquired immunodeficiency syndrome (AIDS). *Dtsch Med Wochenschr* 1985, 110: 1483-7. <http://amedeo.com/lit.php?id=3875471>
83. Wormser GP, Bittker S, Forseter G, et al. Absence of infectious HIV type 1 in "natural" eccrine sweat. *J Infect Dis* 1992, 165: 155-8. <http://amedeo.com/lit.php?id=1345794>
84. Ziegler JB, Cooper DA, Johnson RO, Gold J. Postnatal transmission of AIDS-associated retrovirus from mother to infant. *Lancet* 1985, 1:896-8. <http://amedeo.com/lit.php?id=2858746>



## 2. Acute HIV-1 Infection

Marcus Altfeld and Bruce D. Walker

### Introduction

Acute HIV-1 infection presents in 40 – 90 % of cases as a transient symptomatic illness, associated with high levels of HIV-1 replication and an expansive virus-specific immune response. With 14,000 new cases per day worldwide, it is an important differential diagnosis in cases of fever of unknown origin, maculopapular rash and lymphadenopathy.

The diagnosis of acute infection is missed in the majority of cases, as other viral illnesses (“flu”) are often assumed to be the cause of the symptoms, and there are no HIV-1-specific antibodies detectable at this early stage of infection. The diagnosis therefore requires a high degree of clinical suspicion, based on clinical symptoms and history of exposure, in addition to specific laboratory tests (detection of HIV-1 RNA or p24 antigen and negative HIV-1 antibodies) confirming the diagnosis.

An accurate early diagnosis of acute HIV-1 infection is important, as infection of sexual partners can be prevented and patients may benefit from therapy at this early stage of infection (see below).

### Immunological and virological events during acute HIV-1 infection

During acute HIV-1 infection, the virus replicates extensively in the absence of any detectable adaptive immune response, reaching levels of over 100 million copies HIV-1 RNA/ml. It is during this initial cycle of viral replication that important pathogenic processes are thought to occur. These include the seeding of virus to a range of tissue reservoirs and the destruction of CD4+ T-lymphocytes, in particular within the lymphoid tissues of the gut. The very high levels of HIV-1 viremia are normally short-lived, indicating that the host is able to generate an immune response that controls viral replication. Over the following weeks, viremia declines by several orders of magnitude before reaching a viral setpoint. This setpoint, following resolution of the acute infection, is a strong predictor of long-term disease progression rates (Mellors 1995).

Several factors can influence viral replication during acute infection and the establishment of a viral setpoint. These include the fitness of the infecting virus, host genetic factors and host immune responses. While antibodies against HIV-1 with neutralizing capacities are rarely detectable during primary HIV-1 infection, a number of studies have demonstrated a crucial role of HIV-1-specific cellular immune responses for the initial control of viral replication during this stage of infection. A massive, oligoclonal expansion of CD8+ T-cell responses has been described during acute HIV-1 infection (Pantaleo 1994), and the appearance of HIV-1-specific CD8+ T cells has been temporally associated with the initial decline of viremia (Koup 1994, Borrow 1994). These CD8+ T-cells have the ability to elimi-

nate HIV-1-infected cells directly by MHC class I-restricted cytotoxicity or indirectly by producing cytokines, chemokines or other soluble factors, thus curtailing the generation of new viral progeny (Yang 1997). The biological relevance of HIV-1-specific cytotoxic T cells (CTL) in acute HIV-1 infection was highlighted in recent in-vivo studies demonstrating a dramatic rise of SIV viremia and an accelerated clinical disease progress in macaques after the artificial depletion of CD8<sup>+</sup> T-cells (Schmitz 1999, Jin 1999). Additional evidence for the antiviral pressure of HIV-1-specific CTLs during primary HIV-1 infection has been provided by the rapid selection of viral species with CTL epitope mutations that were detected within a few weeks after HIV-1 and SIV infection in humans and rhesus macaques, respectively (Allen 2000, O'Connor 2002, Price 1997).

During acute HIV-1 infection, the number of CD4<sup>+</sup> T-cells decline, occasionally to levels that allow the development of opportunistic infections at that time (Gupta 1993, Vento 1993). Even though the CD4<sup>+</sup> T-cell count rebounds with the resolution of primary infection, it rarely returns to baseline levels in the absence of antiretroviral therapy. In addition to the decline in CD4<sup>+</sup> T-cell counts, qualitative impairments of CD4<sup>+</sup> T-cell function are perhaps the most characteristic abnormalities detected in HIV-1 infection. The impairment of HIV-1-specific CD4<sup>+</sup> T-cell function occurs very early in acute infection (Rosenberg 1997, Altfeld 2001, Lichterfeld 2004), potentially due to the preferential infection of virus-specific CD4<sup>+</sup> T-cells by the virus (Douek 2002). This is followed by a functional impairment of CD4<sup>+</sup> T-cell responses to other recall antigens, as well as a reduced responsiveness to novel antigens (Lange 2003). The impairment of HIV-1-specific CD4<sup>+</sup> T-helper cell function in acute HIV-1 infection subsequently results in a functional impairment of HIV-1-specific CD8<sup>+</sup> T-cells (Lichterfeld 2004).

In addition to host immune responses, host genetic factors play an important role in both susceptibility and resistance to HIV-1 infection and speed of disease progression following infection. The most important of these is a deletion in the major coreceptor for entry of HIV-1 into CD4<sup>+</sup> T-cells, a chemokine receptor called CCR5 (Samson 1996). Homozygotes for this 32 base pair deletion (CCR5 $\Delta$ 32) do not express the receptor at the cell-surface and can only be infected with HIV strains that are able to use other coreceptors, such as CXCR4. Thus, although CCR5 $\Delta$ 32 homozygotic individuals show a significant degree of resistance to HIV-1 infection (Samson 1996), a number of cases of infection with CXCR4-using HIV-1 strains have been described (O'Brien 1997, Biti 1997). Heterozygotes for the deletion exhibit significant lower viral setpoints and slower progression to AIDS. In addition to mutations in the chemokine receptor genes, a number of HLA class I alleles have been described to be associated with both, lower viral setpoints and slower disease progression, including HLA-B27 and -B57 (O'Brien 2001, Kaslow 1996). Recent studies demonstrated that individuals expressing HLA-B57 presented significantly less frequently with symptomatic acute HIV-1 infection and exhibited a better control of viral replication following acute infection (Altfeld 2003). These data demonstrate that host genetic factors can influence the clinical manifestations of acute HIV-1 infection and have an important impact on subsequent viral setpoints and the speed of disease progression.

## Signs and symptoms

After an incubation period of a few days to a few weeks after exposure to HIV, most infected individuals present with an acute flu-like illness. Acute HIV-1 infection is a very heterogeneous syndrome and individuals presenting with more severe symptoms during acute infection and a longer duration of the acute infection syndrome tend to progress more rapidly to AIDS (Vanhems 1998, Vanhems 2000, Sinicco 1993, Pedersen 1989, Keet 1993, Lindback 1994). The clinical symptoms of acute HIV-1 infection were first described in 1985 as an illness resembling infectious mononucleosis (Cooper 1985). The most common symptoms (see Table 1) are fever, maculopapular rash, oral ulcers, lymphadenopathy, arthralgia, pharyngitis, malaise, weight loss, aseptic meningitis and myalgia (Kahn 1998). In one study (Hecht 2002), fever (80 %) and malaise (68 %) had the highest sensitivity for clinical diagnosis of acute HIV-1 infection, whereas loss of weight (86 %) and oral ulcers (85 %) had the highest specificity. In this study, the symptoms of fever and rash (especially in combination), followed by oral ulcers and pharyngitis had the highest positive predictive value for diagnosis of acute HIV-1 infection. In another study (Daar 2001), fever, rash, myalgia, arthralgia and night sweats were the best predictors for acute HIV-1 infection.

Table 1: Main symptoms of acute HIV-1 infection

Symptom	Frequency	Odds ratio (95% CI)
Fever	80%	5.2 (2.3-11.7)
Rash	51%	4.8 (2.4-9.8)
Oral ulcers	37%	3.1 (1.5-6.6)
Arthralgia	54%	2.6 (1.3-5.1)
Pharyngitis	44%	2.6 (1.3-5.1)
Loss of appetite	54%	2.5 (1.2-4.8)
Weight loss > 2.5 kg	32%	2.8 (1.3-6.0)
Malaise	68%	2.2 (1.1-4.5)
Myalgia	49%	2.1 (1.1-4.2)
Fever and rash	46%	8.3 (3.6-19.3)

From: Hecht FM et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS* 2002, 16: 1119-1129

The symptomatic phase of acute HIV-1 infection lasts between 7 – 10 days, and rarely longer than 14 days. The nonspecific nature of the symptoms poses a great challenge to the clinician and underlines the importance of a detailed history of exposure.

## Diagnosis

The diagnosis of acute HIV-1 infection is based on the detection of HIV-1 replication in the absence of HIV-1 antibodies, as these are not yet present at this early stage of infection. Different tests are available for diagnosis of acute HIV-1 infection. The most sensitive tests are based on detection of plasma HIV-1 RNA.

## 36 Acute HIV-1 Infection

In one study (Hecht 2002), all assays for HIV-1 RNA that were tested (branched chain DNA, PCR and GenProbe) had a sensitivity of 100 %, but occasionally (in 2 – 5 % of cases) led to false positive results. False positive results from these tests are usually below 2,000 copies HIV-1 RNA per ml plasma, and therefore far below the high titers of viral load normally seen during acute HIV-1 infection (in our own studies on average  $13 \times 10^6$  copies HIV-1 RNA/ml with a range of  $0.25 - 95.5 \times 10^6$  copies HIV-1 RNA/ml). Repetition of the assay for HIV-1 RNA from the same sample with the same test led to a negative result in all false positive cases. Measurement of HIV-1 RNA from duplicate samples therefore results in a sensitivity of 100 % with 100 % specificity. In contrast, detection of p24 antigen has a sensitivity of only 79 % with a specificity of 99.5 – 99.96 %. The diagnosis of acute HIV-1 infection must be subsequently confirmed with a positive HIV-1 antibody test (seroconversion) within the following weeks.

During acute HIV-1 infection, there is frequently a marked decrease of CD4+ T-cell count, which later increases again, but usually does not normalize to the initial levels. In contrast, the CD8+ T-cell count rises initially, which may result in a CD4/CD8 ratio of  $< 1$ . Infectious mononucleosis is the most important differential diagnosis. Hepatitis, influenza, toxoplasmosis, syphilis and side effects of medications may also be considered.

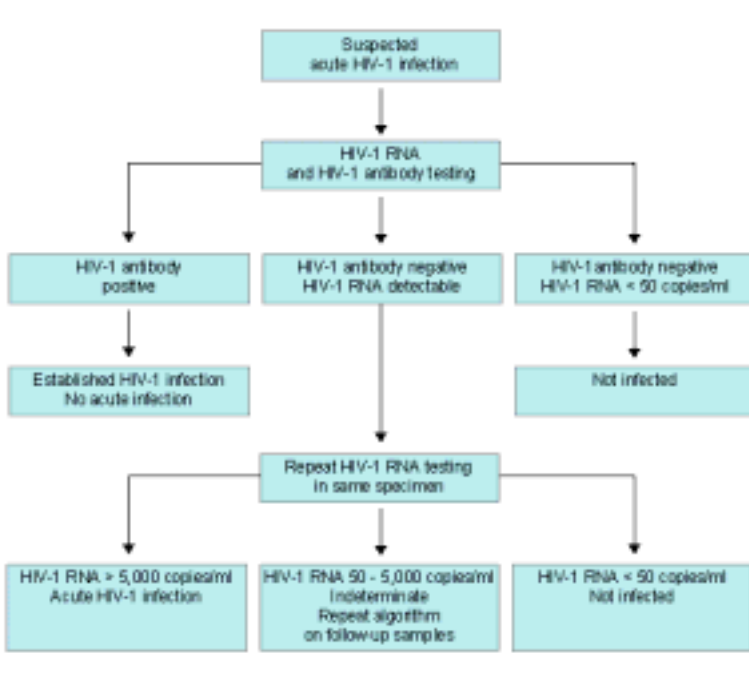


Figure 1: Algorithm for the diagnosis of acute HIV-1 infection

In summary, the most important step in the diagnosis of acute HIV-1 infection is to include it in the differential diagnosis. The clinical suspicion of an acute HIV-1 infection then merely requires performance of an HIV-1 antibody test and possibly

repeated testing of HIV-1 viral load, as shown in the algorithm in Figure 1 (adapted from (Hecht 2002).

## Treatment

The goal of antiretroviral therapy during acute HIV-1 infection is to shorten the symptomatic viral illness, reduce the number of infected cells, preserve HIV-1-specific immune responses and possibly lower the viral set point in the long term. Several studies in recent years have shown that treatment of acute HIV-1 infection allows long-term viral suppression, leads to preservation and even increase of HIV-1-specific T-helper cell responses and allows for the conservation of a very homogeneous virus population.

First pilot studies in patients who were treated during acute HIV-1 infection and subsequently went through structured treatment interruptions show that the HIV-1-specific immune response could be boosted in these patients (Rosenberg 2000). Most patients were subsequently able to discontinue therapy and experienced at least temporal control of viral replication, with viral set points remaining below 5,000 copies/ml for more than 3 years in some patients. However, in the majority of individuals in this study (Kaufmann 2004), as well as in other studies assessing viral control following treated primary infection (Markowitz 1999), viral load rebounded during longer follow-up, requiring the initiation of therapy.

The long-term clinical benefit of early initiation of therapy has not been demonstrated yet. It is also not known how long the period between acute infection and initiation of therapy can be without losing immunological, virological and clinical benefit. In view of all these unanswered questions, patients with acute HIV-1 infection should be treated in controlled clinical trials (Yeni 2002). If this is not possible, the option of standard first-line treatment should be offered and discussed. It is important during counseling to clearly indicate the lack of definitive data on clinical benefit of early initiation of antiretroviral therapy and to address the risks of antiretroviral therapy and treatment interruptions, including drug toxicity, development of resistance, acute retroviral syndrome during viral rebound and HIV-1 transmission and superinfection during treatment interruptions.

## References

1. Allen TM, O'Connor DH, Jing P, Dzuris JL, Mothe BR, Vogel TU, et al. Tat-specific cytotoxic T lymphocytes select for SIV escape variants during resolution of primary viraemia. *Nature* 2000;407:386-390. <http://amedeo.com/lit.php?id=11014195>
2. Altfeld M, Rosenberg ES, Shankarappa R, Mukherjee JS, Hecht FM, Eldridge RL, et al. Cellular Immune Responses and Viral Diversity in Individuals Treated during Acute and Early HIV-1 Infection. *J Exp Med* 2001;193:169-180. <http://amedeo.com/lit.php?id=11148221>
3. Altfeld M, Addo MM, Rosenberg ES, Hecht FM, Lee PK et al. Influence of HLA-B57 on clinical presentation and viral control during acute HIV-1 infection. *AIDS*. 2003 Dec 5;17(18):2581-91. <http://amedeo.com/lit.php?id=14685052>
4. Biti R, French R, Young J, Bennetts B, Stewart G, Liang T. HIV-1 infection in an individual homozygous for the CCR5 deletion allele. *Nat Med* 1997;3:252-253.
5. Borrow P, Lewicki H, Hahn BH, Shaw GM, Oldstone MB. Virus-specific CD8+ cytotoxic T-lymphocyte activity associated with control of viremia in primary human immunodeficiency virus type 1 infection. *J Virol* 1994;68:6103-6110. <http://amedeo.com/lit.php?id=8057491>
6. Cooper DA, Gold J, Maclean P, Donovan B, Finlayson R, Barnes TG, et al. Acute AIDS retrovirus infection. Definition of a clinical illness associated with seroconversion. *Lancet* 1985;1:537-540. <http://amedeo.com/lit.php?id=2857899>

## 38 Acute HIV-1 Infection

7. Daar ES, Little S, Pitt J, Santangelo J, Ho P, Harawa N, et al. Diagnosis of primary HIV-1 infection. Los Angeles County Primary HIV Infection Recruitment Network. *Ann Intern Med* 2001,134:25-29. <http://amedeo.com/lit.php?id=11187417>
8. Douek DC, Brenchley JM, Betts MR, Ambrozak DR, Hill BJ, Okamoto Y, et al. HIV preferentially infects HIV-specific CD4+ T cells. *Nature* 2002,417:95-98. <http://amedeo.com/lit.php?id=11986671>
9. Gupta KK. Acute immunosuppression with HIV seroconversion. *N Engl J Med* 1993,328:288-289.
10. Hecht FM, Busch MP, Rawal B, Webb M, Rosenberg E, Swanson M, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *Aids* 2002,16:1119-1129. <http://amedeo.com/lit.php?id=12004270>
11. Jin X, Bauer DE, Tuttleton SE, Lewin S, Gettie A, Blanchard J, et al. Dramatic rise in plasma viremia after CD8(+) T cell depletion in simian immunodeficiency virus-infected macaques. *J Exp Med* 1999,189:991-998. <http://amedeo.com/lit.php?id=10075982>
12. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. *New England Journal of Medicine* 1998,339:33-39.
13. Kaslow RA, Carrington M, Apple R, Park L, Munoz A, Saah AJ, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat Med* 1996,2:405-411. <http://amedeo.com/lit.php?id=8597949>
14. Kaufmann DE, Lichtenfeld M, Altfeld M, Addo MM, Johnston MN et al. Limited Durability of Viral Control following Treated Acute HIV Infection. *PLOS Medicine*, November 2004. in press. <http://www.plosmedicine.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0010036>
15. Keet IP, Krijnen P, Koot M, Lange JM, Miedema F, Goudsmit J, et al. Predictors of rapid progression to AIDS in HIV-1 seroconverters. *Aids* 1993,7:51-57. <http://amedeo.com/lit.php?id=8095146>
16. Koup RA, Safrit JT, Cao Y, Andrews CA, McLeod G, Borkowsky W, et al. Temporal association of cellular immune responses with the initial control of viremia in primary human immunodeficiency virus type 1 syndrome. *Journal of Virology* 1994,68:4650-4655. <http://amedeo.com/lit.php?id=8207839>
17. Lange CG, Lederman MM, Medvik K, Asaad R, Wild M, Kalayjian R, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. *Aids* 2003,17:2015-2023. <http://amedeo.com/lit.php?id=14502004>
18. Lichtenfeld M, Kaufmann DE, Yu XG, Mui SK, Addo MM, Johnston MN et al. Loss of HIV-1-specific CD8+ T cell proliferation after acute HIV-1 infection and restoration by vaccine-induced HIV-1-specific CD4+ T cells. *J Exp Med*. 2004 Sep 20;200(6):701-12. <http://amedeo.com/lit.php?id=15381726>
19. Lindback S, Brostrom C, Karlsson A, Gaines H. Does symptomatic primary HIV- 1 infection accelerate progression to CDC stage IV disease, CD4 count below 200 x 10(6)/l, AIDS, and death from AIDS? *Bmj* 1994,309:1535-1537. <http://amedeo.com/lit.php?id=7819891>
20. Markowitz M, Vesanen M, Tenner-Racz K, Cao Y, Binley JM, Talal A, et al. The effect of commencing combination antiretroviral therapy soon after human immunodeficiency virus type 1 infection on viral replication and antiviral immune responses. *J Infect Dis* 1999,179:527-537.
21. Mellors JW, Kingsley LA, Rinaldo CR, Jr., Todd JA, Hoo BS, Kokka RP, et al. Quantitation of HIV-1 RNA in plasma predicts outcome after seroconversion. *Ann Intern Med* 1995,122:573-579. <http://amedeo.com/lit.php?id=7887550>
22. O'Brien SJ, Gao X, Carrington M. HLA and AIDS: a cautionary tale. *Trends Mol Med* 2001,7:379-381. <http://amedeo.com/lit.php?id=11530315>
23. O'Brien TR, Winkler C, Dean M, Nelson JA, Carrington M, Michael NL, et al. HIV-1 infection in a man homozygous for CCR5 delta 32. *Lancet* 1997,349:1219.
24. O'Connor DH, Allen TM, Vogel TU, Jing P, DeSouza IP, Dodds E, et al. Acute phase cytotoxic T lymphocyte escape is a hallmark of simian immunodeficiency virus infection. *Nat Med* 2002,8:493-499. <http://amedeo.com/lit.php?id=11984594>
25. Pantaleo G, Demarest JF, Soudeyns H, Graziosi C, Denis F, Adelsberger JW, et al. Major expansion of CD8+ T cells with a predominant V beta usage during the primary immune response to HIV. *Nature* 1994,370:463-467. <http://amedeo.com/lit.php?id=8047166>
26. Pedersen C, Lindhardt BO, Jensen BL, Lauritzen E, Gerstoft J, Dickmeiss E, et al. Clinical course of primary HIV infection: consequences for subsequent course of infection. *Bmj* 1989,299:154-157. <http://amedeo.com/lit.php?id=2569901>
27. Price DA, Goulder PJ, Klenerman P, Sewell AK, Easterbrook PJ, Troop M, et al. Positive selection of HIV-1 cytotoxic T lymphocyte escape variants during primary infection. *Proc Natl Acad Sci U S A* 1997,94:1890-1895. <http://amedeo.com/lit.php?id=9050875>
28. Rosenberg ES, Altfeld M, Poon SH, Phillips MN, Wilkes BM, Eldridge RL, et al. Immune control of HIV-1 after early treatment of acute infection. *Nature* 2000,407:523-526. <http://amedeo.com/lit.php?id=11029005>

29. Rosenberg ES, Billingsley JM, Caliendo AM, Boswell SL, Sax PE, Kalams SA, et al. Vigorous HIV-1-specific CD4+ T cell responses associated with control of viremia. *Science* 1997,278:1447-1450. <http://amedeo.com/lit.php?id=9367954>
30. Samson M, Libert F, Doranz BJ, Rucker J, Liesnard C, Farber CM, et al. Resistance to HIV-1 infection in caucasian individuals bearing mutant alleles of the CCR-5 chemokine receptor gene. *Nature* 1996,382:722-725. <http://amedeo.com/lit.php?id=8751444>
31. Schmitz JE, Kuroda MJ, Santra S, Sasseville VG, Simon MA, Lifton MA, et al. Control of viremia in simian immunodeficiency virus infection by CD8+ lymphocytes. *Science* 1999,283:857-860. <http://amedeo.com/lit.php?id=9933172>
32. Sinicco A, Fora R, Sciandra M, Lucchini A, Caramello P, Giannini P. Risk of developing AIDS after primary acute HIV-1 infection. *J Acquir Immune Defic Syndr* 1993,6:575-581. <http://amedeo.com/lit.php?id=8098750>
33. Vanhems P, Hirschel B, Phillips AN, Cooper DA, Vizzard J, Brassard J, et al. Incubation time of acute human immunodeficiency virus (HIV) infection and duration of acute HIV infection are independent prognostic factors of progression to AIDS. *J Infect Dis* 2000,182:334-337. <http://amedeo.com/lit.php?id=10882619>
34. Vanhems P, Lambert J, Cooper DA, Perrin L, Carr A, Hirschel B, et al. Severity and prognosis of acute human immunodeficiency virus type 1 illness: a dose- response relationship. *Clin Infect Dis* 1998,26:323-329. <http://amedeo.com/lit.php?id=9502449>
35. Vento S, Di Perri G, Garofano T, Concia E, Bassetti D. *Pneumocystis carinii* pneumonia during primary HIV-1 infection. *Lancet* 1993,342:24-25.
36. Yang OO, Kalams SA, Trocha A, Cao H, Luster A, Johnson RP, et al. Suppression of human immunodeficiency virus type 1 replication by CD8+ cells: evidence for HLA class I-restricted triggering of cytolytic and noncytolytic mechanisms. *Journal of Virology* 1997,71:3120-3128. <http://amedeo.com/lit.php?id=9060675>
37. Yeni PG, Hammer SM, Carpenter CC, Cooper DA, Fischl MA, Gatell JM, et al. Antiretroviral treatment for adult HIV infection in 2002: updated recommendations of the International AIDS Society-USA Panel. *Jama* 2002,288:222-235. <http://amedeo.com/lit.php?id=12095387>





### 3. HIV Testing

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Awareness of one's HIV infection is the prerequisite for making best use of the latest available therapeutic options. It is therefore recommended to undergo counseling and HIV testing after a potential exposure. In contrast to the past, HIV testing has now gained immense therapeutic relevance: starting HAART on time may improve the quality of life and indeed prolong life considerably. Consequently, a shift in attitude towards HIV testing has taken place over the past decade: while an HIV test was formerly regarded as primarily a threat to the civil rights of the individual tested, the carer is now, in the age of HAART, obliged to advise – if necessary, emphatically – HIV testing in order to enable the patient to benefit from optimized management of his infection. An HIV test may also be in the interest of a third person, examples being the testing of an index patient after a needlestick injury or the screening of pregnant women.

If a patient suffers from a possibly HIV-related illness, the diagnosis or exclusion of HIV infection offers important clues for further diagnostic and therapeutic management. In most cases this means diagnosing an established HIV infection the patient has had for some time (often years). Special cases are suspected acute primary or vertically acquired infections, as these require particular testing strategies (see below).

Besides individual diagnostic use, HIV tests are used in large numbers in the screening of blood donors, blood products, and transplant organs to guarantee their safety, as well as (often in an anonymous way) for epidemiological surveillance (UNAIDS, 1997a and 2001).

#### How to test

The diagnosis of an HIV infection is normally made indirectly, i.e. through the demonstration of virus-specific antibodies (Gürtler 1996). These are found in virtually 100% of those infected with HIV and constitute a marker of a humoral immune response against the agent. In contrast to many other viruses, the antibodies do not have an immunoprotective effect leading to immunity. Their presence equals the presence of chronic and active HIV infection. Cases in which individuals persistently fail to have detectable antibodies against HIV despite the presence of HIV infection are exceedingly rare and so far play little or no role in clinical practice (Connick 2005). However, this might change in the future (Kassutto 2005).

Besides indirect diagnosis based on detection of antibodies, a direct diagnosis of HIV infection is also possible: either through the demonstration of infectious virus (using cell culture – this is only possible in laboratories of at least biological safety level 3), of viral antigens (p24 antigen ELISA) or of viral nucleic acid (i.e. viral genome); the latter is also termed nucleic acid testing (NAT). Viral genome detection is nowadays most often used, as it does not require a high security laboratory, is more sensitive than antigen detection and allows quantification.

To determine the infection status of a patient, direct virus detection by qualitative tests (providing a "yes/no" answer) is only useful under certain circumstances, such as a suspected primary infection or in the case of babies born to HIV-infected mothers (for details see below). However, quantitative viral genome assays have gained great importance: The determination of the so-called "viral load", i.e. the concentration of viral RNA in plasma, has become an indispensable tool for guiding antiretroviral therapy.

The term "HIV test" (still occasionally but inaccurately referred to as the "AIDS test"), however, almost always refers to testing for HIV-specific antibodies as a marker of infection.

### **HIV antibody diagnosis**

Testing for HIV antibodies invariably necessitates the availability of at least two different assays:

1. A screening test and
2. At least one confirmatory test.

It is important to note that two different specimens from the same patient should be tested before the diagnosis is confirmed (see later).

Most screening tests are based on the ELISA principle (enzyme linked immuno sorbent assay) or other, closely related test formats (UNAIDS, 1997b). Screening tests must be extremely sensitive to minimize the chance of yielding a false-negative result. This means that they have to be able to also detect low-avidity antibodies found e.g. early in the course of a primary infection. They also have to be able to detect antibodies directed against all different HIV types (HIV-1, HIV-2) and subtypes (HIV-1-N, HIV-1-O, HIV-1-M) (UNAIDS/WHO, 1992 and 1997).

If the result of such a screening test is positive, this has to be confirmed by at least one confirmatory assay. For this purpose, some countries such as Germany and the United States, prescribe the use of a so-called Western blot or immunofluorescence assay (IFT or IFA). In others, such as the United Kingdom, confirmation may be achieved through the use of different tests applied in a defined sequence in the form of an algorithm – for example, the use of more specific ELISAs. This latter approach is by no means inferior to confirmation by Western blot and does in fact have several advantages, such as being cheaper and more objective (Tamashiro 1993).

The World Health Organization recommends the following strategy for resource-poor settings (WHO 1992):

- Diagnosis in an healthy individual when population prevalence < 10 %: three immunoassays in series
- Diagnosis in a healthy individual when population prevalence > 10 %, or in a symptomatic individual: two immunoassays in series
- Screening of blood donations: single immunoassay (unless the blood donor is informed of the result).

## ELISA screening test

Many commercial ELISA tests are available as 96-well microtitre plates. Although the test may be carried out completely manually, they also allow automatization and thus the safe and economical testing of large numbers of patient samples. Various other test kits based on similar formats are also available, often performed by large, fully automatic pipetting and analyzing machines.

Different ELISA "formats" can be distinguished; they are all based on the principle of a specific antigen-antibody reaction. Initially, HIV "whole virus" antigen obtained from cell cultures was used (1<sup>st</sup> generation tests); nowadays, a mixture of recombinant virus proteins or synthetic peptides representing immunodominant epitopes is employed (2<sup>nd</sup> and further generation tests).

In order to avoid missing certain virus strains, it is important to know how well the antigens used are able to detect antibodies directed against the potentially occurring virus types (HIV-1, HIV-2) and subtypes (HIV-1-N, HIV-1-O, HIV-1-M). For example, a patient who was infected with HIV-2 in West Africa but is only tested for HIV-1 antibodies – HIV-2 antibodies would not be detected and the infection therefore not be diagnosed. However, because of more or less marked cross-reactivity, a reliable serological differentiation between infections with HIV-1 and HIV-2 is only possible using special assays and, if necessary, will have to be discussed directly with the laboratory.

In most ELISA tests, viral antigen is bound to the so-called solid phase (e.g. on the bottom of the wells in a microtitre plate). Upon addition of patient serum containing antibodies directed specifically against these antigens, antigen-antibody binding will occur. A washing step ensures that all unbound constituents of the serum, including all antibodies not recognizing the viral antigen, are removed.

If antibody has bound to the viral antigen, it is then detected through addition of an enzyme-labeled "conjugate". This conjugate may be either a second (e.g. goat) antibody directed against human antibody molecules ("antiglobulin" assay) or again a viral antigen (often the same antigen that is coated onto the solid phase: "immunometric" or sandwich assay; 3<sup>rd</sup> generation tests), coupled with an enzyme. The advantage of "immunometric" assays is that they detect antibodies of all classes (including the "early" IgM antibodies which do not play an important role in HIV infection). Again, a washing step ensures that all unbound conjugate is removed.

Finally a substrate is added. If in the previous step conjugate has been bound, this substrate is converted by the action of the enzyme contained in the conjugate. This causes a change of color; the intensity ("optical density", O.D.) of this color reaction is measured and is proportional to the antibody activity in the sample. Positive and negative control specimens are included in each test run and the O.D. values obtained on them are often used to calculate the test's cut-off (i.e. the O.D. value used to distinguish positive from negative values).

Another commonly used method is the MEIA (microparticle enzyme immunoassay). It is based on the same principle as an ELISA; however, the "solid phase" is in the form of microparticles in liquid suspension. Detection is by means of trapping the particles on a membrane and detecting enzyme activity, as with the ELISA.

A special case is "competitive" assays: Here, enzyme-labeled HIV antibodies are added to the solid phase together with the patient's sample. These antibodies then

compete for antigen binding sites with the patient's antibodies. If the patient lacks HIV antibodies, all or most of the enzyme-labeled antibody molecules will bind, causing an intense color reaction after addition of the substrate. And vice versa: the more specific the antibodies that are present in the patient's sample, the weaker the color reaction. The intensity of the color reaction is therefore inversely proportional to the antibody activity in the sample. Such "competitive" assays are normally highly specific.

The different formats have different advantages and disadvantages; it is therefore important to know which format a particular assay is based on. So-called 4<sup>th</sup> generation antibody tests combine the detection of HIV antibodies with that of viral p24 antigen, in order to detect antigen in the blood sample prior to the formation of antibodies, thereby reducing the "diagnostic window" (see below) (Brust 2000).

The accuracy of a test lies in the combination of two factors: the test's sensitivity and its specificity. Sensitivity denotes the test's ability to correctly identify a positive sample as positive, whereas specificity measures its ability to correctly identify a negative sample as negative.

Screening tests are extremely sensitive (almost 100 %), which means that even very low HIV antibody activities – e.g. early in the course of a primary infection – are detected. High sensitivity reduces the chance of a "false-negative" test result and thus of an erroneous conclusion: "The patient is not HIV-infected", although he in fact is. Provided a suitable screening test is used, a negative result six or more months after a potential infection risk means, due to the test's high sensitivity, that the chance of infection is virtually nil (Preiser 2000).

HIV tests sold for the first time after 7 December 2003 are subject to new European Union legislation on in vitro diagnostic devices and have to carry the CE mark. Amongst the conditions to be fulfilled is that 600 HIV-positive samples, including 200 HIV-2-positive ones, obtained at different stages of HIV infection and disease, all have to be identified correctly as positive.

For screening tests, the emphasis has to be placed on the utmost sensitivity; any failure to identify a positive sample correctly could have grave consequences. This high sensitivity, however, causes a somewhat lower specificity. This means that the test result may occasionally be a "false-positive". The test result then indicates the presence of antibodies against HIV although in fact some substance present in the sample was erroneously misidentified as HIV antibodies. Such false-positive results may be caused by immune stimulation of some sort (acute virus infections, pregnancy, immunizations, autoimmune diseases). Presently available HIV screening tests have a specificity of at least 99.5 %; i.e. among 4,000 HIV-negative samples tested, a maximum of 20 may show a false-reactive test result.

Due to the possibility of non-specific reactivity inherent in any assay, it is preferable to use the term "reactive" – rather than "positive" – screening test result thus avoiding misunderstandings. All reactive screening test results must be confirmed by confirmatory testing in order to exclude the risk of reporting non-specific reactivity as "positive". Only then should one talk of a "positive HIV test"!

Important: a reactive screening test does not mean HIV infection! Only a positive confirmatory test allows the diagnosis of an HIV infection, and normally only such a result should be communicated to the patient! It is also important to send a second

specimen, as non-specific reactivity can occur due to, for example, the condition of the blood sample, or the samples may have been incorrectly labeled, or switched before testing.

Other potential causes for false-positive (or also false-negative) test results are errors occurring in the laboratory or in the pre- or postanalytical phase. Besides mistakes caused by confusing samples or contamination with positive sample material through suboptimal pipetting techniques etc., clerical errors (incorrect labeling of sample tube or request form, incorrect data entry into laboratory or clinical software etc.) may occur. Utmost attention must be paid also to seemingly unimportant steps in order to safeguard the quality of laboratory testing!

## Western blot confirmatory assay

The Western blot is a methodology commonly used for confirmatory testing of screening test-reactive samples. HIV is propagated in cell cultures, harvested, purified and denatured (i.e. split into its constituents). Then, the viral proteins are separated according to their molecular weight by electrophoresis and blotted onto a nitrocellulose membrane. The membrane is cut into strips. To perform the test, the membrane is incubated with patient serum. If the serum contains antibodies against the various viral proteins, these will bind to the areas on the strip onto which the respective antigens have been blotted. If an antigen-antibody reaction takes place, it is revealed using an enzyme-labeled secondary antibody and matching substrate, causing the so-called "bands" to appear on the test strip.

HIV proteins and corresponding bands on the Western blot are designated "p" (for protein) or "gp" (for glycoprotein), followed by the relative molecular mass in kilodaltons. They can be divided (here using the example of HIV-1 Western blot) into three groups: the env or envelope glycoproteins (gp41, gp120, gp160), the gag or nuclear proteins (p18, p24/25, p55) and the pol or endonuclease-polymerase proteins (p34, p40, p52, p68).

The Western blot is a confirmatory assay that is only carried out if the sample was reactive in the screening assay. Both HIV-1 and HIV-2 Western blots are available commercially. The result of a Western blot may be either positive or negative or (in case of an incomplete pattern of visible bands) equivocal which may reflect borderline or non-specific reactivity.

Different organizations have developed different sets of criteria for interpretation of HIV Western blot results. In order for a Western blot result to be declared positive, the American Red Cross for instance demands at least three bands, one from each group (i.e. one gag, one pol and one env band). The US-American Food and Drug Administration (FDA) demands the p24, the p34 as well as the gp41 or gp120/160 bands (Centers for Disease Control and Prevention, 1989). According to WHO recommendations, however, a Western blot may be judged positive only if two env bands are found. In Germany, the DIN norm 58969 part 41 applies (Deutsches Institut für Normung, 2000): a serum sample is HIV positive if it reacts with at least one viral glycoprotein and one of the other HIV proteins. All other virus-specific band patterns are regarded as questionable.

Among the disadvantages of Western blot are its relatively high price, the comparatively demanding test procedure and the unavoidable subjectivity when reading

and interpreting the result. For these reasons many countries prefer confirmatory tests using suitable testing algorithms, consisting of a combination of different ELISA or rapid tests with well-defined sensitivities and specificities and evaluated in the relevant setting. It should also be noted that in 4<sup>th</sup> generation assays, where both antigen and antibody are detected, confirmation tests might be non-reactive in the period before antibody production, as they detect only antibody.

In addition to the obligatory safeguarding through confirmatory testing e.g. by Western blot, the serological diagnosis of an HIV infection always requires testing of a second, independently obtained blood sample from the patient. If at all possible, the patient should only then be informed about the diagnosis.

## **Rapid / simple test devices**

Nowadays, a number of rapid HIV tests are available; these are also referred to as "point-of-care", "bedside" tests or "rapid/simple test devices". These tests are based on one of four immunodiagnostic principles: particle agglutination, immunodot (dipstick), immunofiltration or immune chromatography (Giles 1999, Branson 2000). In most cases test results are available within fifteen to thirty minutes; often, whole blood or capillary blood (obtained from the tip of a finger or the lobe of the ear) can be used, thus sparing the centrifugation of a venous blood sample obtained through venepuncture.

Many of these rapid tests contain a "built-in" internal control, e.g. as a control band indicating whether the sample material and, if applicable, the reagents were added correctly. If this "built-in" control fails, the test result must not be accepted (important to avoid false-negative results, when e.g. the sample was not added or insufficient time allowed until reading the result).

Such rapid tests may be useful if the result is needed quickly, for instance in emergency rooms, before emergency operations, after needlestick injuries and to minimize the rate of "unclaimed" test results (if the result is only available after a few days, some of those tested will not return to receive it). Rapid tests, which are easy to perform and require little in terms of equipment, are also useful in developing countries (Branson 2003, WHO 2004). Nevertheless, such tests should fulfill the same basic requirements as ELISA screening tests (WHO/UNAIDS 1998). In developed countries, a rapid test should ideally only be used as first guidance, and the patient retested as soon as possible in a regular routine laboratory. Problems commonly encountered with rapid tests – besides the need for adequate training of personnel – are the necessity to counsel the patient before testing and to obtain his consent. Any HIV test which can be performed by laypersons always carries the potential of misuse (such as compulsory testing of prisoners, etc.).

In the meantime, several HIV rapid tests have been licensed by FDA: OraQuick™ (OraSure Technologies, Pennsylvania, USA), Reveal™ (MedMira Laboratories, Halifax, Nova Scotia), Uni-Gold Recombigen™ HIV Test (Trinity Biotech, Ireland) and Murex single use diagnostic system (SUDS). After worrying experiences (at least five HIV-infected individuals were found to have been informed that their reactive rapid test result had been false-positive, i.e. that they were HIV-negative!) the Centers for Disease Control and Prevention (CDC) recently emphasized the need for adequate confirmatory testing and, if necessary, follow-up testing after four weeks (CDC 2004).

## Sample types

In most cases, serum, EDTA plasma, and also occasionally whole blood are used for HIV antibody testing. If sample processing is delayed, it may be preferable to remove the plasma or serum from the corpuscular constituents of blood, as hemolysis may lead to problems with certain tests.

Immunoglobulins may even be eluted from blood spots that were added onto filter paper and dried (Sherman 2005). Testing of such eluates for HIV antibodies is used for the (anonymous and unlinked) screening of pregnant women, using Guthrie test cards with routinely obtained blood spots from newborn babies (whose antibody prevalence mirrors that of their mothers). In developing countries with insufficient facilities for cold storage and transport, dried blood spots may offer a useful and inexpensive tool for sample storage and transport. Once completely dry, blood even from HIV-infected patients does not constitute an infection risk.

Alternatively, urine or oral fluid (oral transudate, often incorrectly referred to as "saliva") may also be employed for some assays (Tamashiro 1994, King 2000). The FDA licensed a rapid test using oral fluid for the diagnosis of HIV infection in March 2004; the same assay, marketed by OraSure Technologies, has been licensed since November 2002 as a rapid test for the detection of HIV antibodies in whole blood (see above). According to available information this assay allows the detection of antibodies against HIV-1 or HIV-2 with a sensitivity of 99.3 % and a specificity of 99.9 %.

Under certain conditions, such non-blood specimen types make testing possible, as they allow non-invasive sampling. However, their sensitivities and specificities are mostly considerably lower. Therefore, blood remains the preferred type of specimen. Whatever type of sample is used, a reactive test result of course requires confirmatory testing.

## Test performance

HIV antibody tests are among the best commercially available immunological assays. Sensitivity (high sensitivity → few false-negative results) and specificity (high specificity → few false-positive results) are the two most important parameters; they have to be calculated for each assay individually. However, in practice it is not so much the sensitivity and specificity of a test that is of interest but rather its predictive value. This is due to one's lack of knowledge of the real HIV status of the patient tested and the need to deduce his/her status from the test's result. The positive predictive value (PPV) is the probability with which a patient with a positive test result is indeed infected; and vice versa, the negative predictive value (NPV) is the likelihood of a patient who tested negative being truly not infected.

Table 1: Two-by-two table.

		Test result:	
		positive	negative
True patient status (e.g. as determined by reference test)	positive	true-positive	false-negative
	negative	false-positive	true-negative

## 48 HIV Testing

Table 1 explains the connection between the parameters

### Sensitivity

= number true-positive / (number true-positive + number false-negative)  
= probability of a positive test result if the patient is infected

### Specificity

= number true-negative / (number true-negative + number false-positive)  
= probability of a negative test result if the patient is not infected

### Positive predictive value (PPV)

= number true-positive / (number true-positive + number false-positive)  
= probability that a patient tested positive is indeed infected

### Negative predictive value (NPV)

= number true-negative / (number true-negative + number false-negative)  
= probability that a patient tested negative is indeed not infected

Although this may initially not seem plausible, the predictive value of a test not only depends on its sensitivity and specificity, but also on the HIV prevalence (i.e. the pre-test-probability of being positive or negative, respectively) in the population tested.

For example:

1. High HIV prevalence: 10 % (i.e. 10 per 100)

Using a test with a sensitivity of 100 % and a specificity of 99 % (i.e. 1 false positive in 100), and screening 1,000 patients, one would expect to see the following:

- 100 true positives per 1,000
- 10 false positives per 1,000
- Positive predictive value: 100 true positives/110 total positives = 91 %

2. Low HIV prevalence: 0.1 % (i.e. 1 per 1,000)

Using the same test (sensitivity of 100 %, specificity of 99 %) and screening 1,000 patients, one would expect to see the following:

- 1 true positive per 1,000
- 10 false positives per 1,000
- Positive predictive value: 1 true positive/11 total positives = 9.1 %

Figure 1 further illustrates this relation, using fictitious populations with HIV seroprevalence rates between 0.02 % (e.g. European blood donors) and 20 % (e.g. sexually active groups in highly endemic countries). It can be seen that in the former, the vast majority of positive (or more aptly, reactive) test results are indeed false positive: only 4.8 % of those who test positive are truly infected! In contrast, 98 % of the positive test results in the high-risk group with a seroprevalence of 20 % are "true" (which is why, according to WHO, confirmatory testing may exceptionally



be omitted here). These examples stress the importance of adequate confirmatory testing strategies for all positive screening test results!

Unfortunately, this statistical phenomenon is frequently, for propaganda purposes, misused: Inevitably, in blood donors e.g. in Germany with a low HIV prevalence, indeed only a small proportion of those with a reactive screening test result are truly infected. However, because any screening test reactivity must be followed up further by confirmatory testing even before the individual concerned is informed, this phenomenon should not have major consequences: for if the Western blot does not confirm the reactive ELISA result, the patient or blood donor is simply not HIV-"positive"! Nevertheless, it is unfortunately often used to "prove" the alleged uselessness of HIV tests.

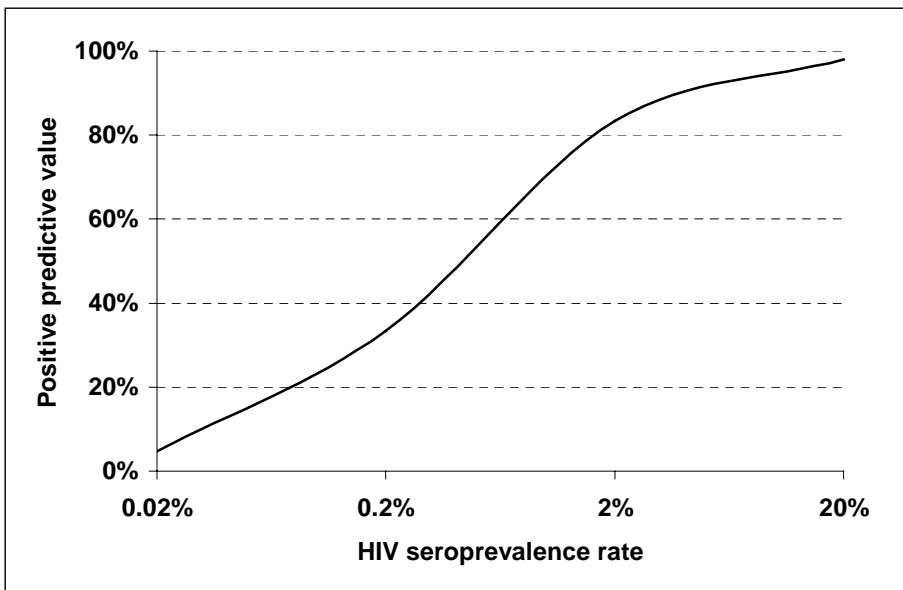


Figure 1: Dependence of the positive predictive value (PPV) on the seroprevalence rate in the population tested, using an antibody test with a constant specificity of 99.6 % (i.e. 4 false-positive results per 1,000 samples tested).

## When to test

After an infection, it normally takes between three to twelve weeks before the antibodies produced through the immune response of the infected individual become detectable. An HIV test should therefore not be performed too early after a potential risk contact, even though, understandably, concerned patients may be anxious and press for it. It is important, however, after an occupational exposure, e.g. a needle-stick injury, to test immediately in order to confirm initial seronegativity in the person exposed to HIV! In around 5 % of newly infected individuals it will take more than two months until antibodies are formed. Another test may therefore be indicated later on.

The chance of having acquired HIV infection is increased if "Yes" can be answered to one of the following questions:

- Have you had sexual intercourse without a condom with someone who is HIV-infected?
- Have you had sexually transmissible infections such as Chlamydia or gonorrhoea lately?
- Have you used the same syringes or cannulas as other intravenous drug addicts (needle sharing)?
- Did you receive a blood transfusion or blood clotting factors between 1978 and 1985?
- Have you ever had sex with someone who would answer one of the above questions with "Yes"?

Increasingly, it is argued that HIV testing "should no longer be accorded any special status" (Manavi 2005, Beckwith 2005). It has been found that, with the epidemiological shift into groups not formerly considered as "high-risk", HIV infections may be missed and that the burden of adequate pre-test counseling may discourage carers to suggest patients to be tested.

## **Problem: The "diagnostic window"**

One important problem of HIV antibody testing is the so-called "diagnostic window". This is the time period that elapses between the time of acquisition of HIV infection until detectable levels of antibodies are present (Busch 1997). The switch from antibody-negative to antibody-positive is called "seroconversion". The screening tests currently used are able to recognize an HIV infection six weeks after primary infection in about 80 % and after the 12<sup>th</sup> week in almost 100 % of cases; only in very rare cases is an infection recognized after just three or even six months. 4<sup>th</sup> generation screening assays attempt to shorten the duration of the "diagnostic window" by detecting HIV antibodies and HIV p24 antigen simultaneously (Gürtler 1998, Ly 2001). Although these 4<sup>th</sup> generation tests become reactive earlier in the course of an acute primary infection, due to methodological reasons (Meier 2001), there may occur a second "diagnostic window" phase later on, during which the tests may again become non-reactive.

Early during seroconversion the antibody screening test will be only borderline or weakly reactive. The Western blot carried out for confirmation may at this stage not show any bands at all or an incomplete band pattern, with the p24 band often the first to become visible. The results obtained in such cases are often indistinguishable from those found in uninfected individuals that display a certain degree of non-specific reactivity; here, too, isolated p24 bands are occasionally seen. This illustrates clearly how important it is to pass important clinical information on to the laboratory carrying out the tests (e.g. "suspected primary infection", "routine screening" etc.)!

Such cases often have to remain unclear for the time being, but are resolved by follow-up testing within a short time. If one is indeed dealing with an early seroconversion, seroreactivity will have increased significantly only a few days later, and within a few weeks a complete band pattern will be found on Western blot. It de-

depends on the individual circumstances whether direct virus detection e.g. by means of PCR is advisable at the outset. Attention: antiretroviral post-exposure prophylaxis may make direct virus detection more difficult and potentially delay seroconversion.

The gradual increase of seroreactivity in the course of seroconversion may be utilized for epidemiological studies to measure HIV incidence (i.e. the rate of new infections – in contrast to standard antibody testing that measures HIV prevalence, i.e. established infections.) There are several methods in use:

**Detuned assays** – by deliberately combining highly sensitive with less sensitive antibody tests, these strategies are able to estimate which proportion of positive samples have only recently undergone primary infection (Parekh 2001, Constantine 2003).

**Avidity assays** – by treating specimens with an agent that breaks weaker antigen-antibody bonds, such as those seen in immature antibodies early in infection, a ratio (avidity index) between treated and untreated specimen can indicate high avidity (old infection) or low avidity (recent infection) (Suligoj 2002, Puchhammer-Stöckl 2005).

**BED IgG capture ELISA** – early in infection, the ratio between HIV-specific antibody and other antibody is low, whereas later it is higher. By capturing all IgG molecules, one can detect the proportion of HIV-specific antibody by detecting the amount of HIV antigen that binds to it. "BED" refers to the use of subtypes B, E, and D in the commercially available assay (Dobbs, 2004).

It should be noted that these assays are NOT intended for the individual diagnosis of a recent or primary HIV infection, but are used for epidemiological studies of HIV incidence in populations.

## Direct detection of HIV

An HIV infection may also be diagnosed through the detection of virus, rather than indirectly through the detection of antibodies. Virus detection is only necessary in certain situations and, because of its higher cost, should only be undertaken if indicated.

Virus isolation in cell cultures is reserved for special cases, as it is demanding, carries a certain risk and therefore requires the use of a specialized laboratory.

Alternatively, assays for the detection of HIV-1 p24 antigen are available. Although the p24 antigen ELISA has generally been replaced by the more sensitive nucleic acid detection assays, 4<sup>th</sup> generation antibody screening tests incorporate p24 antigen detection in addition to HIV antibody detection, to shorten the "diagnostic window" period (see above).

The detection of viral nucleic acid (i.e. of virus genome) may be achieved by different laboratory techniques. These methods may be used to detect either proviral cDNA in leucocytes (which requires EDTA whole blood samples) or viral RNA in the cell-free compartment (which requires EDTA plasma or EDTA whole blood).

Qualitative testing for viral genome serves as a marker of infection. It supplements or substitutes antibody testing for the diagnosis of HIV infection in special situations (such as suspected fresh primary infection: absence of antibodies during the

diagnostic window; newborn of infected mother: presence of maternal antibodies – also see below).

The quantitative detection of HIV RNA in plasma is used as a prognostic marker, to monitor therapy and to estimate infectiousness (Berger 2002). The most sensitive tests can detect as little as approximately 50 copies/ml.

Various commercial and "in house" methods are available for quantitative nucleic acid testing. These may be based on different technologies: polymerase chain reaction (PCR), branched DNA (b-DNA), nucleic acid sequence-based amplification (NASBA), ligase chain reaction (LCR), or quantitative detection of reverse transcriptase activity. So-called "viral load" testing has now become an indispensable clinical tool, both as a prognostic and as a therapeutic marker. However, it should be noted that NO viral load test is intended to be used as a diagnostic tool. Recently, it has been suggested that this method could be of benefit as a screening tool, using pooled (i.e. mixing several individual samples together) or unpooled samples, for seronegative patients in high-risk groups (Pilcher 2004, Pilcher 2005).

### Test results

False-positive results by appropriate confirmatory testing are very rare. A confirmed positive result therefore confirms the presence of HIV-specific antibodies and thus, HIV infection.

A positive test result (i.e. screening and confirmatory tests positive and mistaken sample identity excluded by testing of a second sample) means that the individual tested

- is infected with HIV (i.e. carries the virus that causes AIDS) – except in young children (see below);
- may infect others with HIV unless precautions are taken

A positive test result does NOT mean that the person tested

- has AIDS;
- will necessarily develop AIDS.

A negative test result means:

- HIV antibodies were not detected in the blood of the individual at the point in time when he or she was tested.

A negative test result does NOT mean that:

- the individual is not infected with HIV (the test could have been performed during the "diagnostic window" period);
- the person tested is immune or resistant to HIV;
- the person tested can have sexual intercourse without taking "safe sex" precautions.

It should be noted that people in the window period who test negative for antibody, may be viremic, and at this stage are at their most infectious!

Beyond the "diagnostic window", meaning later than six months after a possible exposure to HIV, an HIV screening test is rarely "false-negative". Thus, a negative test means that the person is not infected with HIV – always assuming of course that in the meantime no renewed exposure has taken place.

A rare "equivocal" result in the confirmatory assay means:

- The test has not given an unequivocal result. As a consequence, follow-up testing after a short while is required. Particularly in the case of clinical symptoms such as fever, lymph node enlargement, a rash or neurological symptoms, there may be the suspicion of an acute HIV infection in which seroconversion has only just begun. First antibody reactivities are found, however the full pattern of Western blot bands is not yet present. Seroconversion tends to follow certain patterns; in Western blot, some bands are positive early on (such as p24 or gp120), others appear later.
- In the case of an unequivocal Western blot and if an acute primary infection is suspected for clinical and/or anamnestic reasons, direct detection of virus should be attempted by means of PCR. The aim of this is to detect and possibly treat an acute HIV infection in time (also see chapter "Acute HIV infection"). The earlier, the better!

Caution: If, in the case of a suspected fresh primary infection, a quantitative HIV RNA assay is used for virus detection in plasma (because it is often more easily available than PCRs for the detection of proviral DNA in leucocytes), one has to keep in mind that such tests may occasionally lead to false-positive results (Rich 1999). Such false-positive results – that may be seen typically – indicate low levels of HIV RNA (normally not more than 2,000 copies/ml) that are very unlikely to be found in true acute infection (which normally presents with high "viral load" values). Nevertheless, this problem has sometimes caused confusion and misdiagnoses.

This phenomenon may probably occur with any of the available viral load assays. If it is not recognized, the patient will be given an erroneous diagnosis of "infected" with all its possibly deleterious consequences. To avoid this problem (assuming error-free running of the assay and sufficient quality control practices in the laboratory), a test for proviral cDNA in the leukocyte fraction of the blood should be used; however, this is offered by relatively few laboratories.

## Special case: Babies born to HIV-infected mothers

Fortunately, the risk of mother-to-child transmission of HIV (MTCT) (see chapter "HIV and pregnancy") has been extremely reduced in industrialized countries and may be as low as 1 %. Nevertheless, HIV diagnosis is essential in all exposed newborns!

In babies born to HIV-infected mothers, HIV antibodies are normally detectable up to around 12 to 15 months of age, and rarely beyond 18 months. These are passively acquired maternal antibodies transferred transplacentally into the unborn child from around the 30<sup>th</sup> week of pregnancy onwards. These maternal IgG antibodies confer some physiological immune protection against many infections but in the case of HIV are without protective efficacy. This means, however, that most

children of HIV-positive mothers, including those not themselves infected (the majority in any setting), will initially have positive HIV antibody test results, albeit with decreasing reactivities over time, until they become negative after complete elimination of maternal antibodies. The laboratory may be able to indicate that the degree of reactivity is decreasing, but confirmation should still take place at a later date, as this is NOT diagnostic.

Therefore, previously one had to wait – normally for nine months or longer – for a significant fall in the child's antibody level; only testing of repeat blood samples taken at regular intervals could exclude HIV infection of the child with certainty (Newell 1995). If HIV antibodies persist in a vertically exposed child beyond the age of 15 months, the child is usually HIV-infected.

Today, PCR allows a more rapid diagnosis. HIV infection of the child should be diagnosed or, hopefully, excluded directly through detection of the virus. So far it is unclear whether the detection of proviral (intracellular) HIV cDNA (from leucocytes) or of (extracellular) HIV RNA (from blood plasma) is more sensitive. In any case, all positive test results must be confirmed immediately on a second sample.

Important: many methods for the detection of HIV nucleic acid may fail in case of "exotic" (i.e. non-subtype B) HIV-1 subtypes (and with HIV-2) and yield false-negative results (Haas 1996). To exclude this, a maternal sample should also be tested if necessary (e.g. if the mother or her source of infection are from outside Europe) to ensure the test's ability to detect the viral strain in question. If the mother tests PCR-positive with the same assay, a negative test result on the child may be used; otherwise a suitable method must be chosen in a specialized laboratory or one has to resort to antibody testing alone with its limitations (see above). As far as quantitative RNA detection methods are concerned, the problem of falsely low-positive results needs to be recognized (see above)!

In exposed babies, at least two negative HIV PCR results are required in order to exclude HIV infection: the first one between the 1st and the 4th month of life, the second after the 4th month, as only then does it reach its full significance for exclusion of infection (Rossi 1992). In addition, PCR should be performed during the first month of life (however not within the first days after delivery, as contamination with maternal virus may occur), as the earliest possible diagnosis of a neonatal infection is important to allow Pneumocystis prophylaxis and early antiretroviral therapy in the first months of life. If this first sample tests positive (and is confirmed), this points to an intrauterine infection (less frequent); in case of perinatal transmission during birth (most common scenario), virus will only be detectable in the samples obtained later. Attention: breastfeeding carries a significant risk of transmission; what is stated above is only valid if postnatal acquisition of infection is excluded!

Also, with negative HIV PCR results, the complete elimination of maternal antibodies should be documented at least once in HIV-exposed children.

## **Special case: Needlestick injury or other occupational HIV exposure**

Here, two aspects need to be considered: testing of the index patient (the "donor" from whom the potential risk of infection arose) and testing of the exposed (the

"recipient"). The national and local regulations pertaining to this must of course be followed, for legal and other reasons.

If the index patient is known, he should be tested – after relevant counseling and consent; ideally the injured individual's superior should be called in immediately – for HIV antibodies, HBsAg (do not forget immunization against hepatitis B virus if necessary), and HCV antibodies. According to the circumstances (e.g. weekend), the use of a rapid assay should be considered (see above). Often a first, preliminary decision must be made even before the test result of the index patient is available; for any delay in instituting HIV post-exposure prophylaxis (HIV PEP) reduces its chances of success (CDC 2001). Therefore, if there is any doubt, the first one or two doses of HIV PEP (that should be readily available day and night in the form of a so-called "starter pack") should be taken and later discontinued once a negative test result becomes available! It would be a mistake to start HIV PEP only once a positive result has been obtained as this will normally mean delaying the first dose beyond the time period during which its chances of preventing infection are at its highest!

If the index patient is seronegative, the chances of him/her – in the absence of any clinical evidence suggesting an acute retroviral syndrome – currently being in the "diagnostic window" phase are remote. It is therefore normally not advisable to employ a method for direct detection of virus (to exclude a fresh primary infection prior to seroconversion)! In case of an unknown index patient the epidemiological situation needs to be taken into account. Important: used injection needles, etc., should not normally be tested for HIV antibodies or HIV genome; effort, cost and particularly the remaining uncertainty (because of the questionable validity of the result) are out of proportion compared to the extremely remote risk of infection with an agent that fortunately has a low stability and tenacity.

If the index patient is HIV-positive, all available information (including the current "viral load", results of resistance assays, etc.) must be considered in the decision on the type of HIV PEP (see the relevant chapter).

In case of an HIV-positive index patient, the injured individual should at once be tested for HIV antibodies by means of a routine screening assay. Demonstration of initial seronegativity is legally important in order to claim compensation and insurance cover in case of occupational transmission! Further follow-up testing is recommended 6 weeks, 3 months and again 6 months after exposure (Ciesielski 1997). If the index patient is HIV-infected, a further follow-up test of the injured recipient is recommended after 12 months; otherwise this is optional (Ridzon 1997). In addition, an HIV test (and possibly also a test for direct detection of virus) should be done immediately if, at anytime after the incident, the recipient develops illness compatible with an acute retroviral syndrome.

## **Special case: Screening of blood donations**

The risk of HIV transmission by transfusion of blood products (or organ transplants) has been minimized by means of carefully selecting donors – attempting to exclude those with potential risk factors for blood-borne infectious diseases, and by screening all donations. This is done using highly sensitive antibody tests, and in addition, more recently, antigen or nucleic acid detection assays. In this setting, the

aim is not to make a diagnosis on a patient, although blood transfusion services usually confirm the reactivity. The aim is to exclude all blood that might be infectious, not only blood confirmed to be infectious.

## What is relevant in practice?

With each and every HIV test, different important aspects need to be taken into account. Unfortunately and regrettably, careless and negligent actions still occur sometimes.

It has to be realized:

Despite all therapeutic progress, a positive test result still has massive psychological consequences for the person concerned! The meaning of a positive test result can hardly be overrated.

Every patient therefore must be informed that he/she is to be tested for HIV – in advance! A "routine pre-operative" check, as it is still sometimes carried out, can, particularly if the result is positive, carry not only unpleasant but often considerable legal consequences for the medical staff in charge. Depending on local policy, consent might not have to be obtained in writing, but the patient's consent has to be documented in the patient notes. With children or patients unable to give legally valid consent, parents or legal carers have to be informed.

On the other hand, while obtaining valid consent is important, this does not always require in-depth discussions about risk factors, consequences, etc. Instead, pre-test counseling should be adequate for the individual's situation. One should avoid causing unnecessary anxiety and psychological distress.

HIV test results should only be communicated by doctors who are either themselves knowledgeable about HIV and AIDS or who know where to refer patients with a newly diagnosed HIV infection without delay. Individuals confronted with this diagnosis for the first time are in need of intensive support, and they need this immediately! Sometimes patients are still provided with outdated information, and it may then take them weeks, sometimes months, until they first get into contact with a competent medical person.

A positive HIV test result should never be communicated to the patient over the telephone. Firstly, this does not allow sufficient post-test counseling, and secondly it makes it impossible to judge the patient's reaction – which may even be suicidal. Occasionally, the reaction is very irrational and emotional, necessitating an extended counseling session. This individual reaction cannot be anticipated. If at all possible, a repeat appointment should be made at the time of drawing the sample, and it should be stressed that results will be given at this appointment, irrespective of whether they are positive or negative, to allow for further counseling and to avoid assumptions being made about not being contacted by telephone. For the reasons mentioned, a rapid test for self-testing is extremely problematic. So-called "point-of-care" or "bedside" tests may be very useful in certain circumstances, e.g. in emergency rooms, but also harbor the problem of unprofessional utilization without adequate counseling and care of the patient.

A reactive screening test result on its own must never, under any circumstances, be communicated to the patient! As there are numerous factors that may cause a



screening test to give a non-specific reactive result, the result of a confirmatory assay always has to be awaited. If the band pattern in Western blot is incomplete, this may represent ongoing seroconversion (i.e. acute infection) or non-specificity. Such tests should always be discussed with the laboratory and with an experienced HIV carer – before the patient is informed. We have seen cases in which the patient was left in the belief to be HIV-infected for days or even years – only because of a cross-reactive ELISA and failure to await the result of confirmatory testing.

But even with HIV seropositivity confirmed by Western blot, the following statement should be added to each first positive result: "The demonstration of HIV-specific antibodies does not mean that the patient is suffering from AIDS. Every positive result must be confirmed on a second, independently obtained blood sample, and the patient should only then be informed!"

With each sample sent for HIV testing, one should be aware of the reason behind its request. AIDS phobia poses a difficult problem and is not so rare – i.e., people who are as firmly as erroneously convinced that they are HIV-infected, almost always without any appreciable risk. Often they want to be tested at short intervals and by different carers, sometimes also requesting expensive PCR tests. Such individuals (who often also suffer from the delusion that positive test results are withheld from them) need psychological and perhaps psychiatric help rather than repeated HIV testing.

## Useful Internet sources relating to HIV testing

- World Health Organization (WHO): <http://www.who.int> with the following web pages:
- Department of Essential Health Technologies: <http://www.who.int/ehd/en/>
- HIV/AIDS Diagnostics: <http://www.who.int/hiv/amds/diagnostics/en/index.html>
- Diagnostics and Laboratory Technology: [http://www.who.int/diagnostics\\_laboratory/en/index.html](http://www.who.int/diagnostics_laboratory/en/index.html) with downloadable reports containing the evaluation results of different commercially available HIV tests.
- The 3 by 5 Initiative: <http://www.who.int/3by5/en/>
- Center for Disease Control and Prevention (CDC), USA, Division of HIV/AIDS Prevention: <http://www.cdc.gov/hiv/testing.htm>, [http://www.cdc.gov/hiv/rapid\\_testing/](http://www.cdc.gov/hiv/rapid_testing/)
- U. S. Food and Drug Administration (FDA), Center for Biologics Evaluation and Research (CBER): Licensed / Approved HIV, HTLV and Hepatitis Tests: <http://www.fda.gov/cber/products/testkits.htm>
- The European Commission, Enterprise & Industry, Medical Devices: [http://europa.eu.int/comm/enterprise/medical\\_devices/index.htm](http://europa.eu.int/comm/enterprise/medical_devices/index.htm) containing information about the In Vitro Diagnostic Directive (IVDD)

## References

1. Beckwith CG, Flanigan TP, del Rio C, Simmons E, Wing EJ, Carpenter CCJ, Bartlett JG. It is time to implement routine, not risk-based, HIV testing. *Clin Infect Dis* 2005; 40:1037–40.
2. Berger A, Preiser W. Viral genome quantification as a tool for improving patient management: the example of HIV, HBV, HCV and CMV. *J Antimicrob Chemother* 2002; 49:713–21. <http://amedeo.com/lit.php?id=12003963>
3. Branson BM. Patientennahe Schnelltests für den Nachweis von HIV-Antikörpern. Point-of-Care Rapid Tests for HIV Antibodies. *J Lab Med* 2003; 27:288–295.
4. Branson BM. Rapid Tests for HIV Antibody. *AIDS Reviews* 2000; 2:76–83.
5. Brust S, Duttman H, Feldner J, Gürtler L, Thorstensson R, Simon F. Shortening of the diagnostic window with a new combined HIV p24 antigen and anti-HIV-1/2/O screening test. *J Virol Meth* 2000; 90:153–65. <http://amedeo.com/lit.php?id=11064116>
6. Busch MP, Satten GA. Time course of viremia and antibody seroconversion following human immunodeficiency virus exposure. *Am J Med* 1997; 102(suppl 5B): 117–24. <http://amedeo.com/lit.php?id=9845513>
7. Centers for Disease Control and Prevention. Interpretation and Use of the Western-Blot Assay for Serodiagnosis of Human Immunodeficiency Virus Type 1 Infections. *MMWR* 1989; 38: 1–7. <http://amedeo.com/lit.php?id=2501638>
8. Centers for Disease Control and Prevention. Protocols for Confirmation of Reactive Rapid HIV Tests. *MMWR* 2004; 53: 221–2. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5310a7.htm>
9. Centers for Disease Control and Prevention. Updated U.S. Public Health Service Guidelines for the Management of Occupational Exposures to HBV, HCV, and HIV and Recommendations for Postexposure Prophylaxis. *MMWR* 2001; 50: 1–54. <http://amedeo.com/lit.php?id=11442229>
10. Ciesielski CA, Metler RP. Duration of time between exposure and seroconversion in healthcare workers with occupationally acquired infection with human immunodeficiency virus. *Am J Med* 1997; 102 (suppl 5B):115–6. <http://amedeo.com/lit.php?id=9845512>
11. Connick E. Incomplete antibody evolution and seroreversion after treatment of primary HIV type 1 infection: What is the clinical significance? *Clin Infect Dis* 2005; 40:874–5. <http://amedeo.com/lit.php?id=15736022>
12. Constantine NT, Sill AM, Jack N, Kreisel K, Edwards J, Cafarella T, Smith H, Bartholomew C, Clegghorn FR, Blattner WA. Improved classification of recent HIV-1 infection by employing a two-stage sensitive/less-sensitive test strategy. *J Acquir Immune Defic Syndr*. 2003 Jan 1;32(1):94–103. <http://amedeo.com/lit.php?id=12514420>
13. Deutsches Institut für Normung e.V. (DIN). DIN-Norm 58969-41. DIN-Taschenbuch 222: Medizinische Mikrobiologie und Immunologie, Diagnostische Verfahren, 3. Auflage, Stand 2000. Berlin, Wien, Zürich: Beuth-Verlag.
14. Dobbs T, Kennedy S, Pau C-P, McDougal JS, Parekh BS. Performance Characteristics of the Immunoglobulin G-Capture BED-Enzyme Immunoassay, an Assay To Detect Recent Human Immunodeficiency Virus Type 1 Seroconversion. *J Clin Microbiol* 2004; 42:2623–2628
15. Giles RE, Perry KR, Parry JV. Simple/rapid test devices for anti-HIV screening: Do they come up to the mark? *J Med Virol* 1999; 59:104–9. <http://amedeo.com/lit.php?id=10440816>
16. Gürtler L, Mühlbacher A, Michl U, et al. Reduction of the diagnostic window with a new combined p24 antigen and human immunodeficiency virus antibody screening assay. *J Virol Meth* 1998; 75:27–38. <http://amedeo.com/lit.php?id=9820572>
17. Gürtler L. Difficulties and strategies of HIV diagnosis. *Lancet* 1996; 348:176–9. <http://amedeo.com/lit.php?id=8684160>
18. Haas J, Geiss M, Böhler T. False-negative polymerase chain reaction-based diagnosis of human immunodeficiency virus type 1 in children infected with HIV strains of African origin. *J Infect Dis* 1996; 174:224–5. <http://amedeo.com/lit.php?id=8656008>
19. Kassutto S, Johnston MN, Rosenberg ES. Incomplete HIV type 1 antibody evolution and seroreversion in acutely infected individuals treated with early antiretroviral therapy. *Clin Infect Dis* 2005; 40:868–73. <http://amedeo.com/lit.php?id=15736021>
20. King SD, Wynter SH, Bain BC, Brown WA, Johnston JN, Delk AS. Comparison of testing saliva and serum for detection of antibody to human immunodeficiency virus in Jamaica, West Indies. *J Clin Virol* 2000; 19:157–61. <http://amedeo.com/lit.php?id=11090751>
21. Ly TD, Laperche S, Couroucé AM. Early detection of human immunodeficiency virus infection using third-and fourth-generation screening assays. *Eur J Clin Microbiol Infect Dis* 2001; 20:104–10. <http://amedeo.com/lit.php?id=11305462>
22. Manavi K, Welsby PD. HIV testing: Should no longer be accorded any special status. *Brit Med J* 2005; 330:492–3. <http://amedeo.com/lit.php?id=15746110>

23. Meier T, Knoll E, Henkes M, Enders G, Braun R. Evidence for a diagnostic window in fourth generation assays for HIV. *J Clin Virol* 2001;23:113-6. <http://amedeo.com/lit.php?id=11595590>
24. Newell ML, Loveday C, Dunn D, Kaye S, Tedder R, et al. Use of polymerase chain reaction and quantitative antibody tests in children born to HIV -1-infected mothers. *J Med Virol* 1995; 47:330-5. <http://amedeo.com/lit.php?id=8636699>
25. Parekh BS, McDougal JS. New Approaches For Detecting Recent HIV-1 Infection. *AIDS Rev* 2001;3:183-93.
26. Pilcher CD, Fiscus SA, Nguyen TQ, Foust E, Wolf L Williams, D Ashby R, Owen O'Dowd J, McPherson JT, Stalzer B Hightow L, Miller WC, Eron JJ, Cohen MS, Leone PA. Detection of Acute Infections during HIV Testing in North Carolina. *N Engl J Med* 2005; 352:1873-1883
27. Pilcher CD, Price MA, Hoffman IF, Galvin S, Martinson FEA, Kazembe PN, Eron JJ, Miller WC, Fiscus SA, Cohen MS. Frequent detection of acute primary HIV infection in men in Malawi. *AIDS* 2004, 18:517–524
28. Preiser W, Brink NS, Hayman A, Waite J, Balfe P, Tedder RS. False-negative HIV antibody test results. *J Med Virol* 2000; 60:43-7. <http://amedeo.com/lit.php?id=10568762>
29. Puchhammer-Stöckl E, Schmied B, Rieger A, Sarclotti M, Geit M, Zangerle R, Hofmann H. Low Proportion of Recent Human Immunodeficiency Virus (HIV) Infections among Newly Diagnosed Cases of HIV Infection as Shown by the Presence of HIV-Specific Antibodies of Low Avidity. *J Clin Microbiol* 2005; 43:497–498
30. Rich JD, Merriman NA, Mylonakis E, Greenough TC, Flanigan TP, Mady BJ, Carpenter CC. Misdiagnosis of HIV infection by HIV-1 plasma viral load testing: a case series. *Ann Intern Med* 1999; 130:37-9. <http://amedeo.com/lit.php?id=9890848>
31. Ridzon R, Gallagher K, Ciesielski C, et al. Simultaneous transmission of human immunodeficiency virus and hepatitis C virus from a needle-stick injury. *N Engl J Med* 1997; 336:919–22. <http://amedeo.com/lit.php?id=9070472>
32. Rossi. Early diagnosis of HIV infection in infants – Report of a consensus workshop, Siena, Italy, January 17-18, 1992. *JAIDS* 1992; 5:1168-78. <http://amedeo.com/lit.php?id=1403648>
33. Sherman GG, Stevens G, Jones SA, Horsfield P, Stevens WS. Dried Blood Spots Improve Access to HIV Diagnosis and Care for Infants in Low-Resource Settings. *J Acquir Immune Defic Syndr* 2005; 38:615-617
34. Suligoi B, Galli C, Massi M, Di Sora F, Sciandra M, Pezzotti P, Recchia O, Montella F, Sinicco A, Rezza G. Precision and Accuracy of a Procedure for Detecting Recent Human Immunodeficiency Virus Infections by Calculating the Antibody Avidity Index by an Automated Immunoassay-Based Method. *J Clin Microbiol* 2002; 40:4015–4020
35. Tamashiro H, Constantine NT. Serological diagnosis of HIV infection using oral fluid samples. *Bull World Health Organ* 1994; 72:135-143. <http://amedeo.com/lit.php?id=8131250>
36. Tamashiro H, Maskill W, Emmanuel J, Fauquex A, Sato P, Heymann D. Reducing the cost of HIV antibody testing. *Lancet* 1993;342:87-90. <http://amedeo.com/lit.php?id=8100916>
37. UNAIDS (1997a): Blood safety and HIV. UNAIDS Technical Update (UNAIDS Best Practice Collection: Technical Update). Geneva: UNAIDS, October 1997. WC 503.3 <http://hiv.net/link.php?id=232>
38. UNAIDS (1997b): HIV testing methods. UNAIDS Technical Update (UNAIDS Best Practice Collection: Technical Update). Geneva: UNAIDS, November 1997. WC 503.1 <http://hiv.net/link.php?id=233>
39. UNAIDS (2001): Guidelines for Using HIV Testing Technologies in Surveillance: Selection, Evaluation, and Implementation. WHO/CDS/CSR/EDC/2001.16. UNAIDS/01.22E. <http://hiv.net/link.php?id=234>
40. UNAIDS / WHO. Recommendations for the selection and use of HIV antibody tests. *Weekly Epidemiological Record* 1992; 67:145-49. <http://amedeo.com/lit.php?id=1599842>
41. UNAIDS / WHO. Revised recommendations for the selection and use of HIV antibody tests. *Weekly Epidemiological Record* 1997;72:81-7. <http://amedeo.com/lit.php?id=9238418>
42. Voß L. HIV-Testpolitik und -Testpraxis in Deutschland – eine Bestandsaufnahme. *Bundesgesundheitsbl - Gesundheitsforsch - Gesundheitsschutz* 2000; 43:683–93.
43. WHO / UNAIDS. The importance of simple/rapid assays in HIV testing - WHO/UNAIDS recommendations. *Weekly Epidemiological Record* 1998;73:321-6.
44. WHO. Rapid HIV tests: Guidelines for use in HIV testing and counseling services in resource-constrained settings. Geneva 2004. <http://www.who.int/hiv/pub/vct/rapidhivtests/en/>
45. WHO. WHO recommendation for HIV antibody testing. *Wkly Epidemiol Rec* 1992; 67: 145–52.



## 4. Pathogenesis of HIV-1 Infection

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Since the initial description of the human immunodeficiency virus type I (HIV-1) in 1983 (Barre-Sonoussi 1983, Gallo 1983) and HIV-2 in 1986 (Clavel 1986), these two viruses have been identified for almost 20 years as the primary cause of the acquired immunodeficiency syndrome (AIDS). As HIV-1 is the major cause of AIDS in the world today, our discussion will be primarily limited to HIV-1 infection. Worldwide, the number of HIV-1 infected persons exceeds 40 million, the majority of whom live in the developing countries of Sub-Saharan Africa, Asia and South America.

The introduction of protease inhibitors and non-nucleotide reverse transcriptase inhibitors (NNRTIs) to antiretroviral treatment regimens in 1995 began the era of highly active antiretroviral therapy (HAART), and resulted in dramatic improvements in the mortality and morbidity of HIV disease, as determined by a decreased incidence of opportunistic infections, tumors, and deaths. Despite all the therapeutic advantages achieved during the last decade, including the development of HAART, once an individual has become infected, eradication of the virus still remains impossible.

In addition, new problems relating to the short- and long-term toxicity of drug treatments and the occurrence of resistance mutations in both circulating and transmitted viruses are emerging. In most countries in South East Asia and Africa, the incidence and prevalence of HIV-1 infection continues to increase and surpass that of Europe and North America. However, due to the high costs of drug regimens and the lack of a healthcare infrastructure in these developing countries, the widespread use of HAART is currently still difficult. The further course of the HIV-1 pandemic, therefore, mainly depends on how and to what degree the developing countries with a high HIV-1 prevalence are able to take advantage of the medical progress achieved in Europe and North America, and whether an effective prophylactic vaccine becomes available in the near future.

An understanding of the immunopathogenesis of HIV-1 infection is a major prerequisite for rationally improving therapeutic strategies, developing immunotherapeutics and prophylactic vaccines. As in other virus infections, the individual course of HIV-1 infection depends on both host and viral factors.

The course of infection with HIV-1 in HIV-infected humans may vary dramatically, even if the primary infections arose from the same source (Liu 1997). In some individuals, with a long-term non-progressive HIV-1 infection (i.e., lack of decline in CD4+ T-cell counts, or chronic infection for at least 7 years without the development of AIDS), a defective virion was identified (Kirchhoff 1995). Thus, infection with a defective virus, or one that has a poor capacity to replicate, may prolong the clinical course of HIV-1 infection. However, in most individuals, HIV-1 infection is characterized by a replication-competent virus with a high daily turnover of virions.

Host factors may also determine whether or not an HIV-1-infected individual rapidly develops clinically overt immunodeficiency, or whether this individual belongs to the group of long-term non-progressors, who represent about 5 % of all infected

patients. The identification and characterization of host factors contributing to the course of HIV infection, including immunological defense mechanisms and genetic factors, will be crucial for our understanding of the immunopathogenesis of HIV infection and for the development of immunotherapeutic and prophylactic strategies.

## 1. The structure of HIV-1

HIV-1 is a retrovirus and belongs to the family of lentiviruses. Infections with lentiviruses typically show a chronic course of disease, a long period of clinical latency, persistent viral replication and involvement of the central nervous system. Visna infections in sheep, simian immunodeficiency virus infections (SIV) in monkeys, or feline immunodeficiency virus infections (FIV) in cats are typical examples of lentivirus infections.

Using electron microscopy, HIV-1 and HIV-2 resemble each other strikingly. However, they differ with regard to the molecular weight of their proteins, as well as having differences in their accessory genes. HIV-2 is genetically more closely related to the SIV found in sootey mangabeys (SIV<sub>sm</sub>) rather than HIV-1 and it is likely that it was introduced into the human population by monkeys. Both HIV-1 and HIV-2 replicate in CD4+ T-cells and are regarded as pathogenic in infected persons, although the actual immune deficiency may be less severe in HIV-2-infected individuals.

### 1.1. The morphologic structure of HIV-1

HIV-1 viral particles have a diameter of 100 nm and are surrounded by a lipoprotein membrane. Each viral particle contains 72 glycoprotein complexes, which are integrated into this lipid membrane, and are each composed of trimers of an external glycoprotein gp120 and a transmembrane spanning protein gp41. The bonding between gp120 and gp41 is only loose and therefore gp120 may be shed spontaneously within the local environment. Glycoprotein gp120 may also be detected in the serum (Oh 1992) as well as within the lymphatic tissue of HIV-infected patients (Sunila 1997). During the process of budding, the virus may also incorporate different host proteins from the membrane of the host cell into its lipoprotein layer, such as HLA class I and II proteins, or adhesion proteins such as ICAM-1 that may facilitate adhesion to other target cells. The matrix protein p17 is anchored to the inside of the viral lipoprotein membrane. The p24 core antigen contains two copies of HIV-1 RNA. The HIV-1 RNA is part of a protein-nucleic acid complex, which is composed of the nucleoprotein p7 and the reverse transcriptase p66 (RT). The viral particle contains all the enzymatic equipment that is necessary for replication: a reverse transcriptase (RT), an integrase p32 and a protease p11 (overview in: Gelderblom 1993) (Fig. 1).

### 1.2. The organization of the viral genome

Most replication competent retroviruses depend on three genes: *gag*, *pol* and *env*: **gag** means “group-antigen”, **pol** represents “polymerase” and **env** is for “envelope” (overview in: Wong-Staal 1991) (Fig. 2). The “classical” structural scheme of a retroviral genome is: 5’LTR-gag-pol-env-LTR 3’. The LTR (“long terminal re-

peat”) regions represent the two end parts of the viral genome, that are connected to the cellular DNA of the host cell after integration and do not encode for any viral proteins. The *gag* and *env* genes code for the nucleocapsid and the glycoproteins of the viral membrane; the *pol* gene codes for the reverse transcriptase and other enzymes. In addition, HIV-1 contains six genes (*vif*, *vpu*, *vpr*, *tat*, *rev* and *nef*) in its 9kB RNA that contribute to its genetic complexity. *Nef*, *vif*, *vpr* and *vpu* were classified as accessory genes in the past, as they are not absolutely required for replication in vitro. However, the regulation and function of these accessory genes and their proteins have been studied and characterized in more detail in the past few years. The accessory genes, *nef*, *tat* and *rev*, are all produced early in the viral replication cycle.

*Tat* and *rev* are regulatory proteins that accumulate within the nucleus and bind to defined regions of the viral RNA: TAR (transactivation-response elements), found in the LTR; and RRE (rev response elements), found in the *env* gene, respectively. The *tat* protein is a potent transcriptional activator of the LTR promoter region and is essential for viral replication in almost all in vitro culture systems. Cyclin T1 is a necessary cellular cofactor for *tat* (Wei 1998). *Tat* and *rev* stimulate the transcription of proviral HIV-1 DNA into RNA, promote RNA elongation, enhance the transportation of HIV RNA from the nucleus to the cytoplasm and are essential for translation. *Rev* is also a nuclear export factor that is important for switching from the early expression of regulatory proteins to the structural proteins that are synthesized later.

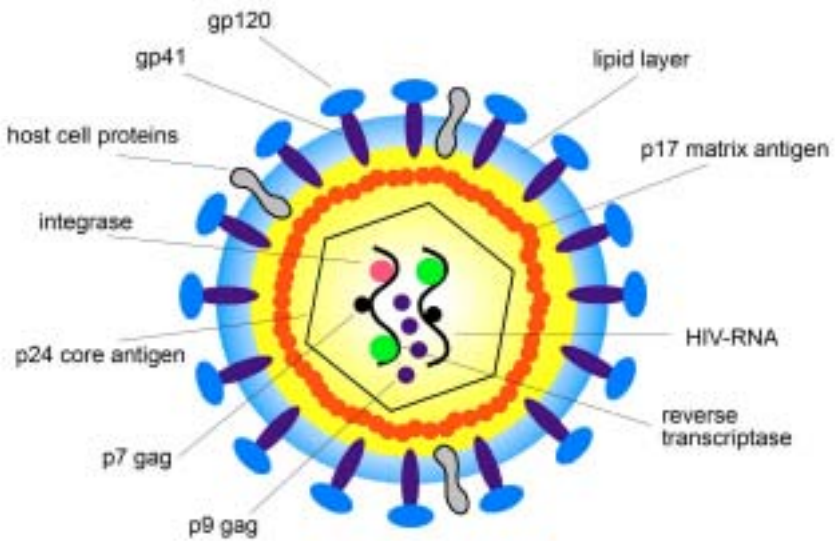


Figure 1: Structure of an HIV virion particle. For detailed explanations see text.

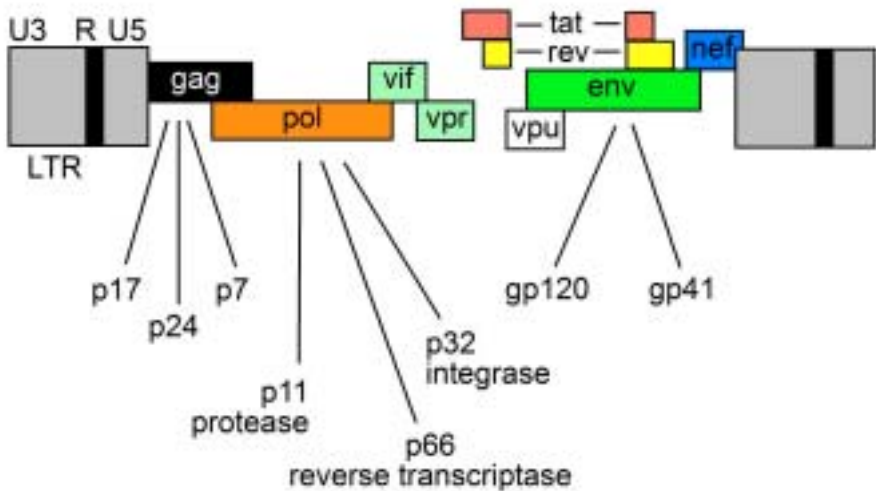


Figure 2: HIV and its genes. For detailed explanations see text.

*Nef* has been shown to have a number of functions. *Nef* may induce downregulation of CD4 (Aiken 1994) and HLA class I molecules (Collins 1998) from the surface of HIV-1-infected cells, which may represent an important escape mechanism for the virus to evade an attack mediated by cytotoxic CD8<sup>+</sup> T-cells and to avoid recognition by CD4<sup>+</sup> T-cells. *Nef* may also interfere with T-cell activation by binding to various proteins that are involved in intracellular signal transduction pathways (Overview in: Peter 1998). In SIV-infected rhesus macaques, an intact *nef* gene was essential for a high rate of virus production and the progression of disease. HIV-1, with deletions in *nef*, was identified in a cohort of Australian long-term non-progressors. However, more recent reports indicate that some of these patients are now developing signs of disease progression together with a decline of CD4<sup>+</sup> T-cells. Thus, although, deletions of the *nef* gene may slow viral replication, they cannot always prevent the development of AIDS.

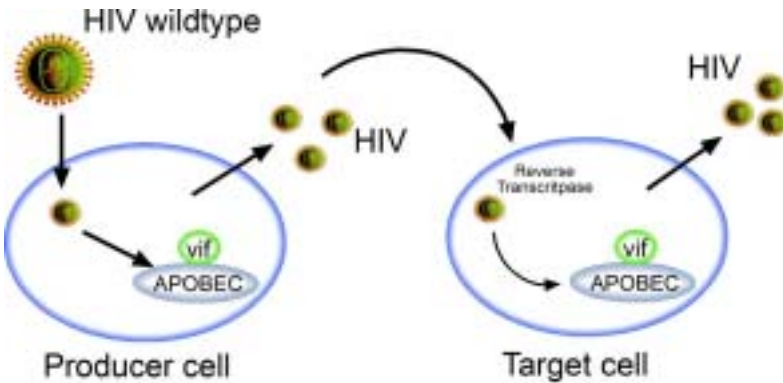
*Vpr* seems to be essential for viral replication in non-dividing cells such as macrophages. *Vpr* may stimulate the HIV-LTR in addition to a variety of cellular and viral promoters. More recently, *vpr* was shown to be important for the transport of the viral pre-integration complex to the nucleus (Overview in: Miller 1997) and may arrest cells in the G2 phase of the cell cycle.

*Vpu* is important for the virus “budding” process, because mutations in *vpu* are associated with persistence of the viral particles at the host cell surface. *Vpu* is also involved when CD4-gp160 complexes are degraded within the endoplasmic reticulum and therefore allows recycling of gp160 for the formation of new virions (Bour 1995, Cullen 1998).

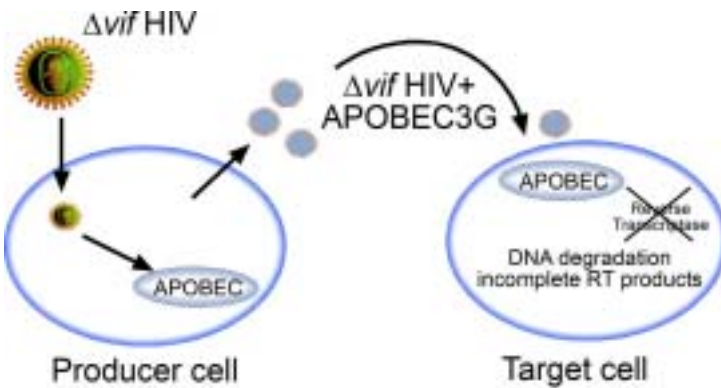
Some recent publications have highlighted a new and important role for *vif* in supporting viral replication (Mariani 2003). *Vif*-deficient HIV-1 isolates do not replicate in CD4<sup>+</sup> T-cells, some T cell lines (“non-permissive cells”) or in macrophages. *Vif*-deficient isolates are able to enter a target cell and initiate reverse transcription,



but synthesis of proviral DNA remains incomplete. In vitro fusion of “permissive” and “non-permissive” cells leads to a “non-permissive” phenotype, suggesting that the replication of HIV depends on the presence or absence of a cellular inhibitor. This endogenous inhibitory factor was recently identified as APOBEC3G (Sheehy 2002). APOBEC3G (“apolipoprotein B mRNA editing enzyme catalytic polypeptide-like 3G”) belongs to a family of intracellular enzymes that specifically deaminate cytosine to uracil in mRNA or DNA resulting in an accumulation of G-to-A mutations that lead to degradation of viral DNA. By forming a complex with APOBEC3G, *vif* blocks the inhibitory activity of APOBEC3G (Figure 3a).



3a



3b

Figure 3: HIV wild-type infection: *vif* interacts with APOBEC3G, binds to APOBEC3G and prevents its incorporation in newly formed viruses (Fig 3a). *Vif*-deleted HIV isolates fail to inhibit intracellular APOBEC3G, which is then incorporated into new viruses and interferes with reverse transcription in the target cell.

Of interest, the antiviral activity of APOBEC3G is highly conserved among various species, whereas the blockade of APOBEC3G by *vif* is highly specific for HIV. HIV-1 *vif* does not complex to murine or rhesus APOBEC3G. In the absence of *vif*, APOBEC3G is incorporated into newly formed viral particles and in subsequently infected target cells, synthesis of proviral DNA is blocked (Figure 3b). In contrast, in the presence of *vif*, APOBEC3G is complexed, degraded and not incorporated in newly formed virions. APOBEC3G is expressed in lymphocytes and macrophages representing the primary target cells of HIV infection.

Currently, there are still a lot of open questions regarding the regulation of intracellular APOBEC3G: for example, whether there is a critical amount of intracellular APOBEC3G that restricts HIV infection in the presence of *vif*, or whether genetic polymorphisms of APOBEC3G exist that may potentially affect the course of disease. In addition, the enzymatic function of intracellular APOBEC3G in lymphocytes may depend on the cellular activation status (Chiu 2005). Meanwhile, the epitopes by which *vif* and APOBEC3G interact with each other have been characterized and the pathway of intracellular degradation of the APOBEC3G-*vif* complex explored. Of note, specific inhibitors that block the interaction of *vif* and APOBEC3G or that interfere with the intracellular degradation of APOBEC3G could represent promising future treatments. In principle, blockade of cellular structures will likely be associated with a minimal risk that the development of resistance might compromise the efficacy of an antiviral agent. Therefore, targeting *vif* and APOBEC3G represents an interesting therapeutic approach.

In summary, these data explain not only why *vif* is essential for HIV replication but also give one reason why HIV replication is species-specific. Another cellular factor (see below) has also been discovered which explains species specificity of HIV replication.

The crucial role for APOBEC3G or other cytidine deaminases might not be restricted to HIV-1. An accumulation of G-to-A mutations was also demonstrated in various HBV isolates. In vitro, the accumulation of HBV-DNA is dramatically reduced in the presence of APOBEC3G but co-transfection with *vif* can revert this inhibition (Trono 2004).

## 2. The HIV replication cycle

### 2.1. HIV entry

#### CD4 as a primary receptor for HIV

CD4 is a 58 kDa monomeric glycoprotein that can be detected on the cell surface of about 60 % of T-lymphocytes, on T-cell precursors within the bone marrow and thymus, and on monocytes and macrophages, eosinophils, dendritic cells and microglial cells of the central nervous system. The extracellular domain of the CD4 on T-cells is composed of 370 amino acids; the hydrophobic transmembrane domain and the cytoplasmic part of CD4 on T-cells consist of 25 and 38 amino acids, respectively. Within the extracellular part of CD4, four regions D1-D4 have been

characterized that represent immunoglobulin-like domains. Residues within the V2 region of CD4 (amino acids 40-55) are important for the bonding of gp120 to CD4 and this region overlaps the part of the CD4 where its natural ligands, HLA class II molecules, bind.

The identification of the gp120 binding site on the CD4 of CD4<sup>+</sup> T-cells stimulated attempts to use soluble CD4 (sCD4) to neutralize the circulating virus in patients, the aim being the inhibition of viral spread (Schooley 1990). However it became evident, that even though laboratory viral isolates were easily neutralized by sCD4, neutralization of primary patient-derived isolates had not been achieved.

In contrast, sCD4 was able to induce conformational changes within the viral envelope that promoted the infection of target cells (Bour 1995).

CD4 attaches to the T cell receptor complex (TCR) on CD4<sup>+</sup> T-cells and binds to HLA class II molecules on antigen-presenting cells. The binding of gp120 to CD4 is not only a crucial step for viral entry, but also interferes with intracellular signal transduction pathways and promotes apoptosis in CD4<sup>+</sup> T-cells (Banda 1992). In the past couple of years, the idea of blocking CD4 as the primary cellular receptor of HIV has regained interest. PRO542 represents a genetically engineered tetravalent CD4-IgG2 fusion protein that not only inhibited viral replication *in vitro*, but also showed an impressive antiviral efficacy in patients with high viral load that were included in initial clinical trials (see HAART chapter).

CD4, as a primary and necessary receptor for HIV-1, HIV-2 and SIV, was already characterized in 1984 (Dalgleish 1984, Klatzmann 1984). However, experiments, using non-human cell lines transfected with human CD4, showed that expression of human CD4 on the cell surface of a non-human cell line was not sufficient to allow entry of HIV. Therefore the existence of additional human coreceptors necessary for viral entry was postulated. On the other hand, some laboratory HIV-1 isolates, as well as some HIV-2 and SIV isolates are able to infect human cells independently from CD4. Interestingly, monoclonal antibodies against CD4 induced conformational (CD4i) epitopes to bind to the gp120 of CD4-independent viruses. This observation suggests that the gp120 of CD4-independent viruses already exposes the regions that are necessary for coreceptor recognition and binding and therefore binding to CD4 is not a prerequisite of entry for these viruses. CD4-independent viruses are easy to neutralize using the serum of HIV-infected patients, suggesting that the immune response selects against CD4-independent viruses (Edwards 2001).

### **Chemokine receptors as coreceptors for HIV entry**

A milestone for the characterization of the early events leading to HIV-1 entry was an observation by Cocchi and his co-workers in 1995. CD8 T cells from HIV-infected patients are able to suppress viral replication in co-cultures with HIV-infected autologous or allogenic CD4<sup>+</sup> T-cells, and this is independent from their cytotoxic activity (Levy 1996). Cocchi identified the chemokines MIP-1 $\alpha$ , MIP-1 $\beta$  and Rantes in supernatants from CD8<sup>+</sup> T-cells derived from HIV-infected patients, and was able to show that these chemokines were able to suppress replication in a dose-dependent manner of some, but not all, viral isolates tested (Cocchi 1995). MIP-1 $\alpha$ , MIP-1 $\beta$  and Rantes are ligands for the chemokine receptor CCR5, and a few months later several groups were able to show that CCR5 is a necessary co-receptor for monocyctotropic (M-tropic) HIV-1 isolates (Deng 1996, Doranz 1996,

Dragic 1998). A few weeks earlier, the chemokine receptor CXCR4 (fusin) was described as being the coreceptor used by T-cell-tropic (T-tropic) HIV isolates (Feng 1996). Monocytotropic (M-tropic) HIV-1 isolates are classically those viruses that are most easily propagated in macrophage cultures, are unable to infect T-cell lines (i.e., immortalized T-cells), but are able to easily infect primary T-cells from peripheral blood samples. Conversely, T-cell-tropic HIV-1 isolates have classically been identified as being those that are easily propagated in T-cell lines, and grow poorly in macrophages, but are also able to easily infect primary T-cells from peripheral blood samples. Thus, it should be noted that both M-tropic and T-tropic HIV-1 variants can easily infect primary human non-immortalized T-cells in vitro.

Chemokines ( “**Chemotactic cytokines**”) and their receptors have been previously characterized with regard to their role in promoting the migration (“chemotaxis”) of leukocytes and their pro-inflammatory activity. They are proteins of 68-120 amino acids which depend on the structure of their common cysteine motif, and which may be subdivided into C-X-C ( $\alpha$ -chemokines), C-C ( $\beta$ -chemokines) and C-chemokines. Chemokines typically show a high degree of structural homology to each other and may share the receptors they bind to. Chemokine receptors belong to the group of receptors with seven transmembrane regions (“7-transmembrane receptors”), which are intracellularly linked to G-proteins.

SDF-1 (“stromal cell-derived factor 1”) was identified as the natural ligand of CXCR4 and is able to inhibit the entry of T-tropic HIV-1 isolates into activated CD4+ T-cells. Rantes (“regulated upon activation T cell expressed and secreted”), MIP-1 $\alpha$  (“macrophage inhibitory protein”) and MIP-1 $\beta$  represent the natural ligands of CCR5 and are able to inhibit the entry of M-tropic HIV-1 isolates into T cells. A schematic model is depicted in Figure 4: T-tropic HIV-1 isolates mainly infect activated peripheral blood CD4+ T-cells and cell lines and use CXCR4 for entry into the CD4+ target cell. M-tropic isolates are able to infect CD4+ T-cells, monocytes and macrophages, and depend on the use of CCR5 and CD4 for viral entry.

The interaction of gp120 and the cellular receptors is now understood in more detail. Gp120 primarily binds to certain epitopes of CD4. Binding to CD4 induces conformational changes in gp120 that promote a more efficient interaction of the V3 loop of gp120 with its respective coreceptor. Membrane fusion is dependent on gp120 coreceptor binding. Gp41, as the transmembrane part of the envelope glycoprotein gp160, is crucial for the fusion of the viral and the host cell membrane. Similar to influenza hemagglutinin, it was postulated that consequent to the binding of gp120 to CD4, a conformational change is induced in gp41 that allows gp41 to insert its hydrophobic NH<sub>2</sub> terminal into the target cell membrane. Gp41 has been compared to a “mouse trap” and a crystallographic analysis of the ectodomainic structure of gp41 seems to confirm that hypothesis (Chan 1997). The identification of crucial amino acid sequences for this process was used to synthesize peptides that bind to gp41 within the domains, are critical for the induction of conformational changes, and that may inhibit membrane fusion.

T20 is the first of several peptides that bind to gp41 and has been tested in clinical trials for suppressing viral replication (see HAART chapter).

Using transfected cell lines, besides CCR5 and CXCR4, other chemokine receptors, such as CCR3, CCR2, CCR8, CCR9, STRL33 (“Bonzo”), Gpr 15 (“Bob”), Gpr 1, APJ and ChemR23, were identified and shown to be used for entry by certain HIV

isolates (Deng 1997, Liao 1997). APJ may represent a relevant coreceptor within the central nervous system. Despite this broad spectrum of potentially available coreceptors, CCR5 and CXCR4 seem to represent the most relevant coreceptors for HIV-1 *in vivo*.

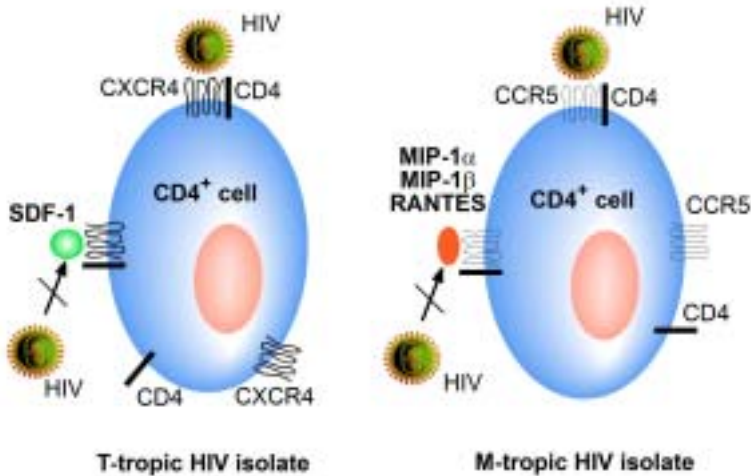


Figure 4: Inhibition of virus entry of CCR5-utilizing (monocytotropic) and CXCR4-utilizing (T-cell tropic) HIV isolates by the natural ligands of the chemokine coreceptors CCR5 and CXCR4.

The importance of CCR5 as the predominant coreceptor for M-tropic HIV isolates is underscored by another observation. The majority of individuals with a genetic defect of CCR5 are resistant to infection with HIV-1 (Liu 1996). *In vitro* experiments show that lymphocytes derived from these individuals are resistant to HIV-1 infection using M-tropic isolates but not to infection with T-tropic isolates. Lymphocytes from these individuals do not express CCR5 on their cell surface and genetically have a 32 base pair deletion of the CCR5 gene. Worldwide, a few patients have been identified that have acquired HIV-1 infection despite a homozygous deletion of the CCR5. As expected, all of them were infected with CXCR4-using HIV-1 isolates (Biti 1997). In epidemiological studies, the allelic frequency of the CCR5 gene deletion is 10-20 % among Caucasians, particularly amongst those of Northern European descent. The frequency of a homozygous individual is about 1% in Caucasians (Dean 1996). Studies conducted on African or Asian populations, however, do not find this 32 base pair deletion of the CCR5, suggesting that this mutation arose after the separation of these populations in evolutionary history.

Individuals that are heterozygous for the 32 bp deletion of the CCR5 show a decreased expression of CCR5 on the cell surface and are more frequently encountered within cohorts of long-term non-progressors compared to patients who have a rapid progression of disease (Dean 1996). In addition, HIV-infected individuals who are heterozygous for the 32 bp deletion of the CCR5, have a slower progression to AIDS, a better treatment response to HAART and lymphoma incidence is

decreased. These data demonstrate that the density of CCR5 on the cell surface is not only a limiting factor for replication of HIV *in vitro* but also *in vivo*.

In addition to the 32bp deletion of the CCR5, other genetic polymorphisms, with regard to the chemokine receptors (CCR2) or their promoters (CCR5), have been described. Based on the occurrence of these polymorphisms within defined patient cohorts, they were associated with a more rapid or a more favorable course of disease, depending on the particular polymorphism (Anzala 1998, Winkler 1998).

In patients who have a rapid progression of disease (rapid drop in CD4+ T-cell count), virus isolates that use CXCR4 as a predominant coreceptor tend to be frequently isolated from their cells, in comparison to patients with a stable CD4+ T-cell count.

The expression of coreceptors on CD4+ T-lymphocytes depends on their activation level. CXCR4 is mainly expressed on naive T-cells, whereas CCR5 is present on activated and effector/memory T-cells. During the early course of HIV-1 infection, predominantly M-tropic HIV-1 isolates are detected. Interestingly, M-tropic HIV-1 isolates are preferentially transmitted regardless of whether or not the “donor” predominantly harbors T-tropic isolates. At present, it remains unclear whether this “*in vivo*” preference of M-tropic HIV-1 isolates is determined by selected transportation of M-tropic isolates by sub-mucosally located dendritic cells or whether the local cytokine/chemokine milieu favors the replication of M-tropic viruses. Recent intriguing studies by Cheng Meyer et al. suggest that M-tropic HIV-1 viruses are able to ‘hide’ more easily from the immune system by replicating in macrophages, in comparison to T-tropic viruses, thus giving them a survival advantage in the infected individual.

The blockade of CCR5, therefore, seems to represent a promising target for therapeutic intervention (Figure 5). *In vitro*, monoclonal antibodies to CCR5 (2D7 and others) are able to block the entry of CCR5-using HIV isolates into CD4+ T cells and macrophages. Small molecule inhibitors of CCR5 have been designed and preliminary clinical trials demonstrate a significant reduction of plasma viremia in HIV-infected patients (Fätkenheuer 2005). *In vitro* studies, as well as experiments using SCID mice, however, suggest that blockade of CCR5-using isolates may alter their tropism towards increased usage of CXCR4.

Small molecule inhibitors such as T22, ALX40-4C or AMD3100 are able to inhibit CXCR4 and are also subject to preclinical and clinical trials (see HAART chapter). Other CCR5 inhibitors have been used as mucosal microbicides in monkey models and could therefore represent a potential future preventive approach (Veazey 2005).

Strategies are currently being developed to modulate expression of chemokine receptors. Intrakinases are chemokines that stay within the cytoplasm and are able to capture and bind to their corresponding receptor on its way to the cell surface (Chen 1997). “Short interfering RNA” (siRNA) represents a new molecular tool that is able to selectively inactivate target genes. Double-stranded RNA is split by the enzyme dicer-1 into short pieces (“21-23mers”). These oligomers may complementary bind to longer RNA sequences that are subsequently degraded. This strategy is currently employed in plants and used for its antiviral activity. The use of siRNA against CCR5 can prevent the expression of CCR5 *in vitro*.

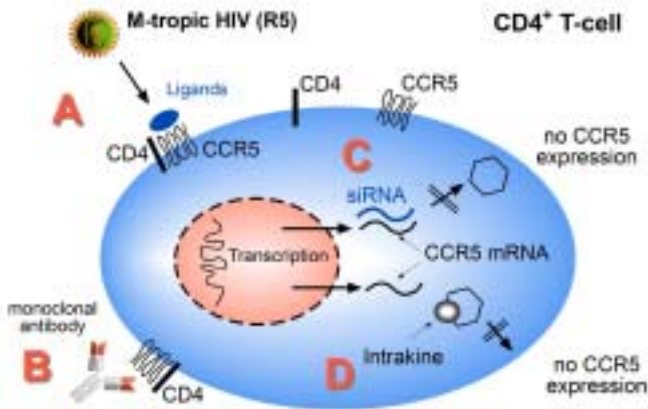


Figure 5: Strategies to block infection by CCR5-tropic HIV. Blockage of CCR5 on the cell surface by non-agonistic ligands (A) or monoclonal antibodies (B). Alternatively, CCR5 cell surface expression can be reduced by siRNA or intrakine. For further details see text.

Although the therapeutic use of chemokine receptor blockers seems promising, a lot of questions still remain unanswered. Using knockout mice it was demonstrated that the absence of CXCR4 or SDF-1 is associated with severe defects in hematopoiesis and in cerebellar development (Zou 1997). Currently, it remains unclear whether the blockade of CXCR4 in postnatal or adult individuals may also affect other organ systems.

## 2.2. Postfusion events

Following membrane fusion the virus core “uncoats” into the cytoplasm of the target cell. These “early events” have recently been studied in more detail. HIV can enter into rhesus lymphocytes but replication is stopped before or during early reverse transcription. This intracellular blockade is mediated by a cellular factor, TRIM5 $\alpha$ , which is a component of cytoplasmic bodies and whose primary function is yet known. TRIM5 $\alpha$  from various species exhibits differential inhibition on various retroviruses. For example, TRIM5 $\alpha$  from rhesus macaques (TRIM5 $\alpha_{rh}$ ) more profoundly inhibits HIV replication than human TRIM5 $\alpha$ , whereas SIV (simian immunodeficiency virus) which naturally infects Old World monkeys, is less susceptible to either form of TRIM5 $\alpha$ , thus explaining in part the species specificity of HIV for human cells (Stremlau 2004). TRIM5 $\alpha$  from human cells or non-human primates is able to inhibit replication of other lentiviruses and represents a novel cellular resistance factor whose definitive biological significance has yet to be fully characterized. It is unclear how exactly TRIM5 $\alpha$  blocks reverse transcription and it has been hypothesized that TRIM5 $\alpha$  interferes with the incoming virus capsid protein targeting it for ubiquitination and proteolytic degradation.

HIV-1 entry into quiescent T cells is comparable to HIV-1 entry into activated T cells, but synthesis of HIV-1 DNA remains incomplete in quiescent cells (Zack 1990). The conversion of viral RNA into proviral DNA, mediated by the viral enzyme reverse transcriptase (RT), occurs in the cytoplasm of the target cell and is a crucial step within the viral replication cycle (Figure 6). Blockade of the RT by the

nucleoside inhibitor zidovudine was the first attempt to inhibit viral replication in HIV-1 infected patients.

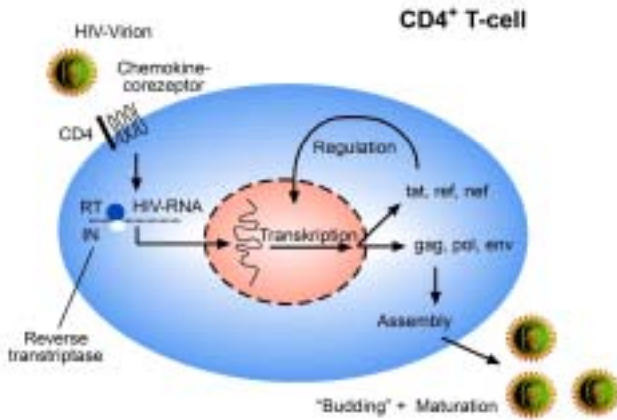


Figure 6: Life cycle of HIV.

Reverse transcription occurs in multiple steps. After binding of the tRNA primers, synthesis of proviral DNA occurs as a minus-strand polymerization starting at the PBS (“primer binding site”) and extending up to the 5’ repeat region as a short R/U5 DNA. The next step includes degradation of RNA above the PBS by the viral enzyme RNAase H and a “template switch” of the R/U5 DNA with hybridization of the R sequence at the 3’ RNA end. Now the full length polymerization of proviral DNA with degradation of the tRNA is completed. Reverse transcription results in double-stranded HIV DNA with LTR regions (“long terminal repeats”) at each end.

HIV-1 enters into quiescent T cells and reverse transcription may result in the accumulation of proviral, non-integrating HIV-DNA. However, cellular activation is necessary for integration of the proviral HIV DNA into the host cell genome after transportation of the pre-integration complex into the nucleus. Cellular activation may occur in vitro after stimulation with antigens or mitogens, in vivo activation of the immune system is observed after antigen contact or vaccination or during an opportunistic infection. In addition, evidence is emerging that HIV-1 gp120 itself may activate the infecting cell to enhance integration. Besides monocytes, macrophages and microglial cells, latently infected quiescent CD4<sup>+</sup> T-cells that contain non-integrated proviral HIV DNA represent important long-living cellular reservoirs of HIV (Chun 1997). Since natural HIV-1 infection is characterized by continuing cycles of viral replication in activated CD4<sup>+</sup> T-cells, viral latency in these resting CD4<sup>+</sup> T-cells likely represents an accidental phenomenon and is not likely to be important in the pathogenesis of this disease. This small reservoir of latent provirus in quiescent CD4<sup>+</sup> T-cells gains importance, however, in individuals who are treated with HAART, since the antivirals are unable to affect non-replicating proviruses and thus the virus will persist in those cells and be replication competent to supply new rounds of infection, if the drugs are stopped. Thus, the existence of



this latent reservoir has prevented HAART from entirely eradicating the virus from infected individuals.

Until recently it was not clear, why HIV replicates poorly in quiescent CD4<sup>+</sup> T-cells. The cellular protein Murr1 that plays a role in copper metabolism is able to inhibit HIV replication in unstimulated CD4<sup>+</sup> T-cells. Murr1 was detected in primary resting CD4<sup>+</sup> T-cells and interferes with activation of the transcription factor NF $\kappa$ B by inhibiting the degradation of I $\kappa$ B $\alpha$ . I $\kappa$ B $\alpha$  prevents NF $\kappa$ B from migrating to the nucleus, especially after cytokine stimulation (e.g., TNF $\alpha$ ). Because the HIV LTR region has multiple sites for NF $\kappa$ B, preventing NF $\kappa$ B migration to the nucleus should inhibit HIV replication. Inhibition of murr-1 by siRNA is associated with HIV replication in quiescent CD4<sup>+</sup> T-cells (Ganesh 2003). Persistence of HIV in quiescent CD4<sup>+</sup> T-cells and other cellular reservoirs seems one of the main reasons why eradication of HIV is not feasible. If it is ever possible to achieve, a more detailed knowledge of how and when cellular reservoirs of HIV are established and how they may be targeted is of crucial importance for the development of strategies aiming at HIV eradication.

Cellular transcription factors such as NF $\kappa$ B may also bind to the LTR regions. After stimulation with mitogens or cytokines, NF $\kappa$ B is translocated into the nucleus where it binds to the HIV-LTR region, thereby initiating transcription of HIV genes. Transcription initially results in the early synthesis of regulatory HIV-1 proteins such as *tat* or *rev*. *Tat* binds to the TAR site (“transactivation response element”) at the beginning of the HIV-1 RNA in the nucleus and stimulates transcription and the formation of longer RNA transcripts. *Rev* activates the expression of structural and enzymatic genes and inhibits the production of regulatory proteins, therefore promoting the formation of mature viral particles. The proteins coded for by *pol* and *gag* form the nucleus of the maturing HIV particle; the gene products coded for by *env* form the gp120 “spikes” of the viral envelope. The gp120 spikes of the envelope are synthesized as large gp160 precursor molecules and are cleaved by the HIV-1 protease into gp120 and gp41. The *gag* proteins are also derived from a large 53 kD precursor molecule, from which the HIV protease cleaves the p24, p17, p9 and p7 *gag* proteins. Cleavage of the precursor molecules by the HIV-1 protease is necessary for the generation of infectious viral particles, and therefore the viral protease represents another interesting target for therapeutic blockade. The formation of new viral particles is a stepwise process: a new virus core is formed by HIV-1 RNA, *gag* proteins and various *pol* enzymes and moves towards the cell surface. The large precursor molecules are cleaved by the HIV-1 protease, which results in the infectious viral particles budding through the host cell membrane. During the budding process, the virus lipid membranes may incorporate various host cell proteins and become enriched with certain phospholipids and cholesterol. In contrast to T cells, where budding occurs at the cell surface and virions are released into the extracellular space, the budding process in monocytes and macrophages results in the accumulation of virions within cellular vacuoles.

The replication of retroviruses is prone to error and is characterized by a high spontaneous mutation rate. On average, reverse transcription results in 1-10 errors per genome and per round of replication. Mutations can lead to the formation of replication-incompetent viral species. But, mutations causing drug resistance may also accumulate, which, provided that there is selection pressure under certain

antiretroviral drugs and incomplete suppression of viral replication, may become dominant.

In addition, viral replication is dynamic and turns over quickly in infected individuals at an average rate of  $10^9$  new virus particles being produced and subsequently cleared per day. Thus, within any individual, because of the extensive virus replication and mutation rates, there exists an accumulation of many closely related virus variants within the 'population' of viruses, referred to as a viral "quasispecies". The selection pressure on mostly the pre-existing mutations may not only be exerted by certain drugs, but also by components of the immune system, such as neutralizing antibodies or cytotoxic T cells (CTL).

### 3. HIV and the immune system

#### 3.1. The role of antigen-presenting cells

##### Dendritic cells as prototypes of antigen-presenting cells

Dendritic cells, macrophages and B cells represent the main antigen-presenting cells of the immune system. Dendritic cells (DC) are the most potent inducers of specific immune responses and are considered essential for the initiation of primary antigen-specific immune reactions. DC precursors migrate from the bone marrow towards the primary lymphatic organs and into the submucosal tissue of the gut, the genitourinary system and the respiratory tracts. They are able to pick up and process soluble antigens and migrate to the secondary lymphatic organs, where they activate antigen-specific T cells. Because DC have a crucial role in adaptive immunity, there is an increasing interest in using dendritic cell to induce or expand HIV-specific T-cells. DC from HIV-infected patients have been purified, incubated with inactivated, non-infectious HIV particles and subsequently used for vaccination (Lu 2004).

DC represent a heterogeneous family of cells with different functional capacities and expression of phenotypic markers, depending on the local microenvironment and the stage of maturation (Shortman 2002). Immature DC have the capacity to pick up and process foreign antigens, but do not have great T cell stimulatory capacities. However, mature DC show a predominant immunostimulatory ability. DC in tissues and Langerhans' cells, which are specialized DC in the skin and mucosal areas, represent a more immature phenotype and may take up antigen. Once these DC have taken up the antigen, they migrate to the lymphoid tissues where they develop a mature phenotype. Viruses may induce plasmacytoid DC to produce substantial amounts of IFN alpha with antiviral activity by stimulating Toll-like receptors (TLR) (Beignon 2005) therefore linking the innate to the adaptive immune system.

The stimulation of CD8 T-lymphocytes and the formation of antigen-specific cytotoxic T cells (CTL) depend on the presentation of a peptide together with MHC class I antigens. DC may become infected with viruses, for instance influenza. Viral proteins are then produced within the cytoplasm of the cell, similar to cellular proteins, then degraded to viral peptides and translocated from the cytosol into the en-

doplasmic reticulum, where they are bound to MHC class I antigens. These peptide-MHC class I complexes migrate to the DC surface. Interestingly, efficacy of presentation of viral antigens is comparable regardless whether DC themselves or productively infected or not.

The number of specific antigen-MHC class I complexes is usually limited and must eventually be recognized by rare T-cell clones, up to a ratio of 1:100.000 or less. The T-cell receptor (TCR) may display only a low binding affinity (1mM or less). The high density of co-stimulatory molecules on the DC surface, however, enhances the TCR-MHC: peptide interaction allowing efficient signaling to occur through the T-cell and resulting in proliferation (clonal expansion) of the T-cell. Virus-infected cells or tumor cells often do not express co-stimulatory molecules, and thus may not be able to induce a clonal expansion of effector cells. This underscores the importance of having a highly specialized system of antigen-presenting cells, i.e., DC, in operation to prime T-cells to expand and proliferate initially.

### **The interaction of dendritic cells and B/T-cells**

B and T-lymphocytes may be regarded as the principle effector cells of antigen-specific immune responses. However, their function is under the control of dendritic cells. DC are able to pick up antigens in the periphery. These antigens are processed and expressed on the cell surface, together with co-stimulatory molecules that initiate T-cell activation. B-cells may recognize antigen after binding to the B-cell receptor. Recognition of antigen by T-cells requires previous processing and presentation of antigenic peptides by DC. T-cells express different T-cell receptors (TCR) that may bind to the peptide: MHC class I on the surface of dendritic cells to allow activation of CD8 T-cells, or to the peptide: MHC class II molecules, to activate CD4+ T-cells. The ability of DC to activate T-cells also depends on the secretion of stimulatory cytokines such as IL-12, which is a key cytokine for the generation and activation of T<sub>H</sub>1 and natural killer (NK) cells.

Only a few DC and small amounts of antigen are sufficient to induce a potent antigen-specific T-cell response, thus demonstrating the immunostimulatory potency of DC. The expression of adhesion molecules and lectins, such as DC-SIGN, support the aggregation of DC and T-cells and promote the engagement of the T-cell receptor (TCR). DC-SIGN is a type C lectin that has also been shown to bind to lentiviruses, such as SIV and HIV-1 and -2 by interaction of gp120 with carbohydrates (Geijtenbeek 2000). Mycobacteria and Dengue virus may also bind to DC-SIGN. In vivo, immunohistochemical studies show expression of DC-SIGN on submucosal and intradermal DC, suggesting an implication of DC-SIGN in vertical and mucosal transmission of HIV. The expression of DC-SIGN was shown to enhance the transmission of HIV to T cells and allows utilization of coreceptors if their expression is limited. Thus DC-SIGN may be a mechanism whereby HIV-1 is taken up by DC in the mucosal tissues. It is then transported by the DC to the lymphoid tissues where HIV-1 can then infect all the residing CD4+ T-cells.

### **3.2. Lymphatic tissue as the site of viral replication**

Viral replication within the lymphatic tissue is already extensive in the early stages of the disease (Embretson 1003, Pantaleo 1993).

During the initial phase of HIV-1 infection, there is a burst of virus into the plasma, followed by a relative decline in viremia. During this time, a strong HIV-1 specific cytotoxic T-cell response is generated, which coincides with the early suppression of plasma viremia in most patients. Virions are trapped by the follicular dendritic cell (FDC) network within the lymphoid tissue. Macrophages, and activated and quiescent CD4+ T-cells are the main targets of infection. Permanent viral reservoirs, mainly in macrophages and latently infected CD4+ T-cells, are established in the early phase of infection and probably represent the major obstacle so far to successful eradication of HIV. During the whole course of infection with HIV-1, the lymphoid tissue represents the principle site of HIV-1 replication. The frequency of cells containing proviral DNA is 5-10x higher in lymphoid tissue than in circulating peripheral mononuclear cells in the blood, and the difference in viral replication in lymphoid tissue exceeds that in the peripheral blood by about 10-100x.

After entry of HIV-1 into a quiescent CD4+ T-cell and after completion of reverse transcription, the viral genome is represented by proviral unintegrated HIV DNA. In vitro experiments have shown that HIV-1 preferentially integrates into active genes ("hot spots") (Schroder 2002). The activation of CD4+ T-cells is necessary for the integration of the HIV DNA into the host cell genome and is therefore a prerequisite for the synthesis of new virions. In this regard, the microenvironment of the lymphoid tissue represents the optimal environment for viral replication. The close cell-cell contact between CD4+ T-cells and antigen-presenting cells, the presence of infectious virions on the surface of the FDC, and an abundant production of pro-inflammatory cytokines such as IL-1, IL-6 or TNF $\alpha$  promotes the induction of viral replication in infected cells and augments viral replication in cells already producing the virus. It should be noted that both IL-1 and TNF $\alpha$  induce NF $\kappa$ B, which binds to the HIV-1 LTR to promote proviral transcription. The importance of an antigen-induced activation of CD4+ T-cells is underlined by several in vivo and in vitro studies that demonstrate an increase in HIV-1 replication in association with a tetanus or influenza vaccination or an infection with *Mycobacterium tuberculosis* (O'Brian 1995). Even though the clinical benefit of vaccination against common pathogens (e.g. influenza and tetanus) in HIV-1-infected patients outweighs the potential risk of a temporary increase in viral load, these studies indicate that in every situation where the immune system is activated, enhanced viral replication can also occur.

Patients undergoing HAART demonstrate a dramatic decrease in the number of productively infected CD4+ T cells within the lymphoid tissue (Tenner-Racz 1998). However, in all patients examined so far, there persists a pool of latently infected quiescent T cells despite successful suppression of plasma viremia. It is these latently infected cells that may give rise to further rounds of viral replication, if the antiviral drugs are stopped.

During the natural course of HIV-1 disease, the number of CD4+ T-cells slowly decreases while plasma viremia rises in most patients. If sequential analysis of the lymphoid tissue is performed, progression of the disease is reflected by destruction of the lymphoid tissue architecture and a decreased viral trapping. Various immunohistological studies indicate that the paracortex of the lymph nodes represents the primary site where HIV replication is initiated (Embretson 1993, Pantaleo 1993). Infection of the surrounding CD4+ T-cells, as well as the initiation of T-cell activa-

tion by DC, contributes to the spreading of HIV-1 within the lymphoid environment. Similar to SIV infection in rhesus macaques, HIV infection, at all stages of disease, is associated with preferential replication and CD4+ T-cell destruction in the gut lamina propria and submucosa than in lymph nodes (Veazey 1998, Brenchley 2004, Mehandru 2004). This is likely because the gut is predominantly populated by CCR5-expressing effector memory CD4+ T-cells, which are ideal targets for HIV replication compared to the mixed populations of CD4+ T-cells found within the lymph nodes. Several studies have demonstrated that, during acute infection, depletion of CD4+CCR5+ memory cells within the mucosa-associated lymphatic tissue is a hallmark of both HIV and SIV infection. In the early phase of SIV infection, up to 60 % of all CD4+ T-cells within the intestinal lamina propria were shown to express viral RNA. Most of these cells are destroyed by direct and indirect mechanisms within a few days. Further disease progression seems to depend largely on the capacity of the host to reconstitute the pool of memory cells within the mucosa-associated lymphoid tissue. In view of this data, some researchers argue that initiation of HAART during acute HIV infection is crucial in order to limit long-term damage to the immune system.

Recent studies have also examined the effect of HIV infection on the thymus gland and its role in CD4+ T-cell depletion and homeostasis. Recent work has suggested that thymic output of CD4+ T-cells is decreased during HIV infection, particularly with older age, and that this defect is due to abnormalities of intra-thymic proliferation of T-cells, whose mechanism is still undefined, as thymocytes do not express CCR5 and should not necessarily be targets of HIV (Mehandru 2004, Douek 2001).

### 3.3. The HLA system and the immune response to HIV

CD8 T-cells recognize “their” antigen (peptide) in context with HLA class I molecules on antigen-presenting cells, whereas CD4+ T-cells require the presentation of antigenic peptides in context with HLA class II molecules. The generation of an HIV-specific immune response is therefore dependent on the individual HLA pattern.

Antigen-presenting cells may bind HIV peptides in different ways within “grooves” on the HLA class I molecules. Therefore, CD8 T-cells can be activated in an optimal or suboptimal way or may not be activated at all. Using large cohorts of HIV-1 infected patients, in whom the natural course of disease (fast versus slow progression) is known, HLA patterns were identified that were associated with a slow versus fast disease progression. These studies suggest that the HLA type could be responsible for the benign course of disease in about 40 % of patients with a long-term non-progressive course of disease. Homozygosity for HLA Bw4 is regarded as being protective. Patients who display heterozygosity at the HLA class I loci characteristically show a slower progression of immunodeficiency than patients with homozygosity at these loci (Carrington 1999). An initial study demonstrated that HLA B14, B27, B51, B57 and C8 are associated with a slow disease progression, however, the presence of HLA A23, B37 and B49 were associated with the rapid development of immunodeficiency (Kaslow 1996). All patients with HLA B35 had developed symptoms of AIDS after eight years of infection. More recent studies suggest that discordant couples with a “mismatch” at the HLA class I have a protective effect towards heterosexual transmission (Lockett 2001).

In vitro studies in HLA B57-positive patients demonstrate that these patients display HLA B57-restricted CTL directed against HIV-1 peptides. However, it is possible that the identification of protective HLA alleles or HLA-restricted peptides in HIV-1-infected patients with a benign course of disease does not necessarily indicate that the same alleles or peptides are crucial for the design of a protective vaccine. Kaul and co-workers were able to show that CD8<sup>+</sup> T-cells from HIV-1-exposed but uninfected African women recognize different epitopes than CD8<sup>+</sup> T-cells from HIV-1-infected African women (Kaul 2001). This suggests that the epitopes, that the immune system is directed against during a natural infection, might be different from those that are protective against infection. In addition, the individual HLA pattern may affect the adaptive immune response and the evolution of viral escape mutations (Friedrich 2004, Leslie 2004). CTL from patients with HLA B57 and B58 may “force” the virus to develop certain mutations in gag that enable the virus to escape the CTL response. However, these mutations result in a reduced replicative competence. If such a virus is transmitted to another individual with a different HLA background, the virus may “back” mutate to the original genotype and regain its full replicative competence.

HLA class II antigens are crucial for the development of an HIV-1-specific CD4<sup>+</sup> T-cell response. Rosenberg (1997) was the first to show that HIV-1-infected patients with a long-term non-progressive course of disease had HIV-1-specific CD4<sup>+</sup> T-cells that could proliferate against HIV-1 antigens. The identification of protective or unfavorable HLA class II alleles is less well elaborated than the knowledge about protective HLA class I alleles. Cohorts of vertically infected children and HIV-infected adults demonstrate a protective effect of HLA DR13 (Keet 1999).

KIR receptors (“Killer cell immunoglobulin like receptors”) represent ligands that bind to HLA class I antigens and by functioning as either activating or inhibiting receptors they regulate the activation status of NK cells. Polymorphisms of KIR genes were shown to correlate with slow or rapid progression of HIV disease, especially when the analysis includes known HLA class I polymorphisms (Fauci 2005). During HIV infection, NK cells may not only be decreased, but may also show a diminished cytolytic activity. Preliminary results suggest that low numbers of NK cells are associated with a more rapid progression of disease.

In summary, various genetic polymorphisms have been identified that have an impact on the course of HIV disease. However, there is currently no rationale to recommend routine testing of individual patients or to base therapeutic decisions on genetic testing.

### **3.4. The HIV-specific cellular immune response**

Cytotoxic T-cells (CTL) are able to recognize and eliminate virus-infected cells. A number of studies clearly demonstrate that CTL are crucial for the control of HIV replication and have a substantial impact on disease progression once infection is established. However, there is little evidence to assume that CTL play a major role in primary protection.

In comparison to HIV-1-infected patients with a rapid decline in CD4<sup>+</sup> T-cell numbers, patients with a long-term non-progressive course of disease (“LTNP” = long-term non-progressors) have high quantities of HIV-1-specific CTL precursors with a broad specificity towards various HIV-1 proteins. The different capacities of cer-

tain HLA alleles to present viral particles more or less efficiently and to induce a generally potent immune response may explain why certain HLA alleles are associated with a more rapid or a slowly progressive course of disease (see above).

Individuals have been described, who developed CTL “escape” mutants after years of stable disease and the presence of a strong CTL response. The evolution of CTL escape mutants was associated with a rapid decline in CD4<sup>+</sup> T-cells in these patients, indicating the protective role of CTL (Goulder 1997).

HIV-specific CTL responses have been detected in individuals exposed to, but not infected by HIV-1. Nef-specific CTL have been identified in HIV-1-negative heterosexual partners of HIV-infected patients and env-specific CTL have been found in seronegative healthcare workers after exposure to HIV-1-containing material by needle stick injuries (Pinto 1995). Unfortunately patients with a broad and strong CTL response do not seem to be protected from superinfection by a different, but closely related HIV isolate (Altfeld 2002).

The presence of a CTL response is not correlated just with the suppression of plasma viremia during the initial phase of HIV infection. Patients who underwent structured therapy interruptions, especially when HAART was initiated early following infection, demonstrated the appearance of HIV-specific CTL during the pauses.

However, it is still unclear in most patients who exhibit a potent temporary CTL response, why this CTL response diminishes later on. The appearance of viral “escape” mutants might explain why previously recognized epitopes are no longer immunodominant.

The *nef* protein may downregulate HLA class I antigens and therefore counteract the recognition of infected cells by CTL. In addition, the majority of infected individuals show detectable CTL responses. It is unclear why they are unable to control the virus. Interestingly, CTL from HIV-infected patients shows a lack of perforin and an immature phenotype in comparison to anti-CMV-directed effector cells (Harari 2002), even though the ability to secrete chemokines and cytokines is not impaired. Another recent study provided evidence that the killing capacity of HIV-specific CTL was associated with the ability to simultaneously produce interferon- $\gamma$  and TNF $\alpha$  (Lichtenfeld 2004).

CD8<sup>+</sup> T-cells may also become infected with HIV (Bevan 2004), although this was not demonstrated for HIV-specific CD8 T-cells. It is unclear, whether CD8 T-cells temporarily express CD4 and which chemokine coreceptors mediate infection of these CD8<sup>+</sup> T-cells.

Proliferation and activation of CTL is dependent on antigen-specific T cell help. Rosenberg and his group were able to demonstrate that initiation of HAART during primary HIV infection was associated with persistence of an HIV-specific CD4<sup>+</sup> T-cell response that was not detected in patients analyzed during the chronic stage of disease (Rosenberg 1997). HIV preferentially infects pre-activated CD4<sup>+</sup> T-cells and as HIV-specific CD4<sup>+</sup> T-cells are among the first cells to be activated during HIV infection, their preferential infection was demonstrated by Douek and his group (Douek 2002). Therefore, it is currently unclear whether the loss of HIV-specific CTL activity during the course of disease reflects an intrinsic defect of CTL or develops secondary to a loss of specific CD4<sup>+</sup> T-cell help.

Various therapeutic vaccine strategies have been developed during the last few years and mostly tested in SIV-infected rhesus macaques aiming at inducing an SIV-specific CTL response that may alter the natural course of disease. Recently, a promising vaccine approach was reported using autologous dendritic cells in SIV-infected rhesus macaques that were pulsed with inactivated SIV (Lu 2003). In contrast to the unvaccinated control group, monkeys that were vaccinated showed a dramatic decrease in the viral load, and the development of anti-SIV-directed humoral and cellular immune responses. Meanwhile, a pilot trial has been initiated in a cohort of 18 HIV-infected antiretroviral-naïve patients with stable viral load. The patients were vaccinated with autologous monocyte-derived dendritic cells that were pulsed with inactivated autologous virus. During the following 112 days, a median decrease of 80 % of the viral load was observed and maintained for more than one year in eight patients. In parallel, gag-specific CD8<sup>+</sup> T-cells and HIV-specific CD4<sup>+</sup> T-cells producing IFN $\gamma$  and/or interleukin-2 were detected (Lu 2004). Therapeutic vaccination using autologous dendritic cells appears to become a potential immunotherapeutic, but more controlled clinical studies are definitely needed.

In addition to the cytotoxic activities directed against HIV-infected cells, CD8<sup>+</sup> T-cells from HIV-1 infected patients exhibit a remarkable, soluble HIV-1 inhibitory activity that inhibits HIV-1 replication in autologous and allogeneic cell cultures (Walker 1996). Despite multiple efforts, the identity of this inhibitory activity (“CAF”) has not been clarified, although chemokines, such as MIP-1 $\alpha$ , MIP-1 $\beta$  or RANTES (Cocchi 1995), IL-16 (Baier 1995), the chemokine MDC (Pal 1997), and defensins (Zhang 2002), may account for at least some of the inhibition.

### **3.5. The T<sub>H1</sub>/T<sub>H2</sub> immune response**

Depending on the secretion pattern of cytokines, CD4<sup>+</sup> T-cells may be differentiated into T<sub>H1</sub> and T<sub>H2</sub> cells. T<sub>H1</sub> CD4<sup>+</sup> T-cells primarily produce interleukin-2 (IL-2) and IFN $\gamma$ , which represent the cytokines that support the effector functions of the immune system (CTL, NK-cells, macrophages). T<sub>H2</sub> cells predominantly produce IL-4, IL-10, IL-5 and IL-6, which represent the cytokines that favor the development of a humoral immune response. Since T<sub>H1</sub> cytokines are critical for the generation of CTLs, an HIV-1-specific T<sub>H1</sub> response is regarded as being a protective immune response. Studies on HIV-exposed but non-infected individuals have shown, that following *in vitro* stimulation with HIV-1 env antigens (gp120/gp160) and peptides, T-cells from these individuals secrete IL-2 in contrast to non-exposed control persons (Clerici 1991). Similar studies were undertaken in healthcare workers after needle-stick injuries and in newborns from HIV-infected mothers. Although these observations may indicate that a T<sub>H1</sub>-type immune response is potentially protective, it should be considered, that similar immune responses might also have been generated after contact with non-infectious viral particles and therefore do not necessarily imply a means of protection against a replication-competent virus.

### **3.6. HIV-1 specific humoral immune responses**

The association between an HIV-1-specific humoral immune response and the course of disease is less well characterized.



In a SIV model, injection of an antibody cocktail consisting of various neutralizing antibodies is able to prevent SIV infection after a mucosal virus challenge (Ferrantelli 2004), indicating that primary protection is mainly dependent on a broad humoral immune response. This data suggests that HIV-specific antibodies are necessary for a preventive vaccine strategy. In contrast, B-cell depletion by a monoclonal antibody directed against B-cells in monkeys with already established SIV infection, does not affect the course of plasma viremia (Schmitz 2003).

A slow progression of immunodeficiency was observed in patients with high titers of anti-p24 antibodies (Hogervorst 1995), persistence of neutralizing antibodies against primary and autologous viruses (Montefiori 1996), and lack of antibodies against certain gp120 epitopes (Wong 1993).

Long-term non-progressors with HIV tend to have a broad neutralizing activity towards a range of primary isolates and show persistence of neutralizing antibodies against autologous virus. At present, it is unclear whether the presence of neutralizing antibodies in LTNP represents part of the protection or whether it merely reflects the integrity of a relatively intact immune system. Individuals that have a substantial risk for HIV-1 infection, but are considered “exposed, non-infected”, by definition represent individuals with a lack of a detectable antibody response to HIV-1. This definition implies that a systemic humoral immune response may not represent a crucial protective mechanism. It has been shown that these individuals may demonstrate a local (mucosal) IgA response against HIV-1 proteins that are not detected by the usual antibody testing methods (Saha 2001). Thus, local IgA, rather than systemic IgG, may be associated with protection against HIV-1 infection. There is also some evidence that some anti-HIV-1 antibodies can enhance the infection of CD4+ T-cells.

A number of old and recent studies have shown that neutralizing antibodies do exist in HIV-1-infected individuals, however, there is a time lag in their appearance. That is, individuals will develop neutralizing antibodies to their own viruses with time, however, by the time these antibodies develop, the new viruses circulating in the individual’s plasma will become resistant to neutralization, even though the older ones are now sensitive to the current antibodies in the patient’s serum. Thus, the antibody response appears to be hitting a ‘moving’ target, allowing viruses to escape continuously. Further knowledge gained on understanding the mechanisms of humoral escape will likely lead to potential new therapies.

A few years ago, selected patients with advanced HIV infection were treated with plasma from HIV-infected patients at an earlier stage of the disease. No significant effect on the course of disease was notable (Jacobson 1998). The therapeutic application of neutralizing antibodies with defined specificity looked more promising, since a few acute and chronically infected patients were able to control their viral load at least temporarily after stopping antiretroviral therapy (Trkola 2005).

### **3.7. A vaccine against HIV ?**

Improved knowledge and understanding of the pathophysiological mechanisms during the course of HIV-1 infection have not only contributed to the development of antiretroviral treatment strategies, but have given rise to new therapeutic approaches, such as cytokine therapies, e.g., IL-2 and therapeutic vaccination. However, the most important challenge and thus, the demand for a better understanding

of the immunopathogenesis of HIV-1 infection, remains the development of a protective vaccine, which is urgently needed to interrupt the epidemic especially in countries of the Sub-Sahara and Southeast Asia.

The documentation of exposed but uninfected individuals and findings in LTNP suggests that, besides a genetic predisposition, HIV-specific protective immune mechanisms could potentially confer protective and possibly even preventive immunity. Results from animal studies suggest that immune protection might be generated when the immune system is stimulated in the appropriate way. The induction of an HIV-specific CD8 response in non-human primates is able to ameliorate the course of disease. On the other hand, *in vivo* depletion of CD8+ T-cells in non-human primates by monoclonal antibodies will lead to an increase in viral load. Immunogens that induce neutralizing antibodies in non-human primates will prevent infection with the homologous viral strain. Transfer of neutralizing antibodies to uninfected primates or human SCID mice is able to prevent infection with the homologous HIV strain.

The spectrum of vaccine strategies against HIV includes HIV-derived peptides or proteins, the use of viral or bacterial vectors, naked DNA, pseudovirions or the use of live attenuated HIV strains. The discussion about whether a vaccine should primarily aim at inducing a humoral or a cellular based protective immune response has now resulted in the belief that both humoral and cellular mechanisms contribute to protection.

Many neutralizing antibodies either do not or only poorly show inhibition of primary viral isolates. A major problem lies in the high variability of the gp120 glycoprotein itself. Furthermore, gp120 epitopes may be highly glycosylated and certain structural domains are hidden, at least temporarily, so that immunodominant epitopes may not be recognized (Chen 2005, Derdeyn 2005). In addition, there is no evidence that a cytotoxic T-cell response can prevent an uninfected individual from exogenous HIV infection. A report from Altfeld (2002) is interesting in this regard. It concerns an HIV-infected patient who was started on HAART during primary infection. The patient developed a robust anti-HIV CD8+ T-cell response that was closely monitored and documented by *in vitro* experiments. In spite of the strong CTL response, superinfection with a second HIV strain occurred, despite cross-reactive CTL epitopes.

The discussion about how to best monitor the induction of protective immune responses remains controversial. Does a CTL response as measured by its cytolytic activity or by cytokine production *in vitro* correlate of protection? How are *in vitro* tests linked to *in vivo* protection? Despite all efforts undertaken so far, the way to an effective and universally applicable preventive vaccine still seems to be a long one.

## References

1. Aiken C, Konner J, Landau NR, Lenburg ME, Trono D. Nef induces CD4 endocytosis: Requirement for a critical dileucine motif in the membrane-proximal CD4 cytoplasmic domain. *Cell* 1994; 76: 853-64. <http://amedeo.com/lit.php?id=8124721>
2. Altfeld M, Allen TM, Yu XG, et al. HIV-1 superinfection despite broad CD8+ T-cell responses containing replication of the primary virus. *Nature*. 2002; 420: 434-9. <http://amedeo.com/lit.php?id=12459786>

3. Anzala AO, Ball TB, Rostron T, O'Brien SJ, Plummer FA, Rowland-Jones SL. CCR2-64I allele and genotype association with delayed AIDS progression in African women. *Lancet* 1998, 351: 1632-3.
4. Baier M, Werner A, Bannert N, Metzner K, Kurth R. HIV suppression by interleukin-16. *Nature* 1995, 378: 563.
5. Barre-Sinoussi F, Chermann JC, Rey F, et al. Isolation of a T-lymphotropic retrovirus from a patient at risk for AIDS. *Science* 1983, 220: 868-71. <http://amedeo.com/lit.php?id=6189183>
6. Beignon AS, McKenna K, Skoberne M, et al. Endocytosis of HIV-1 activates plasmacytoid dendritic cells via Toll-like receptor- viral RNA interactions. *J Clin Invest* 2005; <http://amedeo.com/lit.php?id=16224540>
7. Biti R, Ffrench RF, Young J, Bennetts B, Stewart G, Liang T. HIV-1 infection in an individual homozygous for the CCR5 deletion allele. *Nature Med* 1997, 3: 252-3.
8. Bour S, Geleziunas R, Wainberg MA. The HIV type 1 (HIV-1) CD4 receptor and its central role in promotion of HIV-1 infection. *Microbiol Rev* 1995, 59: 63-93. <http://amedeo.com/lit.php?id=7708013>
9. Bour S, Schubert U, Strebel K. The HIV type 1 vpu protein specifically binds to the cytoplasmic domain of CD4: Implications for the mechanism of degradation. *J Virol* 1995, 69: 1510-20. <http://amedeo.com/lit.php?id=7853484>
10. Brechley JM, Schacker TW, Ruff LE et al. CD4 T cell depletion during all stages of HIV disease occurs predominantly in the gastrointestinal tract. *J Exp Med* 2004; 200: 749-59
11. Carrington M, Nelson GW, Martin MP, et al. HLA and HIV-1: heterozygote advantage and B\*35-Cw\*04 disadvantage. *Science* 1999; 12, 28: 1748-52. <http://amedeo.com/lit.php?id=10073943>
12. Chan DC, Fass D, Berger JM, Kim PS. Core structure of gp41 from the HIV envelope glycoprotein. *Cell* 1997, 89: 263-73. <http://amedeo.com/lit.php?id=9108481>
13. Chen JD, Bai X, Yang AG et al. Inactivation of HIV-1 chemokine co-receptor CXCR-4 by a novel intrakine strategy. *Nat Med* 1997; 3:1110-6. <http://amedeo.com/lit.php?id=9334722>
14. Chiu YL, Soros VB, Kreisberg JF, Stopak K, Yonemoto W, Greene WC. Cellular APOBEC3G restricts HIV-1 infection in resting CD4+ T cells. *Nature* 2005; 435: 108-14. Epub 2005 Apr 13. <http://amedeo.com/lit.php?id=15829920>
15. Chun TW, Carruth L, Finzi D, et al. Quantification of latent tissue reservoirs and total body viral load in HIV-1 infection. *Nature* 1997, 387:183-8. <http://amedeo.com/lit.php?id=9144289>
16. Clavel F, Guetard D, Brun-Vezinet F, Chamaret S, Rey MA, Santos-Ferreira O. Isolation of a new human retrovirus from West African patients with AIDS. *Science* 1986, 233: 343
17. Clerici M, Giorgi JV, Chou CC, et al. Cell-mediated immune response to HIV (HIV) type-1 in seronegative homosexual men with a recent sexual exposure to HIV-1. *J Infect Dis* 1992, 165: 1012-9. <http://amedeo.com/lit.php?id=1533867>
18. Cocchi F, DeVico AL, Garzino-Demo A, Arya S, Gallo RC, Lusso P. Identification of RANTES, MIP-1a, and MIP-1 $\beta$  as the major HIV-suppressive factors produced by CD8+ T cells. *Science* 1995, 270: 1811-5. <http://amedeo.com/lit.php?id=8525373>
19. Collins KL, Chen BK, Walker BD, Baltimore D. HIV-1 nef protein protects infected primary cells against killing by cytotoxic T lymphocytes. *Nature* 1998, 391: 397-401. <http://amedeo.com/lit.php?id=9450757>
20. Dalgleish AG, Beverley PC, Clapham PR, et al. The CD4 (T4) antigen is an essential component of the receptor for the AIDS retrovirus. *Nature* 1984, 312: 763-7. <http://amedeo.com/lit.php?id=6096719>
21. Dean M, Carrington M, Winkler C, et al. Genetic restrictions of HIV-1 infection and progression to AIDS by a deletion allele of the CKR5 structural gene. *Science* 1996, 273: 1856-62. <http://amedeo.com/lit.php?id=8791590>
22. Deng H, Liu R, Ellmeier W, et al. Identification of a major co-receptor for primary isolates of HIV-1. *Nature* 1996, 381: 661-6. <http://amedeo.com/lit.php?id=8649511>
23. Deng HK, Unutmaz D, Kewalramani VN, Littman DR. Expression cloning of new receptors used by simian and human immunodeficiency viruses. *Nature* 1997, 388: 296-300. <http://amedeo.com/lit.php?id=9230441>
24. Derdeyn CA, Decker JM, Bibollet-Ruche F, et al. Envelope-constrained neutralization-sensitive HIV-1 after heterosexual transmission. *Science* 2004; 303: 2019-22. <http://amedeo.com/lit.php?id=15044802>
25. Dion ML, Poulin JF, Bordi R et al. HIV infection rapidly induces and maintains a substantial suppression of thymocyte proliferation. *Immunity* 2004; 21: 757-68
26. Doranz BJ, Rucker J, Yi Y, et al. A dual-tropic primary HIV-1 isolate that uses fusin and the  $\beta$ -chemokine receptors CKR-5, CKR-3, and CKR-2b as fusion cofactors. *Cell* 1996, 85: 1149-58. <http://amedeo.com/lit.php?id=8674120>
27. Douek DC, Betts MR, Hill BJ et al. Evidence for increased T cell turnover and decreased thymic output in HIV infection. *J Immunol* 2001; 167: 6663-8

## 84 Pathogenesis of HIV-1 Infection

28. Douek DC, Brenchley JM, Betts MR et al. HIV preferentially infects HIV-specific CD4 T cells. *Nature* 2002; 417: 95-98
29. Dragic T, Litwin V, Allaway GP, et al. HIV-1 entry into CD4+ cells is mediated by the chemokine receptor CC-CKR-5. *Nature* 1996, 381: 667-73. <http://amedeo.com/lit.php?id=8649512>
30. Edwards TG, Hoffman TL, Baribaud F, et al. Relationships between CD4 independence, neutralization sensitivity and exposure of a CD4-induced epitope in an HIV-1 envelope protein. *J Virol* 2001, 75:5230-9. <http://amedeo.com/lit.php?id=11333905>
31. Embretson J, Zupancic M, Ribas JL, et al. Massive covert infection of helper T lymphocytes and macrophages by HIV during the incubation period of AIDS. *Nature* 1993, 362: 359-62. <http://amedeo.com/lit.php?id=8096068>
32. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. *Nat Med* 2005; 11: 1170-2. Epub 2005 Oct 5. <http://amedeo.com/lit.php?id=16205738>
33. Feng Y, Broder CC, Kennedy PE, Berger EA. HIV-1 entry cofactor: functional cDNA cloning of a seven-transmembrane, G protein-coupled receptor. *Science* 1996, 272: 872-7. <http://amedeo.com/lit.php?id=8629022>
34. Ferrantelli F, Rasmussen RA, Buckley KA et al. Complete protection of neonatal rhesus macaques against oral exposure to pathogenic simian-human immunodeficiency virus by human anti-HIV monoclonal antibodies. *J Infect Dis* 2004; 189: 2167-2173
35. Friedrich TC, Dodds EJ, Yant LJ, et al. Reversion of CTL escape-variant immunodeficiency viruses in vivo. *Nat Med* 2004; 10: 275-81. Epub 2004 Feb 15. <http://amedeo.com/lit.php?id=14966520>
36. Gallo RC, Sarin PS, Gelmann EP, et al. Isolation of human T cell leukemia virus in acquired immune deficiency syndrome (AIDS). *Science* 1983, 220: 865-7. <http://amedeo.com/lit.php?id=6601823>
37. Ganesh L, Burstein E, Guha-Niyogi A et al. The gene product murr1 restricts HIV-1 replication in resting CD4+ lymphocytes. *Nature* 2003; 426: 853-857
38. Geijtenbeek TB, Torensma R, van Vliet SJ, et al. Identification of DC-SIGN, a novel dendritic cell-specific ICAM-3 receptor that supports primary immune responses. *Cell* 2000, 100: 575-85. <http://amedeo.com/lit.php?id=10721994>
39. Gelderblom HR, Gentile M, Scheidler A, Özel M, Pauli G. Zur Struktur und Funktion bei HIV. *AIFO* 1993, 5: 231.
40. Goulder PJ, Phillips RE, Colbert RA, et al. Late escape from an immunodominant cytotoxic T-lymphocyte response associated with progression to AIDS. *Nat Med* 1997, 3: 212-7. <http://amedeo.com/lit.php?id=9018241>
41. Harari A, Rizzardi GP, Ellefsen K et al. Analysis of HIV-1 and CMV specific memory CD4 T cell responses during primary and chronic infection. *Blood* 2002; 100: 1381-1387
42. Hogervorst E, Jurriaans S, de Wolf F, et al. Predictors for non-and slow progression in HIV type 1 infection: low viral RNA copy numbers in serum and maintenance of high HIV-1 p24-specific but not V3-specific antibody levels. *J Infect Dis* 1995, 171: 811-21. <http://amedeo.com/lit.php?id=7706807>
43. Jacobson JM. Passive immunization for the treatment of HIV infection. *Mt Sinai J Med* 1998; 65: 22 – 26.
44. Kaslow RA, Carrington M, Apple R, et al. Influence of combinations of human major histocompatibility complex genes on the course of HIV-1 infection. *Nat Med* 1996; 2: 405-11. <http://amedeo.com/lit.php?id=8597949>
45. Kaul R, Rowland-Jones SL, Kimani J, et al. New insights into HIV-1 specific cytotoxic T-lymphocyte responses in exposed, persistently seronegative Kenyan sex workers. *Immunol Lett* 2001, 79: 3-13. <http://amedeo.com/lit.php?id=11595284>
46. Keet IP, Tang J, Klein MR, et al. Consistent associations of HLA class I and II and transporter gene products with progression of HIV type 1 infection in homosexual men. *J Infect Dis* 1999, 180: 299-309. <http://amedeo.com/lit.php?id=10395843>
47. Kilby JM, Hopkins S, Venetta TM, et al. Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. *Nat Med* 1998, 4: 1302-7. <http://amedeo.com/lit.php?id=9809555>
48. Kirchhoff F, Greenough TC, Brettler DB, Sullivan JL, Desrosiers RC. Brief report: Absence of intact nef sequences in a long-term survivor with nonprogressive HIV-1 infection. *N Engl J Med* 1995, 332: 228-32
49. Klatzmann D, Champagne E, Chamaret S, et al. T-lymphocyte T4 molecule behaves as the receptor for human retrovirus LAV. *Nature* 1984, 312: 767-8. <http://amedeo.com/lit.php?id=6083454>
50. Kohl NE, Emimi EA, Schleif WA, et al. Active HIV protease is required for viral infectivity. *Proc Natl Acad Sci USA*, 1988, 85: 4686-90. <http://amedeo.com/lit.php?id=3290901>
51. Leslie AJ, Pfafferott KJ, Chetty P, et al. HIV evolution: CTL escape mutation and reversion after transmission. *Nat Med* 2004; 10: 282-9. Epub 2004 Feb 8. <http://amedeo.com/lit.php?id=14770175>

52. Levy JA, Mackewicz CE, Barker E. Controlling HIV pathogenesis: the role of the noncytotoxic anti-HIV response of CD8+ T cells. *Immunol Today* 1996, 17: 217-24. <http://amedeo.com/lit.php?id=8991383>
53. Liao F, Alkhatib G, Peden KWC, Sharma G, Berger EA, Farber JM. STRL-33, a novel chemokine receptor-like protein, functions as a fusion cofactor for both macrophage-tropic and T cell line-tropic HIV-1. *J Exp Med* 1997, 185: 2015-23. <http://amedeo.com/lit.php?id=9166430>
54. Lichtenfeld M, Yu XG, Waring MT et al. HIV-1 specific cytotoxicity is preferentially mediated by a subset of CD8+ T cells producing both interferon gamma and tumor necrosis factor alpha. *J Exp Med* 2004, 194, 487-494
55. Liu R, Paxton WA, Choe S, et al. Homozygous defect in HIV-1 coreceptor accounts for resistance of some multiply-exposed individuals to HIV-1 infection. *Cell* 1996, 86: 367-77. <http://amedeo.com/lit.php?id=8756719>
56. Liu SL, Schacker T, Musey L, et al. Divergent patterns of progression to AIDS after infection from the same source: HIV type 1 evolution and antiviral responses. *J Virol* 1997, 71: 4284-95. <http://amedeo.com/lit.php?id=9151816>
57. Lockett SF, Robertson JR, Brettle RP, et al. Mismatched human leukocyte antigen alleles protect against heterosexual HIV transmission. *J Acq Imm Defic Syndr* 2001; 27: 277-80. <http://amedeo.com/lit.php?id=11464148>
58. Lu W, Wu X, Lu Y, Guo W, Andrieu JM. Therapeutic dendritic-cell vaccine for simian AIDS. *Nat Med* 2003; 9: 13-14
59. Lu W, Arraes LC, Ferreira WT, Andrieu JM. Therapeutic dendritic-cell vaccine for chronic HIV-1 infection. *Nat Med* 2004; 10: 1359-65. Epub 2004 Nov 28. <http://amedeo.com/lit.php?id=15568033>
60. Mariani R, Chen D, Schröfelbauer B et al. Species-specific exclusion of APOBEC3G from HIV-1 virions by vif. *Cell* 2003; 114: 21-31
61. Martin MP, Gao X, Lee JH, et al. Epistatic interaction between KIR3DS1 and HLA-B delays the progression to AIDS. *Nat Genet.* 2002, Aug;31(4):429-34. <http://amedeo.com/lit.php?id=12134147>
62. Mazzoli S, Trabattini D, Lo Caputo S, et al. HIV-specific mucosal and cellular immunity in HIV-seronegative partners of HIV-seropositive individuals. *Nat Med* 1997, 3:1250-7. <http://amedeo.com/lit.php?id=9359700>
63. Mehndru S, Poles MA, Tenner-Razc K et al. Primary HIV-1 infection is associated with preferential depletion of CD4 T lymphocytes from effector sites in the gastrointestinal tract. *J Exp Med* 2004; 200: 761-70
64. Miller RH, Sarver N. HIV accessory proteins as therapeutic targets. *Nat Med* 1997, 3: 389-94.
65. Montefiori DC, Pantaleo G, Fink LM, et al. Neutralizing and infection-enhancing antibody responses to HIV type 1 in long-term nonprogressors. *J Infect Dis* 1996, 173: 60-7. <http://amedeo.com/lit.php?id=8537683>
66. Murakami T, Nakajima T, Koyanagi Y, et al. A small molecule CXCR4 inhibitor that blocks T cell line-tropic HIV-1 infection. *J Exp Med* 1997, 186: 1389-93. <http://amedeo.com/lit.php?id=9334379>
67. O'Brien WA, Grovit-Ferbas K, Namazi A, et al. HIV-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. *Blood* 1995, 86: 1082-9. <http://amedeo.com/lit.php?id=7620162>
68. Oh SY, Cruickshank WW, Raina J, et al. Identification of HIV-1 envelope glykoprotein in the serum of AIDS and ARC patients. *J Acquired Immune Defic Syndr* 1992, 5: 251.
69. Olson W, Israel R, Jacobson J et al. Viral resistance and pharmacologic analyses of phase I/II study patients treated with the HIV-1 entry inhibitor PRO542. Abstract 561, 10<sup>th</sup> CROI 2003, Boston. Abstract 561
70. Pal R, Garzino-Demo A, Markham PD, et al. Inhibition of HIV-1 infection by the  $\alpha$ -chemokine MDC. *Science* 1997, 278: 695-8. <http://amedeo.com/lit.php?id=9381181>
71. Pantaleo G, Graziosi C, Demarest JF, et al. HIV infection is active and progressive in lymphoid tissue during the clinically latent stage of disease. *Nature* 1993, 362: 355-8. <http://amedeo.com/lit.php?id=8455722>
72. Peter F. HIV nef: The mother of all evil? *Immunity*, 1998, 9: 433-7.
73. Pinto LA, Sullivan J, Berzofsky JA, et al. Env-specific cytotoxic T lymphocyte responses in HIV seronegative health care workers occupationally exposed to HIV contaminated body fluids. *J Clin Invest* 1995, 96: 867-76. <http://amedeo.com/lit.php?id=7635981>
74. Rosenberg ES, Billingsley JM, Caliendo AM, et al. Vigorous HIV-1-specific CD4 T cell responses associated with control of viremia. *Science* 1997, 278: 1447-50. <http://amedeo.com/lit.php?id=9367954>
75. Saha K, Zhang J, Gupta A et al. Isolation of primary HIV-1 that target CD8+ T lymphocytes using CD8 as a receptor. *Nat Med* 2001, 7: 65-72. <http://amedeo.com/lit.php?id=11135618>

## 86 Pathogenesis of HIV-1 Infection

76. Schmitz JE, Kuroda MJ, Santra S et al. Effect of humoral immune responses on controlling viremia during primary infection of rhesus monkeys with simian immunodeficiency virus. *J Virol* 2003; 77: 2165-2173
77. Schols D, Struyf S, Van Damme J, et al. Inhibition of T-tropic HIV strains by selective antagonization of the chemokine receptor CXCR4. *J Exp Med* 1997, 186: 1383-8. <http://amedeo.com/lit.php?id=9334378>
78. Schroder AR, Shinn P, Chen H, Berry C, Ecker JR, Bushman F. HIV-1 integration in the human genome favors active genes and local hotspots. *Cell* 2002; 110: 521-9. <http://amedeo.com/lit.php?id=12202041>
79. Sheehy AM, Gaddis NC, Choi JD et al. Isolation of a human gene that inhibits HIV-1 infection and is suppressed by the viral vif protein. *Nature* 2002; 418: 646-650 <http://amedeo.com/lit.php?id=12167863>
80. Stremlau M, Owens CM, Perron MJ et al. The cytoplasmic body component TRIM5alpha restricts HIV-1 infection in Old World monkey s. *Nature* 2004; 427: 848-853
81. Sunila I, Vaccarezza M, Pantaleo G, Fauci AS, Orenstein JM. Gp120 is present on the plasma membrane of apoptotic CD4 cells prepared from lymph nodes of HIV-1-infected individuals: an immunoelectron microscopic study. *AIDS* 1997, 11: 27-32. <http://amedeo.com/lit.php?id=9110072>
82. Tenner-Racz K, Stellbrink HJ, van Lunzen J, et al. The unenlarged lymph nodes of HIV-1-infected, asymptomatic patients with high CD4 T cell counts are sites for virus replication and CD4 T cell proliferation. The impact of HAART. *J Exp Med* 1998, 187: 949-59. <http://amedeo.com/lit.php?id=9500797>
83. Trkola A, Kuster H, Rusert P, et al. Delay of HIV-1 rebound after cessation of antiretroviral therapy through passive transfer of human neutralizing antibodies. *Nat Med* 2005; 11: 615-22. Epub 2005 May 8. <http://amedeo.com/lit.php?id=15880120>
84. Turelli P, Mangeat B, Jost S, Vianin S, Trono D. Inhibition of hepatitis B virus replication by APOBEC3G. *Science* 2004; 303: 1829
85. Veazey RS, DeMaria MA, Chailfoux LV et al. Gastrointestinal tract as a major site of CD4 T cell depletion and viral replication in SIV infection. *Science* 1998; 280: 427-31
86. Veazey RS, Klasse PJ, Schader SM, et al. Protection of macaques from vaginal SHIV challenge by vaginally delivered inhibitors of virus-cell fusion. *Nature* 2005; 438: 99-102. Epub 2005 Oct 30. <http://amedeo.com/lit.php?id=16258536>
87. Walker CM, Moody DJ, Stites DP, Levy JA. CD8+ lymphocytes can control HIV infection in vitro by suppressing viral replication. *Science* 1986, 234: 1563-6. <http://amedeo.com/lit.php?id=2431484>
88. Wei P, Garber ME, Fang SM, Fischer WH, Jones KA. A novel CDK9-associated C-type cyclin interacts directly with HIV-1 Tat and mediates its high-affinity, loop-specific binding to TAR RNA. *Cell* 1998, 92: 451-62. <http://amedeo.com/lit.php?id=9491887>
89. Winkler C, Modi W, Smith MW, et al. Genetic restriction of AIDS pathogenesis by an SDF-1 chemokine gene variant. *Science* 1998, 279: 389-93. <http://amedeo.com/lit.php?id=9430590>
90. Wong MT, Warren RQ, Anderson SA, et al. Longitudinal analysis of the humoral immune response to HIV type 1 gp160 epitopes in rapidly progressing and nonprogressing HIV-1 infected subjects. *J Infect Dis* 1993, 168: 1523-7. <http://amedeo.com/lit.php?id=7504036>
91. Wong-Staal F. HIVs and their replication. In: *Fundamental Virology*, Ed.: Fields BN, Knipe DM et al. Raven Press, Ltd., New York 1991.
92. Zack JA, Arrigo SJ, Weitsman SR, Go AS, Haislip A, Chen ISY. HIV-1 entry into quiescent primary lymphocytes: Molecular analysis reveals a labile, latent viral structure. *Cell* 1990, 61: 213-22. <http://amedeo.com/lit.php?id=2331748>
93. Zhang L, Yu W, He T et al. Contribution of human alpha-defensin 1, 2, and 3 to the anti-HIV-1 activity of CD8 antiviral factor. *Science* 2002, 298: 995-1000.
94. Zou YR, Kottmann AH, Kuroda M, Taniuchi I, Littman DR. Function of the chemokine receptor CXCR4 in haematopoiesis and in cerebellar development. *Nature* 1998, 393: 595-9. <http://amedeo.com/lit.php?id=9634238>

Part 2

HAART





## 5. ART 2006

### 1. Perspective

Christian Hoffmann, Fiona Mulcahy

The development of antiretroviral therapy has been one of the most dramatic progressions in the history of medicine. Few other areas have been subject to such fast- and short-lived trends. Those who have experienced the rapid developments of the last few years have been through many ups and downs.

The early years, from 1987-1990, brought great hope and the first modest advances using monotherapy (Volberding 1990, Fischl 1990). But, by the time the results of the Concorde Study had arrived (Hamilton 1992, Concorde 1994), both patients and clinicians had plunged into a depression that was to last for several years. Zidovudine was first tested on humans in 1985, and introduced as a treatment in March 1987 with great expectations. Initially, at least, it did not seem to be very effective. The same was true for the nucleoside analogs zalcitabine, didanosine and stavudine, introduced between 1991 and 1994. The lack of substantial treatment options led to a debate that lasted for several years about which nucleoside analogs should be used, when, and at what dose. One such question was: Should the alarm clock be set to go off during the night for a sixth dose of zidovudine?

Many patients, who were infected during the early and mid-80s, began to die. Hospices were established, as well as more and more support groups and ambulatory nursing services. One became accustomed to AIDS and its resulting death toll. There was, however, definite progress in the field of opportunistic infections (OI) – cotrimoxazole, pentamidine, ganciclovir, foscarnet and fluconazole saved many patients’ lives, at least in the short-term. Some clinicians started to dream of a kind of “mega-prophylaxis”. But the general picture was still tainted by an overall lack of hope. Many remember the somber, almost depressed mood of the IX<sup>th</sup> World AIDS Conference in Berlin, in June 1993. Between 1989 and 1994, morbidity and mortality rates were hardly affected.

Then, in September 1995, the preliminary results of the European-Australian DELTA Study (Delta 1995) and the American ACTG 175 Study (Hammer 1996) attracted attention. It became apparent that combination therapy with two nucleoside analogs was more effective than monotherapy. Indeed, the differences made on the clinical endpoints (AIDS, death) were highly significant. Both studies demonstrated that it was potentially of great importance to immediately start treatment with two nucleoside analogs, as opposed to using the drugs “sequentially”.

This was by no means the final breakthrough. By this time, the first studies with protease inhibitors (PIs), a completely new drug class, had been ongoing for several months. PIs had been designed in the lab using the knowledge of the molecular structure of HIV and protease – their clinical value was initially uncertain. Preliminary data, and many rumors, were already in circulation. In the fall of 1995, a fierce competition started up between three companies: Abbott, Roche and MSD. The licensing studies for the three PIs, ritonavir, saquinavir and indinavir, were pursued with a great amount of effort, clearly with the goal of bringing the first PI onto the

market. The monitors of these studies in the different companies “lived” for weeks at the participating clinical sites. Deep into the night, case report files had to be perfected and thousands of queries answered. All these efforts led to a fast track approval, between December 1995 and March 1996, for all three PIs – first saquinavir, followed by zidovudine and didanosine – for the treatment of HIV.

Many clinicians (including the author) were not really aware at the time of what was happening during these months. AIDS remained ever present. Patients were still dying, as only a relatively small number were participating in the PI trials – and very few were actually adequately treated by current standards. Doubts remained. Hopes had already been raised too many times in the previous years by alleged miracle cures. Early in January 1996, other topics were more important: palliative medicine, treatment of CMV, MAC and AIDS wasting syndrome, pain management, ambulatory infusion therapies, even euthanasia.

In February 1996, during the 3<sup>rd</sup> Conference on Retroviruses and Opportunistic Infections (CROI) in Washington, many caught their breath as Bill Cameron reported the first data from the ABT-247 Study during the late breaker session. The auditorium was absolutely silent. Riveted, listeners heard that the mere addition of zidovudine oral solution decreases the frequency of death and AIDS from 38 % to 22 % (Cameron 1998). These were sensational results in comparison to everything else that had been previously published!

But for many, the combination therapies that became widely used from 1996 onwards still came too late. Some severely ill patients with AIDS managed to recover during these months, but, even in 1996, many still died. Although the AIDS rate in large centers had been cut in half between 1992 and 1996 (Brodt 1997), in smaller centers roughly every fifth patient died in this year.

However, the potential of the new drugs was slowly becoming apparent, and the World AIDS Conference in Vancouver a few months later, in June 1996, was like a big PI party. Even regular news channels reported in great depth on the new “AIDS cocktails”. The strangely unscientific expression “highly active antiretroviral therapy” (HAART) began to spread irreversibly. Clinicians were only too happy to become infected by this enthusiasm.

By this time, David Ho, Time magazine’s “Man of the Year” in 1996, had shed light on the hitherto completely misunderstood kinetics of HIV with his breakthrough research (Ho 1995, Perelson 1996). A year earlier, Ho had already initiated the slogan “hit hard and early”, and almost all clinicians were now taking him by his word. With the new knowledge of the incredibly high turnover of the virus and the relentless daily destruction of CD4+ T-cells, there was no longer any consideration of a “latent phase” – and no life without antiretroviral therapy. In many centers almost every patient was treated with HAART. Within only three years, from 1994-1997, the proportion of untreated patients in Europe decreased from 37 % to barely 9 %, whilst the proportion of HAART patients rose from 2 % to 64 % (Kirk 1998).

Things were looking good. By June 1996, the first non-nucleoside reverse transcriptase inhibitor, nevirapine, was licensed, and a third drug class introduced. Nelfinavir, another PI, also arrived. Most patients seemed to tolerate the drugs well. 30 pills a day? No problem, if it helps. And how it helped! The number of AIDS cases was drastically reduced. Within only four years, between 1994 and 1998, the incidence of AIDS in Europe was reduced from 30.7 to 2.5 per 100 patient years – i.e.

to less than a tenth. The reduction in the incidence of several feared OIs, particularly CMV and MAC, was even more dramatic. HIV ophthalmologists had to look for new areas of work. The large OI trials, planned only a few months before, faltered due to a lack of patients. Hospices, which had been receiving substantial donations, had to shut down or reorientate themselves. The first patients began to leave the hospices, and went back to work; ambulatory nursing services shut down. Other patients occupied AIDS wards.

In 1996 and 1997, some patients began to complain of an increasingly fat stomach, but was this not a good sign after the years of wasting and supplementary nutrition? Not only did the PIs contain lactose and gelatin, but also the lower viremia was thought to use up far less energy. It was assumed that, because patients were less depressed and generally healthier, they would eat more. At most, it was slightly disturbing that the patients retained thin faces. However, more and more patients also began to complain about the high pill burden.

In June 1997, the FDA published the first warning about the development of diabetes mellitus associated with the use of PIs (Ault 1997). In February 1998, the CROI in Chicago finally brought home the realization among clinicians that protease inhibitors were perhaps not as selective as had long been believed. One poster after the next, indeed whole walls of pictures showed fat abdomens, buffalo humps, thin legs and faces. A new term was introduced at the beginning of 1998, which would influence the antiretroviral therapy of the years to come: lipodystrophy. And so the old medical wisdom was shown to hold true even for HAART: all effective drugs have side effects. The actual cause of lipodystrophy remained completely unclear. Then, in early 1999, a new hypothesis emerged from the Netherlands: “mitochondrial toxicity”. It has become a ubiquitous term in HIV medicine today.

The dream of eradication (and a cure), still widely hoped for in the beginning, also had to be abandoned eventually. Mathematical models are evidently not suitable for predicting what will really happen. In 1997, it was still estimated that viral suppression, with a maximum duration of three years, was necessary; after this period, it was predicted that all infected cells would presumably have died. Eradication was the magic word. At every conference since then, the duration of three years has been adjusted upwards. Nature is not so easy to predict, and more recent studies have come to the sobering conclusion that HIV remains detectable in latent infected cells, even after long-term suppression. To date, nobody knows how long these latent infected cells survive, and whether even a small number of them would be sufficient for the infection to flare up again as soon as treatment is interrupted. Finally, during the Barcelona World AIDS Conference, experts in the field admitted to bleak prospects for eradication. The most recent estimate for eradication of these cells stands at 73.3 years (Siciliano 2003). HIV will not be curable within the next few years. The latent reservoirs will not simply let themselves be wiped out, and even the many observed trials from recent years with valproic acid are unlikely to change this (Lehrman 2005).

Instead of eradication, it is currently more realistic to consider that HIV infection is a chronic disease which, although incurable, is controllable lifelong with therapy. This means, however, that drugs have to be administered over many years, which demands an enormous degree of discipline from patients. Those who are familiar with the management of diabetes understand the challenges that patients and clini-

cians have to face and how important it will be to develop better combinations in the coming years. Not many people will be in the position to take the currently available pills several times daily at fixed times for the next twenty or thirty years. But this will also not be necessary. There will be new and improved treatment regimens. Once-daily regimens are already available; maybe even once-weekly treatments will be developed. New classes of drugs are appearing. Coreceptor antagonists, as well as attachment-, integrase-, and maturation inhibitors opened up fascinating new possibilities in 2005. These novel drug classes may lead to other problems, but will certainly not cause lipodystrophy. It is possible, that they will either entirely or at least partially replace the current antiretroviral therapy.

At the same time, the knowledge of the risks of antiretroviral therapy has changed the approach of many clinicians towards treatment in recent years. In 2000, many strict recommendations from previous years were already being revised. Instead of “hit hard and early”, today we hear “hit HIV hard, but only when necessary” (Harrington 2000). The simple question of “when to start?” is now being addressed at long symposia. It is a question that requires great sensitivity.

Despite all the worries about possible side effects, it is important not to forget what HAART can do. HAART can often achieve miracles! Cryptosporidiosis and Kaposi's sarcoma simply disappear; even such a terrible disease as PML can be cured completely; secondary prophylaxis for CMV can be stopped; and above all: patients feel significantly better, even if some activists still do not want to admit this.

HIV clinicians are well advised to keep an open mind for new approaches. Those, who do not make an effort to broaden their knowledge several times a year at different conferences, will not be able to provide adequate treatment for their patients in a field that changes direction at least every two to three years. Those who adhere strictly to evidence-based HIV medicine, and only treat according to guidelines, quickly become outdated. HIV medicine is ever changing. Treatment guidelines remain just guidelines. They are often out of date by the time of publication. There are no laws set in stone. Articles on HIV that refer only to stolid terms such as “unavoidable” or “essential” can be confidently disposed of. However, those who confuse therapeutic freedom with random choices, and assume that data and results coming from basic research can be ignored, are also missing the point. Individualized treatment is not random treatment. In addition, it cannot be stressed enough, that clinicians are also responsible for the problem of bad compliance. Even if many experienced clinicians have come to disregard this: every patient has the right to know why he is taking which therapy or, indeed, why it has been omitted.

HIV remains a dangerous and cunning opponent. Patients and clinicians must tackle it together. The following describes how this can be done.

## References

1. Ault A. FDA warns of potential protease-inhibitor link to hyperglycaemia. *Lancet* 1997, 349:1819.
2. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999, 354:1112-5. <http://amedeo.com/lit.php?id=10509516>
3. Brodt HR, Kamps BS, Gute P, et al. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. *AIDS* 1997, 11:1731-8. <http://amedeo.com/lit.php?id=9386808>
4. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998, 351:543-9. <http://amedeo.com/lit.php?id=9492772>

5. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994, 343:871-81. <http://amedeo.com/lit.php?id=7908356>
6. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996, 348: 283-91. <http://amedeo.com/lit.php?id=8709686>
7. Fischl MA, Parker CB, Pettinelli C, et al. A randomized controlled trial of a reduced daily dose of zidovudine in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1990; 323:1009-14. <http://amedeo.com/lit.php?id=1977079>
8. Gulick RM, Mellors JW, Havlir D, et al. 3-year suppression of HIV viremia with indinavir, zidovudine, and lamivudine. *Ann Intern Med* 2000, 133:35-9. <http://amedeo.com/lit.php?id=10877738>
9. Hamilton JD, Hartigan PM, Simberkoff MS, et al. A controlled trial of early versus late treatment with zidovudine in symptomatic HIV infection. *N Engl J Med* 1992, 326:437-43. <http://amedeo.com/lit.php?id=1346337>
10. Hammer SM, Katzenstein DA, Hughes MD et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500 per cubic millimeter. *N Engl J Med* 1996, 335:1081-90. <http://amedeo.com/lit.php?id=8813038>
11. Harrington M, Carpenter CC. Hit HIV-1 hard, but only when necessary. *Lancet* 2000, 355:2147-52. <http://amedeo.com/lit.php?id=10902643>
12. Ho DD. Time to hit HIV, early and hard. *N Engl J Med* 1995, 333:450-1.
13. Ho DD, Neumann AU, Perelson AS, Chen W, Leonard JM, Markowitz M. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995, 373:123-6. <http://amedeo.com/lit.php?id=7816094>
14. Kirk O, Mocroft A, Katzenstein TL, et al. Changes in use of antiretroviral therapy in regions of Europe over time. *AIDS* 1998, 12: 2031-9. <http://amedeo.com/lit.php?id=9814872>
15. Lehrman G, Hogue IB, Palmer S, et al. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. *Lancet* 2005, 366:549-55. <http://amedeo.com/lit.php?id=16099290>
16. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. *Lancet* 2000, 356:291-6. <http://amedeo.com/lit.php?id=11071184>
17. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996, 271:1582-6. <http://amedeo.com/lit.php?id=8599114>
18. Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nature Med* 2003;9:727-728. <http://amedeo.com/lit.php?id=12754504>
19. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic HIV infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *N Engl J Med* 1990, 322:941-9. <http://amedeo.com/lit.php?id=1969115>

## 2. Overview of antiretroviral agents

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Table 2.1: Antiretroviral agents

Trade name	Abbrev.	Drug	Manufacturer
<b>Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (NRTIs)</b>			
Combivir™	CBV	AZT+3TC	GSK
Emtriva™	FTC	Emtricitabine	Gilead
Epivir™	3TC	Lamivudine	GSK
HIVID™*	ddC	Zalcitabine	Roche
Kivexa/Epizicom™	KVX	3TC+ABC	GSK
Retrovir™	AZT	Zidovudine	GSK
Trizivir™	TZV	AZT+3TC+ABC	GSK
Truvada™	TVD	FTC+TDF	Gilead
Videx™	ddl	Didanosine	BMS
Viread™	TDF	Tenofovir	Gilead
Zerit™	d4T	Stavudine	BMS
Ziagen™	ABC	Abacavir	GSK
<b>Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTIs)</b>			
Rescriptor™	DLV	Delavirdine	Pfizer
Sustiva/Stocrin™	EFV	Efavirenz	BMS/MSD
Viramune™	NVP	Nevirapine	Boehringer Ingelheim
<b>Protease Inhibitors (PIs)**</b>			
Aptivus™	TPV	Tipranavir	Boehringer-Ingelheim
Agenerase™	APV	Amprenavir	GSK
Crixivan™	IDV	Indinavir	MSD
Invirase 500™	SQV	Saquinavir	Roche
Kaletra™	LPV	Lopinavir/ritonavir	Abbott
Norvir™	RTV	Ritonavir	Abbott
Reyataz™	ATV	Atazanavir	BMS
Telzir/Lexiva™	FPV	Fosamprenavir	GSK
Viracept™	NFV	Nelfinavir	Roche/Pfizer
<b>Fusion inhibitors</b>			
Fuzeon™	T-20	Enfuvirtide	Roche

\*Distribution ceased.

Four classes of drugs are currently available: nucleoside and nucleotide analogs (NRTIs or “nukes”), non-nucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors (PIs) and the fusion inhibitor T-20. Over 20 drug products have now been licensed, including formulations of both individual and combined antiretroviral agents. Licensing of a number of other drugs and new classes of drugs can be expected in the next few years. Related research is also focusing on immunomodulatory approaches with vaccines or cytokines.

The following chapter provides an overview of antiretroviral agents and their specific features and problems. Common combinations are described in the chapter on “Which HAART to Start With”.

## Nucleoside analogs (“nukes”, NRTIs)

### Mechanism of action

Nucleoside analogs (“nukes”) are also referred to as nucleoside reverse transcriptase inhibitors. Their target is the HIV enzyme reverse transcriptase. Acting as alternative substrates, they compete with physiological nucleosides, differing from them only by a minor modification in the ribose molecule. The incorporation of nucleoside analogs induces the abortion of DNA synthesis, as phosphodiester bridges can no longer be built to stabilize the double strand.

Nucleoside analogs are converted to the active metabolite only after endocytosis, whereby they are phosphorylated to triphosphate derivatives. AZT and d4T are thymidine analogs, while ddC, FTC and 3TC are cytidine analogs. Combinations containing AZT plus d4T, ddC plus 3TC or FTC plus 3TC are therefore pointless, since both drugs would compete for the same bases. ddI is an inosine analog, which is converted to dideoxyadenosine; abacavir is a guanosine analog. There is a high degree of cross-resistance between nucleoside analogs (see also “Resistance” chapter).

Nucleoside analogs are easy to take, and once-daily dosing is sufficient for most. Overall tolerability is fairly good. However, frequent complaints during the first weeks are fatigue, headache and gastrointestinal problems, which range from mild abdominal discomfort to nausea, vomiting and diarrhea. The gastrointestinal complaints are easily treated symptomatically (see “Side Effects”).

However, nucleoside analogs can cause a wide variety of long-term side effects, including myelotoxicity, lactate acidosis, polyneuropathy and pancreatitis. Although lipodystrophy was initially linked exclusively to treatment with protease inhibitors, many disorders of lipid metabolism (especially lipodystrophy) are now also attributed to nucleoside analogs (Galli 2002). Long-term side effects that are probably related to mitochondrial toxicity were first described in 1999 (Brinkmann 1999). Mitochondrial function requires nucleosides. The metabolism of these important organelles is disrupted by the incorporation of false nucleosides, leading to mitochondrial degeneration. More recent clinical and scientific data indicates that there are probably considerable differences between individual drugs with regard to mitochondrial toxicity: d4T is, for example, more toxic than abacavir. For further details see “Mitochondrial toxicity”.

Nucleoside analogs are eliminated mainly by renal excretion and do not interact with drugs that are metabolized by hepatic enzymes. There is therefore little potential for interaction. However, ribavirin, for example, can also reduce intracellular phosphorylation of AZT or d4T (Piscitelli 2001).

### Individual agents: Special features and problems

**Abacavir (Ziagen™)** is a guanosine analog with good CNS penetration. Earlier studies have shown that this drug can lower viral load by approximately 1.4 logs within 4 weeks, but that resistance develops relatively rapidly (Harrigan 2000). Abacavir is phosphorylated intracellularly to carbovir triphosphate, which has a

long half-life (Harris 2002). In October 2004, following larger studies, abacavir was licensed for once-daily therapy (Clumeck 2004, Moyle 2005, Sosa 2005).

Abacavir is also a component of Trizivir™, together with AZT+3TC, and numerous studies have therefore tested abacavir in this combination (see Triple Nuke). In the 5095 Study, the combination proved virologically less effective than efavirenz plus AZT+3TC (Gulick 2004). The randomized, double blind CNA3005 Study had also shown lower efficacy in comparison to indinavir, particularly with higher viral load (Staszewski 2001). However, abacavir was more effective than indinavir in the randomized, open label CNA3014 Study, due to better compliance (Vibhagool 2004). In another study, efficacy was comparable to nelfinavir (Matheron 2003). Abacavir, in addition to 3TC, is also a component of Kivexa™. The nucleoside backbone of abacavir+3TC is about as effective as AZT+3TC (DeJesus 2004) and d4T+3TC (Podzamczar 2004), although it causes less lipodystrophy than the latter.

Several studies, such as CNA3002 and CNA3009, have shown that a regimen that is failing virologically can be successfully intensified with abacavir if it is added early enough, and if the viral load is not too high (Katlama 2000, Rozenbaum 2001). Abacavir is also frequently used to replace a PI or NNRTI in order to simplify HAART. Several studies such as TRIZAL, NEFA, CNA30017 and Simplify-HAART have demonstrated that patients on a successful PI- or NNRTI-containing HAART regimen can switch relatively safely to abacavir plus two other nucleoside analogs (Clumeck 2001, Katlama 2003, Martinez 2003, Bonjoch 2004). However, there is a certain degree of risk associated with this strategy, because, particularly in extensively pretreated patients, it can cause virological failure (Opravil 2002, Martinez 2003). Caution must be taken when combining tenofovir with 3TC as resistance mutations can rapidly develop (see section on “Triple Nuke”).

With respect to mitochondrial toxicity, abacavir seems to compare favorably to d4T. However, switching from d4T to abacavir led to moderate changes at best and sometimes only subclinical effects in cases with existing lipodystrophy (Carr 2002, John 2003, Moyle 2003, McComsey 2005). In vitro studies also confirm that improvement of lipoatrophy is associated with an increase in mitochondrial DNA (Hoy 2004, Martin 2004, McComsey 2004+2005).

One drawback to the use of abacavir is the risk of a hypersensitivity reaction (HSR). This occurs in 4-6 % of patients, almost always (93 %) within the first six weeks of treatment. Every treating physician should be familiar with this syndrome. In acutely infected HIV patients, the risk seems to be significantly higher (up to 18 %), and abacavir should generally be avoided (Stekler 2004). On re-exposure, HSR can even be fatal. Cases of severe HSR have been reported after only a single abacavir tablet (De la Rosa 2004) or even after treatment interruption despite prior tolerability (El-Sahly 2004). The combination of strongly worded warnings contained in the package insert and the unspecific symptoms of HSR poses a constant challenge to the treating physician. A genetic predisposition probably exists, so that patients with HLA type B5701 are at a higher risk than others (Mallal 2002, Hetherington 2002). It is possible that the HSR occurs more frequently on once-daily administration of abacavir than with twice-daily dosing (Goedken 2005).

**AZT – Zidovudine (Retrovir™)** was the first antiretroviral agent to be put on the market, in 1987. Even very early studies still testing AZT monotherapy were able to show a significant survival benefit – at least in significantly immunocompromised



patients (Fischl 1987). In contrast, two other early, very large studies, ACTG 016 and ACTG 019, were not able to demonstrate significant survival benefit (in asymptomatic patients), although the risk for progression was significantly reduced in both (Fischl 1990b, Volberding 1990). Even at that time, it started to become apparent that the success of AZT monotherapy was likely to be limited. The Concorde Study has even brought AZT from time to time into disrepute by showing that there was no long-term benefit of AZT treatment. In addition, the higher doses that were given in these first few years led to considerable myelotoxicity (Fischl 1990a), something which should also not be underestimated for the standard current doses.

This is the reason why, even today, monitoring of blood count is obligatory whilst on AZT. Long-term treatment almost always increases MCV (mean corpuscular volume of erythrocytes), which in turn is suitable as a means of controlling adherence. Initial gastrointestinal complaints may present a problem. AZT-related myopathy or even cardiomyopathy is quite rare. AZT seems to have a more favorable profile with regard to long-term toxicity. Lack of neurotoxicity and good CNS penetration are advantages of this drug. One disadvantage of AZT is that it has to be taken twice daily, disqualifying it as a substance for once-daily combinations. Furthermore, AZT finally came under distinct pressure when, in the Gilead 934 study, it scored significantly worse than tenofovir, mainly due to poorer tolerability (Galant 2006).

At present, AZT remains a component of many HAART regimens and transmission prophylaxes. AZT is also a component of both Combivir™ and Trizivir™, at a slightly higher dose (300 mg instead of 250 mg). This may occasionally lead to higher myelotoxicity and therefore anemia. It is also of note that the patent protection of AZT has expired, so that AZT could soon become much cheaper.

**ddC - Zalcitabine (HIVID™)** was the third nucleoside analog to reach the market in 1992. Cross-resistance with ddI and 3TC, unfavorable pharmacokinetics, problems with peripheral neuropathy, stomatitis, and lack of data in the HAART era, have had the effect that ddC is hardly ever used now. It will be withdrawn from the market in June 2006.

**ddI – Didanosine (Videx™)** was, in 1991, the second nucleoside analog to be licensed. The introduction of acid-resistant tablets, which, in 2000, replaced the chewable tablets used for many years, improved tolerability significantly. Randomized studies such as Delta 1, ACTG 175 and CPCRA007 showed improvement in survival rates of treatment-naïve patients with AZT+ddI compared to AZT monotherapy. This effect was less marked in AZT-pretreated patients. Therefore, the addition of ddI in Delta 2 led to significant survival benefit, although this was not the case in CPCRA007 (Saravolatz 1996). In ACTG 175, monotherapy with ddI was more potent than AZT, even with regard to disease progression (Hammer 1996). However, this advantage for ddI could not be shown in other studies (Dolin 1995, Florida 1997). Following failure of AZT, ddI is probably more effective than d4T (Havliir 2000).

Gastrointestinal complaints and polyneuropathy are the main side effects. Pancreatitis is more specific, occurring in up to 10 %, and can be fatal in individual cases. This toxicity is probably dose-dependent (Jablonowski 1995). The cause for this is unclear, but could possibly be related to disorders of purine metabolism (Moyle 2004). Special caution should be given to combinations with d4T, hydroxyurea or

tenofovir (Havlir 2001, Martinez 2004). Patients with a history of pancreatitis should not be treated with ddI. If the body weight is less than 60 kg, the dose should be reduced from 400 mg to 300 mg. Combination with tenofovir should be avoided for various reasons (see especially the section “Problems with Initial Therapies”), as well as the combination with the HCV drug ribavirin. Combination with d4T is no longer recommended, at least in primary therapy.

ddI has to be taken under fasting conditions. In the last few years, the drug has significantly lost its attractiveness due to its toxicity. Today, it is only used for certain resistance situations (Molina 2005).

**d4T – Stavudine (Zerit™)** was the second thymidine analog to be introduced after AZT. It is often initially tolerated better (less gastrointestinal side effects and limited myelotoxicity), is definitely just as effective as AZT (Spruance 1997, Squires 2000), and used to be one of the most frequently prescribed antiretroviral agents of all. However, several randomized studies have since placed the drug under a lot of pressure. In the Gilead 903 Study, d4T was tested in a double blind design against tenofovir (combined with 3TC+efavirenz) in treatment-naïve patients. Both drugs showed comparable efficacy, but d4T had a much worse tolerability, particularly with respect to mitochondrial toxicity and lipid changes (Gallant 2004). In fact, the FTC-301 Study, in which d4T was tested in a double blind design against FTC (both combined with ddI+efavirenz) had to be prematurely terminated, because d4T was not only more toxic, but also significantly weaker than FTC (Saag 2004).

It is now beyond a doubt that lipoatrophy occurs more frequently with d4T than with other nucleoside analogs. The data is depressing: not only laboratory studies (Thompson 2003, Van der Valk 2003, Martin 2004, McComsey 2004), but also clinical observations confirm the mitochondrial toxicity of d4T. A small prospective study showed that d4T was the most important factor contributing to loss of fat tissue on arms and legs (Mallon 2003). In a German cohort, the risk of lipoatrophy on d4T doubled in one year (Mauss 2002); in a Swiss cohort it tripled in two years (Bernasconi 2002). Other data, with one exception (Bogner 2001), points in the same direction (Mallal 2000, Chene 2002, Saves 2002). Numerous studies have now been published in which substitution of d4T with other nucleoside analogs, particularly abacavir or tenofovir, had positive effects on lipoatrophy and other metabolic disorders (Carr 2003, John 2003, Moyle 2003, Martin 2004, McComsey 2004, Suleiman 2004). However, the effect on increases in subcutaneous fat tissue was usually not detectable clinically, only on dexa scan. Thus, it may take years for lipoatrophy to visibly improve following discontinuation of d4T. Therefore, based on current data, there is only one option for patients with lipoatrophy: d4T should be replaced, ideally with abacavir or tenofovir if the resistance profile permits. There is, however, no assurance for resolution of lipoatrophy, and, above all, great patience is required.

Mitochondrial toxicity of d4T also causes problems beyond lipodystrophy. It is a risk factor for lactic acidosis, hyperlactacidemia and Guillain-Barré-like syndromes, particularly in combination with ddI or 3TC, (Gerard 2000, John 2001, Miller 2000, Mokrzycki 2000, Marcus 2002, Shah 2003). Whether these problems will be lessened by the introduction of the new d4T PRC capsules (see “New Drugs”) is questionable.

**FTC - Emtricitabine (Emtriva™)** is a new cytidine analog, which was originally developed under the name Coviracil. It is biochemically very similar to 3TC, but has a longer half-life. Once-daily dosing with 200 mg is possible, and the drug also has HBV efficacy. Tolerability is good, although hyperpigmentation occurred in one study. FTC is more effective than 3TC *in vitro* (Van der Horst 2001), which was recently demonstrated in a small *in vivo* study (Rousseau 2003). However, as with 3TC, efficacy is limited by the M184V point mutation. Subsequent to data from the FTC-301 Study (Saag 2004), which was prematurely discontinued, the drug was swiftly licensed in 2003. This randomized, double blind trial showed that FTC was clearly more effective and tolerable than d4T (both in combination with ddI and efavirenz). The combination of tenofovir+FTC was superior to AZT+3TC in the 24-week analysis of another study, as there was better tolerability (Gazzard 2004). AZT+FTC are as effective as AZT+3TC (Benson 2004). FTC seems to have a low affinity for the mitochondrial polymerase, so the risk of mitochondrial toxicity is likely to be relatively low. The ALIZE study has since confirmed the good long-term tolerability and efficacy of a once-daily combination of FTC+ddI+efavirenz (Molina 2003). FTC is already an important HAART component, particularly of once-daily regimens. In 2005, a fixed-dose combination of FTC and tenofovir (Truvada™) was licensed.

**3TC – Lamivudine (Epivir™)** is a well-tolerated nucleoside analog. Its main disadvantage is rapid development of resistance, and a single point mutation (M184V) is sufficient for loss of effectiveness. As a result, 3TC is weaker than other nucleoside analogs for monotherapy, since resistance is likely to develop after only a few weeks (Eron 1995). The full effect of 3TC only emerges in combination with other nucleoside analogs. Indeed, several large studies such as NUCB 3002 or CAESAR showed significant impact on disease progression and survival when 3TC was added to nucleoside therapy (Staszewski 1997). As a component of Combivir™ and Trizivir™, 3TC is the most frequently used antiretroviral drug. The M184V point mutation even has advantages: not only does it improve the susceptibility of certain AZT-resistant viruses in some patients (Boucher 1993), but it also impairs viral fitness (Miller 2002). Keeping 3TC as part of a combination despite proven resistance is therefore sensible to conserve the M184V mutation and thus reduce the replicative capacity of HIV. This has now been demonstrated in a study on monotherapy in treatment-experienced patients with the M184V mutation: maintaining 3TC monotherapy was associated with a lower increase in viral load and fall in CD4+ cell levels than completely stopping HAART (Castagna 2004, see “Salvage” chapter).

In the Atlantic Study, 3TC in combination with d4T+ddI proved significantly weaker virologically than indinavir or nevirapine (Van Leeuwen 2003). Combination with abacavir and tenofovir is also not good, as recently published data from the ESS30009 Study has shown (Gallant 2003, see also the section “Triple Nuke”).

Once-daily dosing is now possible and has been licensed (Sension 2002, DeJesus 2004). 3TC is therefore likely to continue to play an important role in many once-daily combinations. A pleasant effect of 3TC is also its good efficacy against hepatitis B viruses, although this is again limited by the relatively rapid development of resistance (Dienstag 1999, Dore 1999).

**Tenofovir (Viread™)** acts as a false building block similar to nucleoside analogs, targeting the enzyme reverse transcriptase. However, in addition to the pentose and nucleic base, it is monophosphorylated and therefore referred to as a nucleotide analog. The accurate description of the substance is tenofovir DF (disoproxil fumarate = TDF), referring to the phosphonate form from which the phosphonate component is only removed by a serum esterase, and which is activated intracellularly in two phosphorylation steps (Robbins 1998).

In the 902 and 907 studies, in which tenofovir was added to existing HAART, the viral load fell by approximately 0.6 logs after 48 weeks (Schooley 2002, Squires 2003). Tenofovir is tolerated very well: side effects in these studies were comparable to the placebo arms. The 903 Study was a double blind study in which treatment-naïve patients were given tenofovir or d4T (with a backbone regimen of 3TC+efavirenz). Results showed at least equivalent potency (Gallant 2004). With a significantly reduced incidence of polyneuropathy and lipid changes, which are analogous to the *in vitro* data, it has been shown that phosphorylated tenofovir has a low affinity for mitochondrial polymerases (Suo 1998). As a result of this convincing clinical data and its licensing in 2001, the drug is now very widely used in antiretroviral therapies. In the 934 study, TDF+FTC were significantly better than AZT+3TC (Gallant 2006), particularly due to the improved tolerability.

This extensive use has revealed a few problems. There seem to be significant interactions: tenofovir reduces the breakdown of ddI via inhibition of the purine nucleotide phosphorylase. Pancreatitis and life-threatening lactic acidosis (Rivas 2003) can occur despite dose reduction (Blanchard 2003, Martinez 2004). Because ddI increases the risk of nephrotoxicity, the combination of tenofovir + ddI should be avoided (see “Problems with Initial Therapies”). A further unfavorable interaction with atazanavir, which causes the drug levels to drop means that this PI should be boosted with ritonavir (Taburet 2004).

However, the potential risk of nephrotoxicity is a serious problem for tenofovir, which is associated with a mild to moderate disturbance of renal function (Gallant 2005, Mauss 2005, Thompson 2006, Heffelfinger 2006). Several cases of renal failure on tenofovir have also been reported, partly in the context of a Fanconi syndrome, a defect of proximal tubular transport (Karras 2003, Schaaf 2003, Peyriere 2004). Patients with renal disease should either not be treated with tenofovir, or at least receive a lower dose (see “Drugs” chapter). Elderly and lighter patients are particularly at risk (Crane 2006). According to the current data, it is important to remain alert and to regularly check the renal function of patients on tenofovir, especially when on long-term therapy. In addition, newer data reports poor efficacy with certain triple nuke therapies (see here), for which tenofovir currently does not seem to be a good candidate. If virological treatment failure occurs, the K65R mutation, a problematic nucleoside analog resistance mutation, frequently appears.

### **The choice of nuke backbones**

Until now, all classical HAART regimens have always contained two nucleoside analogs or nucleotide analogs as the “backbone” of treatment (“nuke backbone”). This has mainly historical reasons: nucleoside analogs were the first HIV drugs, and when protease inhibitors appeared on the scene years later, treatment with two nucleoside analogs was standard. As knowledge has grown about the mitochondrial

toxicity of some nucleoside analogs, this concept is now being questioned by an increasing number of experts (see “Nuke Sparing”). However, data on combinations without nucleoside analogs are still relatively sparse, so that there are currently no recommendations for such strategies. In comparison, nucleoside analogs have been well investigated – countless studies over the years, especially before the introduction of PIs and NNRTIs, concentrated on figuring out the optimal combination of two nucleoside analogs.

The typical nuke backbone includes AZT or d4T, a thymidine analog. However, because of the toxicity of both substances, as well as the problematic resistance associated with failure of therapy (see chapter on “Resistance”), this method is being questioned more and more. Nowadays, d4T is hardly used, and in many regimens, thymidine analogs are avoided completely.

Today, many combinations exist besides AZT+3TC, the long-standing “standard backbone”. These include TDF+3TC, TDF+FTC, and also ABC+3TC. These combinations have the advantage that they can be administered once daily: TDF+FTC and ABC+3TC can even be taken in a single tablet.

### **AZT+3TC**

In many international guidelines, AZT+3TC is still regarded as the standard backbone for first-line therapy. There is more experience with this combination than with any other. The resistance profile is favorable: the M184V mutation that frequently develops during 3TC treatment probably increases sensitivity to AZT. AZT+3TC are usually given as Combivir™. Although the licensing study for Combivir™ showed no differences in toxicity (Eron 2000), in our experience the 300 mg AZT dose in Combivir™ is too high for some patients (e.g. pregnant women) and can lead to anemia. In such cases, it is worth trying AZT+3TC as individual formulations, so that the dose of AZT can be reduced to 250 mg.

AZT+3TC has comparable efficacy to the combinations d4T+ddI and d4T+3TC, or AZT+FTC, which were frequently used earlier (Foudraine 1998, Carr 2000, Eron 2000, French 2002, Gathe 2002, Squires 2000, Benson 2004). The ACTG 384 Study even showed superiority of AZT+3TC over d4T+ddI (Robbins 2003, Shafer 2003), and several other studies found a lower rate of lipodystrophy (Molina 1999, Chene 2002). However, AZT+3TC are currently losing ground for three main reasons: firstly – once daily dosing is not possible, and secondly, mitochondrial toxicity is likely even on AZT+3TC. In the ACTG 384 Study, the development of lipodystrophy occurred only slightly later than with d4T+ddI (Robbins 2003, Shafer 2003). Thirdly, AZT+3TC were shown by the Gilead 934 Study to be less effective (tolerated less) than TDF+FTC (Gallant 2006).

### **TDF+3TC/FTC**

Good data is not only available for tenofovir-based therapy in combination with the PI lopinavir (Molina 2004), but also for the combined therapy with NNRTIs, especially efavirenz. In the Gilead 903 Study, the combination of TDF+3TC was not only as virologically effective as d4T+3TC, but was also tolerated much better (Gallant 2004). Since the introduction of FTC and the combined tablet Truvada™ in August 2004, tenofovir has more frequently been administered together with FTC. In the Gilead 934 Study (Gallant 2006), using 509 treatment-naive patients,

the TDF+FTC combination was tested against AZT+3TC in an open design (all patients also received efavirenz). At 48 weeks, a larger proportion of patients in the TDF+FTC arm reached less than 50 copies/ml (80 versus 70 %). This was even true for patients with a higher baseline viral load. The significant differences were primarily related to the poorer tolerability of Combivir™, which often resulted in the discontinuation of therapy (9 versus 4 %). Virological failure and resistance mutations were approximately equal in both arms and were infrequent. Providing no undesirable surprises arise with regard to nephrotoxicity, tenofovir therapy will play an even more important role - at the latest, following the results of this study.

### **ABC+3TC**

Another alternative to AZT+3TC is ABC+3TC, which is available in a fixed combination as Kivexa™ or Epzicom™. The double blind randomized CNA30024 Study showed the non-inferiority of ABC+3TC in comparison to Combivir™ (DeJesus 2004). ABC+3TC even led to a significantly higher rise in CD4<sup>+</sup> T-cells, although there was also a higher rate of allergies at 9 versus 3 % (DeJesus 2004). Studies such as CLASS or ZODIAC also demonstrated good potency for ABC+3TC and efavirenz (Bartlett 2002, Moyle 2004). In the ABCDE Study, ABC+3TC had the same efficacy as d4T+3TC (Podzamczar 2004), but were also less toxic. It is important to note that ABC+3TC have significantly shorter half-lives than TDF+FTC. This could mean that ABC+3TC is less forgiving if tablets are taken irregularly, and resistance may be more likely to occur. On the other hand, an advantage to TDF+FTC could be that L74V, usually occurring alongside the M184V mutation, is associated with less cross-resistance than the tenofovir-associated K65R mutation.

One disadvantage of the combination with NNRTIs is the higher risk of occurrence of allergies under both abacavir and NNRTIs, making it difficult to distinguish between a NNRTI rash and the abacavir HSR. We therefore do not recommend using these at the same time, as treatment options may be unnecessarily eliminated.

It should be noted that most of the studies cited here were investigating first-line therapy. In treatment-experienced patients, numerous other individually tailored backbones may become necessary as a result of resistance and intolerance. However, the combinations discussed below should be avoided if possible.

### **Poor and non-recommended backbones**

Many newer guidelines explicitly recommend avoiding the previously popular d4T+ddI combination. Mitochondrial toxicity is too high, and it performed more poorly than AZT+3TC in the ACTG 384 Study (Robbins 2003). In cases of treatment failure, thymidine analog mutations (TAMs) are usually present, which can limit future treatment options. In view of the wide selection of nucleoside analogs available today, ddI+d4T is no longer justified for first-line therapy.

d4T+3TC is another combination recommended only in certain situations for first-line therapy. Although it is very well tolerated initially, d4T leads to problems with long-term toxicity. We would only use this combination today when neither AZT nor tenofovir could be used due to co-morbidity. Studies such as ABCDE or 903 have shown that d4T+3TC causes notably more lipodystrophy than ABC+3TC or TDF+3TC (Podzamczar 2004, Gallant 2004). Because ddI has to be taken on an

empty stomach, and, in particular, due to the greater risk of gastrointestinal side effects, AZT+ddI is contraindicated (AZT is tolerated better when taken with a meal). TDF+ddI are relatively toxic and, in the last few years, many studies have shown lower virological and immunological efficacies (see also “Problems with Initial Therapies”). TDF+ABC are likely to be problematic due to rapid development of resistance. All combinations with ddC should be avoided, which will be withdrawn from the market in summer 2006. AZT+d4T and FTC+3TC are antagonistic.

Even alternating backbones, with regular changes from one backbone to another, can currently not be recommended, although initial studies indicate that this strategy is at least not harmful (Molina 1999, Martinez-Picado 2003).

## References on nucleoside and nucleotide analogs

- Bartlett JA, Benoit SL, Johnson VA, et al. Lamivudine plus zidovudine compared with zalcitabine plus zidovudine in patients with HIV infection. A randomized, double-blind, Placebo-controlled trial. *Ann Intern Med* 1996, 125: 161-72. <http://amedeo.com/lit.php?id=8686973>
- Bartlett JA, Johnson J, Herrera G, et al. Abacavir/lamivudine in combination with efavirenz, amprenavir/ritonavir or stavudine: ESS40001 (CLASS) preliminary 48-week results. Abstract TuOrB1189, XIV International AIDS Conference 2002, Barcelona.
- Benson CA, van der Horst C, Lamarca A, et al. A randomized study of emtricitabine and lamivudine in stably suppressed patients with HIV. *AIDS* 2004, 18:2269-76. <http://amedeo.com/lit.php?id=15577539>
- Bernasconi E, Boubaker K, Junghans C, et al. Abnormalities of body fat distribution in HIV-infected persons treated with antiretroviral drugs: J Acquir Immune Defic Syndr 2002, 31:50-5. <http://amedeo.com/lit.php?id=12352150>
- Blanchard JN, Wohlfeiler M, Canas A, et al. Pancreatitis treated with didanosine and tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; 37: e57-62. <http://amedeo.com/lit.php?id=12942419>
- Bogner JR, Vielhauer V, Beckmann RA, et al. Stavudine versus zidovudine and the development of lipodystrophy. *J AIDS* 2001, 27: 237-44. <http://amedeo.com/lit.php?id=11464142>
- Bonjoch A, Miralles C, Miranda J, et al. Efficacy of three NRTIs (Trizivir) or two NRTIs (Combivir) plus nevirapine as simplified strategies in HIV-1 infected patients with viral suppression : SimplifyHAART study. Abstract H-562, 44th ICAAC 2004, Washington.
- Boucher CA, Cammack N, Schipper P, et al. High-level resistance to (-) enantiomeric 2'-deoxy-3'-thiacytidine in vitro is due to one amino acid substitution in the catalytic site of HIV type 1 reverse transcriptase. *Antimicrobial Agents Chemother* 1993, 37:2231-2234. <http://amedeo.com/lit.php?id=7504909>
- Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of ART-related lipodystrophy. *Lancet* 1999, 354:1112-5. <http://amedeo.com/lit.php?id=10509516>
- CAESAR Co-ordinating Committee. Randomised trial of addition of lamivudine or lamivudine plus loviride to zidovudine-containing regimens for patients with HIV-1 infection: the CAESAR trial. *Lancet* 1997, 349:1413-1421. <http://amedeo.com/lit.php?id=9164314>
- Carr A, Chuah J, Hudson J, et al. A randomised, open-label comparison of three HAART regimens including two nucleoside analogues and indinavir for previously untreated HIV-1 infection: the OzCombo1 study. *AIDS* 2000, 14: 1171-80. <http://amedeo.com/lit.php?id=10894281>
- Carr A, Martin A, Rinald C et al. Long-term changes in lipodystrophy after switching from thymidine analogues to abacavir. *Antiviral Therapy* 8:L15, 2003.
- Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with HIV lipodystrophy: a randomized trial. *JAMA* 2002, 288:207-15. <http://amedeo.com/lit.php?id=12095385>
- Chene G, Angelini E, Cotte L, et al. Role of long-term nucleoside-analogue therapy in lipodystrophy and metabolic disorders in HIV-infected patients. *Clin Infect Dis* 2002, 34: 649-57. <http://amedeo.com/lit.php?id=11810598>
- Clumeck N, Goebel F, Rozenbaum W, et al. Simplification with abacavir-based triple nucleoside therapy versus continued protease inhibitor-based highly active antiretroviral therapy in HIV-1-infected patients with undetectable plasma HIV-1 RNA. *AIDS* 2001, 15:1517-26.
- Clumeck N, Lamarka A, Fu K, et al. Safety and efficacy of a fixed-dose combination of ABC/3TC OAD versus ABC BID and 3TC OAD as separate entities in antiretroviral-experienced HIV-1-infected patients: CAL30001. Abstract 558, 44th ICAAC 2004, Washington.

17. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994, 343:871-81. <http://amedeo.com/lit.php?id=7908356>
18. Crane H, Harrington R, Van Rompaey S, Kitahata M. Didanosine and lower baseline body weight are associated with declining renal function among patients receiving tenofovir. Abstract 780, 13th CROI 2006, Denver.
19. De la Rosa R, Harris M, Uyeda L, et al. Life-threatening reaction after first ever dose of abacavir in an HIV-1-infected patient. *AIDS* 2004, 18:578-9.
20. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis* 2004, 39:1038-46. <http://amedeo.com/lit.php?id=15472858>
21. DeJesus E, McCarty D, Farthing CF, et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naive adults with HIV infection: a randomized equivalence trial. *Clin Infect Dis* 2004, 39:411-8. <http://amedeo.com/lit.php?id=15307010>
22. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet* 1996, 348: 283-91. <http://amedeo.com/lit.php?id=8709686>
23. Dienstag JL, Schiff ER, Wright TL, et al. Lamivudine as initial treatment for chronic hepatitis B in the United States. *New Eng J Med* 1999, 341:1256-1263, 1999. <http://amedeo.com/lit.php?id=10528035>
24. Dolin R, Amato DA, Fischl MA, et al. Zidovudine compared to didanosine in patients with advanced HIV-1 infection and little or no previous experience with zidovudine. *Arch Int Med* 1995, 155:961-97. <http://amedeo.com/lit.php?id=7726705>
25. Dore GJ, Cooper DA, Barrett C, et al. Dual efficacy of lamivudine treatment in HIV/hepatitis B virus coinfecting persons in a randomized, controlled study (CAESAR). *J Infect Dis* 1999, 180:607-613. <http://amedeo.com/lit.php?id=10438346>
26. El-Sahly HM. Development of abacavir hypersensitivity reaction after rechallenge in a previously asymptomatic patient. *AIDS* 2004, 18:359-60.
27. Eron JJ JR, Murphy RL, Peterson D, et al. A comparison of stavudine, didanosine and indinavir with zidovudine, lamivudine and indinavir for the initial treatment of HIV-1 infected individuals: selection of thymidine analog regimen therapy (START II). *AIDS* 2000, 14: 1601-10. <http://amedeo.com/lit.php?id=10983647>
28. Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *New Eng J Med* 1995, 333:1662. <http://amedeo.com/lit.php?id=7477218>
29. Fischl MA, Parker CB, Pettinelli C, et al. A randomized controlled trial of a reduced daily dose of zidovudine in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1990; 323:1009-14. <http://amedeo.com/lit.php?id=1977079>
30. Fischl MA, Richman DD, Grieco MH, et al. The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, Placebo-controlled trial. *N Engl J Med* 1987; 317:185-91. <http://amedeo.com/lit.php?id=3299089>
31. Fischl MA, Richman DD, Hansen N, et al. The safety and efficacy of zidovudine (AZT) in the treatment of subjects with mildly symptomatic HIV infection. A double-blind, Placebo-controlled trial. *Ann Intern Med* 1990; 112:727-37. <http://amedeo.com/lit.php?id=1970466>
32. Fischl MA, Stanley K, Collier AC et al. Combination and monotherapy with zidovudine and zalcitabine in patients with advanced HIV disease. *Ann Int Med* 1995, 122:24-32. <http://amedeo.com/lit.php?id=7985892>
33. Floridia M, Vella S, Seeber AC, et al. A randomized trial (ISS 902) of didanosine versus zidovudine in previously untreated patients with mildly symptomatic HIV infection. *J Infect Dis* 1997, 175:255-264. <http://amedeo.com/lit.php?id=9203645>
34. Foudraine NA, de Jong JJ, Weverling J, et al. An open randomized controlled trial of zidovudine plus lamivudine versus stavudine plus lamivudine. *AIDS* 1998, 12: 1513-9. <http://amedeo.com/lit.php?id=9727573>
35. French M, Amin J, Roth N, et al. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 Infection: the OzCombo 2 study. *HIV Clin Trials* 2002, 3:177-85. <http://amedeo.com/lit.php?id=12032876>
36. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006, 354:251-60. <http://amedeo.com/lit.php?id=16421366>
37. Gallant JE, Parish MA, Keruly JC, Moore RD. Changes in renal function associated with tenofovir disoproxil fumarate treatment, compared with nucleoside reverse-transcriptase inhibitor treatment. *Clin Infect Dis* 2005, 40:1194-8. <http://amedeo.com/lit.php?id=15791522>



38. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004, 292: 191-201. <http://amedeo.com/lit.php?id=15249568>
39. Galli M, Ridolfo AL, Adorni F, et al. Body habitus changes and metabolic alterations in protease inhibitor-naïve HIV-1-infected patients treated with two nucleoside reverse transcriptase inhibitors. *JAIDS* 2002, 29: 21-31. <http://amedeo.com/lit.php?id=11782586>
40. Gathe J Jr, Badaro R, Grimwood A, et al. Antiviral activity of enteric-coated didanosine, stavudine, and nelfinavir versus zidovudine plus lamivudine and nelfinavir. *JAIDS* 2002;31:399-403. <http://amedeo.com/lit.php?id=12447010>
41. Gerard Y, Maulin L, Yazdanpanah Y, et al. Symptomatic hyperlactataemia: an emerging complication of ART. *AIDS* 2000, 14:2723-30. <http://amedeo.com/lit.php?id=11125891>
42. Goedken AM, Herman RA. Once-daily abacavir in place of twice-daily administration. *Ann Pharmacother* 2005, 39:1302-8. <http://amedeo.com/lit.php?id=15956231>
43. Gulick RM, Ribaldo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004, 350:1850-1861. <http://amedeo.com/lit.php?id=15115831>
44. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500/ul. *N Engl J Med* 1996, 335:1081-90. <http://amedeo.com/lit.php?id=8813038>
45. Harrigan PR, Stone C, Griffin P, et al. Resistance profile of the HIV type 1 reverse transcriptase inhibitor abacavir (1592U89) after monotherapy and combination therapy. *JID* 2000, 181:912-920. <http://amedeo.com/lit.php?id=10720512>
46. Harris M, Back D, Kewn S, et al. Intracellular carbovir triphosphate levels in patients taking abacavir once a day. *AIDS* 2002, 16:1196-7
47. Havlir DV, Gilbert PB, Bennett K, et al. Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001, 15: 1379-88. <http://amedeo.com/lit.php?id=11504959>
48. Havlir DV, Tierney C, Friedland GH, et al. In vivo antagonism with zidovudine plus stavudine combination therapy. *J Infect Dis* 2000, 182: 321-5. <http://amedeo.com/lit.php?id=10882616>
49. Heffelfinger J, Hanson D, Voetsch A, et al. Renal impairment associated with the use of tenofovir. Abstract 779, 13th CROI 2006, Denver.
50. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* 2002, 359:1121-2. <http://amedeo.com/lit.php?id=11943262>
51. Hoy JF, Gahan ME, Carr A, et al. Changes in mitochondrial DNA in peripheral blood mononuclear cells from HIV-infected patients with lipodystrophy randomized to receive abacavir. *J Infect Dis* 2004, 190:688-92. <http://amedeo.com/lit.php?id=15272394>
52. Jablonowski H, Arasteh K, Staszewski S, et al. A dose comparison study of didanosine in patients with very advanced HIV infection who are intolerant to or clinically deteriorate on zidovudine. *AIDS* 1995, 9:463-469. <http://amedeo.com/lit.php?id=7639971>
53. John M, McKinnon EJ, James IR, et al. Randomized, controlled, 48 week study of switching stavudine and/or protease inhibitors to Combivir/abacavir to prevent or reverse lipodystrophy in HIV-infected patients. *JAIDS* 2003, 33: 29-33. <http://amedeo.com/lit.php?id=12792352>
54. John M, Moore CB, James IR, et al. Chronic hyperlactatemia in HIV-infected patients taking ART. *AIDS* 2001, 15: 717-23. <http://amedeo.com/lit.php?id=11371686>
55. Karras A, Lafaurie M, Furco A, et al. Tenofovir-related nephrotoxicity in HIV-infected patients: three cases of renal failure, Fanconi syndrome, and nephrogenic diabetes insipidus. *Clin Infect Dis* 2003; 36:1070-1073
56. Katlama C, Clotet B, Plettenberg A, et al. The role of abacavir (ABC, 1592) in antiretroviral therapy-experienced patients: results from a randomized, double-blind, trial. *AIDS* 2000, 14:781-789. <http://amedeo.com/lit.php?id=10839585>
57. Katlama C, Fenske S, Gazzard B, et al. TRIZAL study: switching from successful HAART to Trizivir (abacavir-lamivudine-zidovudine combination tablet): 48 weeks efficacy, safety and adherence results. *HIV Medicine* 2003, 4: 79-86. <http://amedeo.com/lit.php?id=12702127>
58. Kearney BP, Isaacson E, Sayre J, et al. Didanosine and tenofovir DF drug-drug interaction: assessment of didanosine dose reduction. Abstract 533, 10th CROI 2003, Boston. <http://www.retroconference.org/2003/Abstract/Abstract.aspx?AbstractID=181>
59. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B\*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002, 359:727-32. <http://amedeo.com/lit.php?id=11888582>

60. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000, 14:1309-1316. <http://amedeo.com/lit.php?id=10930144>
61. Mallon PW, Miller J, Cooper DA, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. *AIDS* 2003, 17: 971-979
62. Marcus K, Truffa M, Boxwell D, Toerner J. Recently identified adverse events secondary to NRTI therapy in HIV-infected individuals: cases from the FDA's adverse event reporting system. Abstract LB14, 9<sup>th</sup> CROI 2002, Seattle. <http://www.retroconference.org/2002/Abstract/14036.htm>
63. Martin A, Smith DE, Carr A, et al. Reversibility of lipoatrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS* 2004, 18:1029-36.
64. Martinez E, Arnaiz JA, Podzamczar D, et al. Substitution of nevirapine, efavirenz or abacavir for protease inhibitors in patients with HIV infection. *N Eng J Med* 2003, 349:1036-46. <http://amedeo.com/lit.php?id=12968087>
65. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet* 2004, 364:65-7. <http://amedeo.com/lit.php?id=15234858>
66. Martinez-Picado J, Negro E, Ruiz L, et al. Alternation of antiretroviral drug regimens for HIV infection. A randomized, controlled trial. *Ann Intern Med* 2003; 139: 81-9. <http://amedeo.com/lit.php?id=12859157>
67. Matheron S, Descamps D, Boue F, et al. Triple nucleoside combination zidovudine/lamivudine/abacavir versus zidovudine/lamivudine/ nelfinavir as first-line therapy in HIV-1-infected adults: a randomized trial. *Antivir Ther* 2003, 8:163-71. <http://amedeo.com/lit.php?id=12741629>
68. Mauss S, Berger F, Schmutz G. Antiretroviral therapy with tenofovir is associated with mild renal dysfunction. *AIDS* 2005, 19:93-5.
69. Mauss S, Corzillius M, Wolf E, et al. Risk factors for the HIV-associated lipodystrophy syndrome in a closed cohort of patients after 3 years of antiretroviral treatment. *HIV Med* 2002, 3:49-55. <http://amedeo.com/lit.php?id=12059951>
70. McComsey GA, Paulsen DM, Loneragan JT, et al. Improvements in lipoatrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine. *AIDS* 2005, 19:15-23. <http://amedeo.com/lit.php?id=15627029>
71. McComsey GA, Ward DJ, Hesselthaler SM, et al. Improvement in lipoatrophy associated with HAART in HIV-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. *CID* 2004, 38:263-270. <http://amedeo.com/lit.php?id=14699460>
72. Miller KD, Cameron M, Wood LV, et al. Lactic acidosis and hepatic steatosis associated with use of stavudine: report of four cases. *Ann Intern Med* 2000, 133:192-6. <http://amedeo.com/lit.php?id=10906833>
73. Miller V, Stark T, Loeliger AE, Lange JM. The impact of the M184V substitution in HIV-1 reverse transcriptase on treatment response. *HIV Med* 2002, 3:135-45. <http://amedeo.com/lit.php?id=12010361>
74. Mokrzycki MH, Harris C, May H, Laut J, Palmisano J. Lactic acidosis associated with stavudine administration: a report of five cases. *Clin Infect Dis* 2000, 30: 198-200. <http://amedeo.com/lit.php?id=10619755>
75. Molina JM, Chene G, Ferchal F, et al. The ALBI trial: a randomized controlled trial comparing stavudine plus didanosine with zidovudine plus lamivudine and a regimen alternating both combinations in previously untreated patients infected with HIV. *J Infect Dis* 1999, 180: 351-8. <http://amedeo.com/lit.php?id=10395849>
76. Molina JM, Journot V, Morand-Joubert L, et al. Simplification therapy with once-daily emtricitabine, didanosine, and efavirenz in HIV-1-infected adults with viral suppression receiving a protease inhibitor-based regimen: a randomized trial. *J Infect Dis* 2005, 191:830-9. <http://amedeo.com/lit.php?id=15717256>
77. Molina JM, Marcelin AG, Pavie J, et al. Didanosine in HIV-1-infected patients experiencing failure of antiretroviral therapy: a randomized placebo-controlled trial. *J Infect Dis* 2005, 191:840-7. <http://amedeo.com/lit.php?id=15717257>
78. Moyle G, Baldwin C, Langroudi B, Mandalia S, Gazzard BG. A 48 week, randomized, open label comparison of three abacavir-based substitution approaches in the management of dyslipidemia and peripheral lipoatrophy. *J AIDS* 2003, 33: 22-28. <http://amedeo.com/lit.php?id=12792351>
79. Moyle G, Boffito M. Unexpected drug interactions and adverse events with antiretroviral drugs. *Lancet* 2004, 364:8-10.
80. Moyle GJ, Dejesus E, Cahn P, et al. Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naive HIV-infected adults: results of the ziagen once daily in antiretroviral combination study. *J AIDS* 2005;38:417-425. <http://amedeo.com/lit.php?id=16518962>

81. Negrodo E, Moltó J, Burger D, et al. Unexpected CD4 cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load. *AIDS* 2004, 18:459-463. <http://amedeo.com/lit.php?id=15090798>
82. Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in HIV infection. *J Inf Dis* 2002, 185:1251-1260. <http://amedeo.com/lit.php?id=12001042>
83. Peyriere H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. *J AIDS* 2004, 35:269-73. <http://amedeo.com/lit.php?id=15076241>
84. Piscitelli SC, Gallicano KD. Interactions among drugs for HIV and opportunistic infections. *N Engl J Med* 2001, 344:984-96.
85. Podzamczar D, Ferrer E, Sanchez P, et al. Toxicity and Efficacy of 3TC/EFV Associated with Stavudine or Abacavir in Antiretroviral-naive Patients: 48-week Results of a Randomized Open and Multicenter Trial (ABCDE Study). Abstract 716, 11th CROI 2004, San Francisco.
86. Rivas P, Polo J, de Gorgolas M, Fernandez-Guerrero ML. Drug points: Fatal lactic acidosis associated with tenofovir. *BMJ* 2003; 327: 711.
87. Robbins BL, Srinivas RV, Kim C, et al. Anti-HIV activity and cellular metabolism of a potential prodrug of the acyclic nucleoside phosphonate 9-R-(2-PMPA), Bis PMPA. *Antimicrob Agents Chemother* 1998, 42:612-7. <http://amedeo.com/lit.php?id=9517941>
88. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349: 2293-303. <http://amedeo.com/lit.php?id=14668455>
89. Rousseau FS, Wakeford C, Mommeja-Marin H, et al. Prospective randomized trial of emtricitabine versus lamivudine short-term monotherapy in HIV-infected patients. *J Infect Dis* 2003;188:1652-8. <http://amedeo.com/lit.php?id=14639535>
90. Rozenbaum W, Katlama C, Massip P, et al. Treatment intensification with abacavir in HIV-infected patients with at least 12 weeks previous lamivudine/zidovudine treatment. *Antiviral Therapy* 2001, 6:135-42. <http://amedeo.com/lit.php?id=11491418>
91. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA* 2004, 292:180-9. <http://amedeo.com/lit.php?id=15249567>
92. Saravolatz LD Winslow DL, Collins G, et al. Zidovudine alone or in combination with didanosine or zalcitabine in HIV-infected patients with the AIDS or fewer than 200 CD4 cells per cubic millimeter. *New Eng J Med* 1996, 335:1099-1106. <http://amedeo.com/lit.php?id=8813040>
93. Saves M, Raffi F, Capeau J, et al. Factors related to lipodystrophy and metabolic alterations in patients with HIV infection receiving highly active antiretroviral therapy. *Clin Inf Dis* 2002, 34: 1396-1405.
94. Schaaf B, Aries SP, Kramme E, Steinhoff J, Dalhoff K. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. *Clin Infect Dis* 2003, 37:e41-3. <http://amedeo.com/lit.php?id=12884188>
95. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS* 2002, 16:1257-63. <http://amedeo.com/lit.php?id=12045491>
96. Senson MG, Bellos NC, Johnson J, et al. Lamivudine 300 mg QD versus continued lamivudine 150 mg BID with stavudine and a protease inhibitor in suppressed patients. *HIV Clin Trials* 2002, 3:361-70. <http://amedeo.com/lit.php?id=12407485>
97. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349: 2304-15. <http://amedeo.com/p2.php?id=14668456&s=hiv>
98. Shah SS, Rodriguez T, McGowan JP. Miller Fisher variant of Guillain-Barre syndrome associated with lactic acidosis and stavudine therapy. *Clin Infect Dis* 2003, 36:e131-3. <http://amedeo.com/lit.php?id=12746793>
99. Sosa N, Hill-Zabala C, Dejesus E, et al. Abacavir and lamivudine fixed-dose combination tablet once daily compared with abacavir and lamivudine twice daily in HIV-infected patients over 48 weeks (ESS30008, SEAL). *J AIDS* 2005, 40:422-7. <http://amedeo.com/lit.php?id=16280696>
100. Spruance SL, Pavia AT, Mellors JW, et al. Clinical efficacy of monotherapy with stavudine compared with zidovudine in HIV-infected, zidovudine-experienced patients. A randomized, double-blind, controlled trial. *Ann Int Med* 1997, 126:355-363. <http://amedeo.com/lit.php?id=9054279>
101. Squires K, Pozniak AL, Pierone G, et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection. *Ann Int Med* 2003, 139: 313-320. <http://amedeo.com/lit.php?id=12965939>
102. Squires KE, Gulick R, Tebas P, et al. A comparison of stavudine plus lamivudine versus zidovudine plus lamivudine in combination with indinavir in antiretroviral naive individuals with HIV infection: selec-

- tion of thymidine analog regimen therapy (START I). *AIDS* 2000, 14: 1591-600. <http://amedeo.com/lit.php?id=10983646>
103. Staszewski S, Hill AM, Bartlett J, et al. Reductions in HIV-1 disease progression for zidovudine/lamivudine relative to control treatments: a meta-analysis of controlled trials. *AIDS* 1997, 11:477-483. <http://amedeo.com/lit.php?id=9084795>
  104. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral naïve HIV-infected adults: a randomized equivalence trial. *JAMA* 2001, 285: 1155-1163. <http://amedeo.com/lit.php?id=11231744>
  105. Stekler J, Maenza J, Stevens C, et al. Abacavir hypersensitivity reaction in primary HIV infection. *Abstr* 168, 44th ICAAC 2004, Washington.
  106. Suleiman JM, Lu B, Enejosa J, Cheng A. Improvement in lipid parameters associated with substitution of stavudine to tenofovir DF in HIV-infected patients participating in GS 903. Abstract H-158, 44th ICAAC 2004, Washington.
  107. Suo Z, Johnson KA. Selective inhibition of HIV-1 reverse transcriptase by an antiviral inhibitor, (R)-9-(2-Phosphonylmethoxypropyl)adenine. *J Biol Chem* 1998, 273:27250-8. <http://amedeo.com/lit.php?id=9765248>
  108. Taburet AM, Pikeetty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2004, 48:2091-6. <http://amedeo.com/lit.php?id=15155205>
  109. Thompson M, Haubrich R, D Margolis D, et al. Differences in calculated glomerular filtration rate in efavirenz- or tenofovir-treated adults in ESS40006. Abstract 777, 13th CROI 2006, Denver.
  110. Van der Horst C, Sanne I, Wakeford C, et al. Two randomised controlled equivalence trials of emtricitabine (FTC) to lamivudine (3TC). Abstract 18, 8th CROI 2001, Chicago. <http://www.retroconference.org/2001/abstracts/abstracts/18.htm>
  111. Van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003, 17:987-99. <http://amedeo.com/lit.php?id=12700448>
  112. Vibhagool A, Cahn P, Schechter M, et al. Triple nucleoside treatment with abacavir plus the lamivudine/zidovudine combination tablet (COM) compared to indinavir/COM in antiretroviral therapy-naïve adults: results of a 48-week open-label, equivalence trial (CNA3014). *Curr Med Res Opin* 2004, 20:1103-14. <http://amedeo.com/lit.php?id=15265255>
  113. Volberding PA, Lagakos SW, Koch MA, et al. Zidovudine in asymptomatic HIV infection. A controlled trial in persons with fewer than 500 CD4-positive cells per cubic millimeter. *N Engl J Med* 1990; 322:941-9.

## Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

### Mechanism of action and efficacy

NNRTIs were first described in 1990. As with the nucleoside analogs, the target enzyme is reverse transcriptase. However, NNRTIs bind directly and non-competitively to the enzyme at a position in close proximity to the substrate binding site for nucleosides. The resulting complex blocks the catalyst activated binding site of the reverse transcriptase. This, in turn, can bind fewer nucleosides, slowing polymerization down significantly.

In contrast to NRTIs, NNRTIs do not require activation within the cell. The three available NNRTIs – nevirapine, delavirdine and efavirenz – were introduced between 1996 and 1998. Although studies such as the ACTG 241, INCAS or 0021II had already clearly demonstrated the superiority of triple therapy compared to double nuke therapy (D’Aquila 1996, Raboud 1999, Conway 2000), the “rise” of the NNRTIs was rather hesitant, and did not receive the media attention given to the PIs. This was due to the early observation that functional monotherapy with NNRTIs, i.e. the mere addition of an NNRTI to a failing regimen, showed practically no effect. There were also initial difficulties in dealing with the development of problematic resistance: the risk of resistance is not only very high, but it can de-

velop very rapidly. Once it occurs, it almost always indicates resistance to the entire class. Waiting too long when there is insufficient suppression of viral load is almost certain to lead to complete resistance to this class of drugs. One point mutation at position 103 (K103N) of the hydrophobic binding site is enough to eliminate the entire drug class! Resistance has now even been described in mothers who have taken a single dose of nevirapine as transmission prophylaxis (Eshleman 2002). In large studies, the frequency of NNRTI mutations following, in some cases, a single perinatal nevirapine mono-prophylaxis was between 14 and worryingly 65 % (Cunningham 2002, Jourdain 2004, Johnson 2005). This is possibly promoted by the long half-life of NNRTIs (Muro 2005). Thus, NNRTIs should always be stopped a few days prior to the other drugs if a break in therapy is planned (see chapter on Treatment Interruption). The rapid development of resistance is also reflected in the increasing number of primary transmitted resistances: in 2001/2002 almost 10 % of all acute infections in Europe had a NNRTI resistance (Wensing 2005). If there is resistance to one NNRTI, there is no need to start or continue treatment with a NNRTI – it will not change the immunological or virological status (Picketty 2004), because the ability of HIV to replicate is not reduced as much by NNRTI mutations as by some PI or NRTI mutations.

Despite the problems with resistance, both randomized and large cohort studies have demonstrated that NNRTIs are extremely effective when combined with nucleoside analogs. The immunological and virological potency of NNRTIs in treatment-naïve patients is at least equivalent, if not superior, to that of PIs (Staszewski 1999, Friedl 2001, Torre 2001, Podzamczar 2002, Robbins 2003, Squires 2003). In contrast to PIs, however, the clinical benefit has not yet been proven, as the studies that led to the licensing of NNRTIs all used surrogate markers. The efficacy of NNRTIs in treatment-experienced patients is probably weaker in comparison to PIs (Yazdanpanah 2004). In contrast to NNRTIs, some resistance mutations cause hypersensitivity (see below), which can be made use of in salvage therapy.

The simple dosing and the overall good tolerability have enabled nevirapine and efavirenz to become important components of HAART regimens, which are often even ranked above those containing PIs. Over the last few years, many randomized studies have demonstrated that it is possible to switch from a PI to a NNRTI if good virological suppression has already been achieved. The efficacy was sometimes even better on NNRTIs than on the continued PI regimen (see also the chapter “When to change”).

Like efavirenz, nevirapine is metabolized by the cytochrome p450 system (Miller 1997). Nevirapine is an inducer, whereas efavirenz is an inductor and an inhibitor of p450. In the combination of efavirenz and saquinavir or lopinavir the effects are so strong that dosage adjustment is necessary.

So far, no study has provided definitive evidence that one NNRTI is more potent than another. Although delavirdine no longer has any significant role, due to various reasons (see below), nevirapine and efavirenz have an equal standing. Cohort studies from the last few years suggest a slight superiority of efavirenz (Phillips 2001, Cozzi-Lepri 2002). However, these studies have only limited value as they included very heterogeneous patient groups. Overall, differences are likely to be small, particularly in treatment-naïve patients. A randomized pilot study from Spain

(SENC Study) at least showed no significant differences between nevirapine and efavirenz in this group of patients (Nunez 2002).

In the 2NN Study ("The Double Non-Nucleoside Study"), both substances were compared for the first time in a large-scale randomized study (Van Leth 2004). A total of 1,216 patients received a nucleoside backbone of d4T+3TC with either nevirapine 1 x 400 mg, nevirapine 2 x 200 mg, efavirenz 1 x 600 mg or efavirenz 1 x 800 mg plus nevirapine 1 x 400 mg. The proportion of patients with a viral load below 50 copies/ml after 48 weeks was 56 %, 56 %, 62 % and 47 %, respectively. The only significant virological difference was an advantage of the efavirenz arm over the double NNRTI arm, mainly due to higher toxicity in the latter. In the nevirapine arm with 1 x 400 mg, severe hepatic side effects occurred more frequently than in the efavirenz arm; on the other hand, lipids were more favorably influenced in the nevirapine group. However, more recent sub-analyses of 2NN have shown that the hepatic toxicity associated with once-daily doses of nevirapine was observed in a single center in Thailand. Outside of this center, toxicity was invariably infrequent (Storfer 2005). 2NN as well as switch studies, such as the Spanish Nefza trial (Martinez 2003), demonstrate that the choice of NNRTI should be based mainly on the different side effect profiles (see below), and patient-specific factors should also be taken into account (Recent review: Sheran 2005).

### Special features of individual agents

**Nevirapine (Viramune™)** was the first licensed NNRTI. Nevirapine with AZT+ddI is probably the oldest HAART combination of all. It was investigated in 1993, in the ACTG 193A Study, where it proved to be superior to monotherapy and dual therapy in severely immunocompromised patients. This was true for both survival and progression – although the difference in survival was not significant (Henry 1998). In addition, the AZT+ddI+nevirapine combination was well investigated in the INCAS and ACTG 241 Studies (Raboud 1999, D'Aquila 1996). INCAS demonstrated a suppression of the viral load to below 20 copies/ml after one year with AZT+ddI+nevirapine in 51 % of patients – compared to 12 % of those on AZT+ddI and 0 % on AZT+nevirapine. Clinical progression rates were 12 % (versus 25 % and 23 %), which was not a significant difference due to the small sample size. In pretreated patients in ACTG 241 (AZT+ddI plus nevirapine or placebo), however, no trend could be shown in favor of this combination.

Nevirapine has also been tested against protease inhibitors in randomized studies. In the Atlantic Study, combination with d4T+ddI was comparable to combination with indinavir (van Leeuwen 2003). Given with AZT+3TC in the Combine Study, there was at least a trend towards higher virological efficacy in comparison to nelfinavir (Podzamczar 2002). The pharmacokinetics of nevirapine appears to allow once-daily dosing (Van Heeswijk 2000). Various studies such as 2NN, SCAN, VIRGO or Atlantic have already successfully used 400 mg once daily (Garcia 2000, Raffi 2000, van Leeuwen 2003, Van Leth 2004), although this dosage has not yet been approved in all countries.

Nevirapine causes elevation of liver enzymes in up to 20 %, which may occasionally be severe. Lead-in dosing is always required. One study which reported that lead-in dosing is not required if efavirenz was previously administered (Winston 2004) still requires confirmation. During the first eight weeks on nevirapine, bi-

weekly monitoring of transaminases is recommended. A rash develops in 15-20 % of cases and leads to discontinuation in up to 7 % of patients (Miller 1997). Prophylactic administration of antihistamines or steroids does not prevent the rash (GESIDA26/02 2004, Launay 2004). In the case of an isolated rash or isolated elevation of transaminases (up to five times the upper limit of normal), treatment can usually be continued. But, caution when both occur simultaneously! It is recommended to stop treatment if a rash occurs together with even a slight elevation of transaminases (>2-fold of norm). Patients with chronic hepatitis are at a higher risk, as are women with a low body weight (Sulkowski 2000, Sanne 2005, Kappelhoff 2005). An increased risk has also been reported for patients with good immune status. Women with CD4<sup>+</sup> T-cell counts above 250/μl have a 12-fold elevated risk (11 versus 0.9 %), and the FDA even issued a warning relating to this in 2004. It is important to note that hepatic toxicity may occur even after several months (Sulkowski 2002). There does not appear to be any correlation between side effects and drug plasma levels (Almond 2004, Dailly 2004, Kappelhoff 2005), as was originally postulated (Gonzalez 2002). Hepatotoxicity can still occur after several months (Sulkowski 2002). There is probably a genetic disposition for reactions to nevirapine (Martin 2005). Permanent and significant γGT elevations are very common, which may subject patients to false suspicions of excess alcohol consumption.

Nevirapine has a good lipid profile. Studies such as Atlantic or 2NN, discovered comparably favorable lipid changes for cholesterol and triglycerides (Van der Valk 2001, Van Leth 2004) – an effect that was also demonstrated in the Spanish Nefa Study, albeit to a lesser extent, as well as with efavirenz (Fisac 2005). Whether these positive effects will have clinical relevance over time and really help to prevent cardiovascular events remains to be seen.

**Efavirenz (Sustiva™ or Stocrin™)** was the third NNRTI to be approved, and the first for which it could be shown that NNRTIs were at least as effective and probably even better than PIs in untreated or only slightly treatment-experienced patients. In particular, the 006 Study, a milestone in HIV therapy (Staszewski 1999) – showed a superiority of efavirenz over indinavir (each given in combination with AZT+3TC). Since then, efavirenz has been compared to other drugs in many large randomized studies. Efavirenz usually did well – in the CLASS study, efavirenz in combination with ABC+3TC was significantly more effective than d4T or boosted amprenavir (Bartlett 2002). In ACTG 5095, efavirenz in combination with AZT+3TC was better than abacavir (Gulick 2004); in ACTG 384 it was better than nelfinavir (Robbins 2003, Shafter 2003); and in AI424-034 it was at least as effective as atazanavir (Squires 2004).

Mild CNS side effects are often typical for efavirenz, which should therefore be taken in the evening before sleeping. Patients should be warned about these side effects, which usually include dizziness and numbness, but may also manifest as vivid dreams or even nightmares. In addition, patients should be warned about potentially hazardous tasks such as driving or operating machinery. The side effects probably correlate with high plasma levels (Marzolini 2001), and black African patients in particular seem to have a genetic predisposition (Haas 2004). Newer studies show that efavirenz disrupts the sleep architecture (Gallego 2004). In one study, after four weeks of treatment with efavirenz, 66 % of patients complained of dizziness, 48 % of abnormal dreams, 37 % of somnolence and 35 % of insomnia

(Fumaz 2002). Although these symptoms seem to resolve during the course of treatment, they may persist in about one fifth of patients (Lochet 2003). In such cases, efavirenz should be replaced if possible.

Liver problems occur less frequently than with nevirapine, and lead-in dosing is not necessary. Once-daily dosing is safe due to the long half-life, and, in contrast to nevirapine, has been licensed for years. However, lipids are not as favorably affected as with nevirapine. Gynecomastia is also typical for efavirenz, which is not only a psychological burden, but can also be painful (Rahim 2004). In such cases, efavirenz should be replaced with nevirapine if possible. Efavirenz is contraindicated in pregnancy.

Table 2.2. Frequency of the most important side effects of nevirapine and efavirenz (The numbers are based on various studies referenced in this chapter)

	Nevirapine	Efavirenz
CNS side effects	Rare	58-66 %
Severe CNS side effects	Very rare	5-7 %
Hepatotoxicity	17 %	8 %
Dyslipidemia	No	Frequent
Gynecomastia	No	Occasional
Rash	15 %	5 %

**Delavirdine (Rescriptor™)** was, in April 1997, the second NNRTI to be licensed by the FDA. Due to the pill burden and the required three times daily dosing, delavirdine is currently rarely prescribed. Delavirdine is not licensed in Europe where, in 1999, an application for licensure was rejected due to insufficient efficacy data. Nevertheless, delavirdine is likely to be as effective as the other NNRTIs (Conway 2000). In DLV 21, AZT+3TC+delavirdine was tested against AZT+3TC and AZT+delavirdine on 369 mostly treatment-naïve patients. After one year, 68 % had a viral load below 50 copies/ml in the triple combination arm compared to less than 10 % in the other two arms (Conway 2000). Rash (30 %) probably occurs more frequently than with other NNRTIs. Delavirdine increases plasma levels of various PIs, including saquinavir (Fletcher 2000, Harris 2002). However, use of this as a strategy for boosting, has not been widely accepted.

## References on NNRTIs

1. Almond LM, Boffito M, Hoggard PG, et al. The relationship between nevirapine plasma concentrations and abnormal liver function tests. *AIDS Res Hum Retroviruses* 2004, 20:716-22. <http://amedeo.com/lit.php?id=15307917>
2. Bartlett JA, Johnson J, Herrera G, et al. Abacavir/lamivudine in combination with efavirenz, amprenavir/ritonavir or stavudine: ESS40001 (CLASS) preliminary 48 week results. Abstract TuOrB1189, XIV International AIDS Conference 2002, Barcelona.
3. Conway B. Initial therapy with protease inhibitor-sparing regimens: evaluation of nevirapine and delavirdine. *Clin Infect Dis*. 2000, Suppl 2:S130-4. <http://amedeo.com/lit.php?id=10860897>
4. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. Virologic and immunologic response to regimens containing nevirapine or efavirenz in combination with 2 nucleoside analogues in the I.Co.N.A.) study. *J Infect Dis* 2002, 185: 1062-9. <http://amedeo.com/lit.php?id=11930316>
5. Cunningham CK, Chaix ML, Rekacewicz C, et al. Development of resistance mutations in women receiving standard antiretroviral therapy who received intrapartum nevirapine to prevent perinatal HIV type 1 transmission: a substudy of pediatric ACTG 316. *JID* 2002, 186:181-8.



6. Dailly E, Billaud E, Reliquet V, et al. No relationship between high nevirapine plasma concentration and hepatotoxicity in HIV-1-infected patients naive of antiretroviral treatment or switched from protease inhibitors. *Eur J Clin Pharmacol* 2004, 60:343-8.
7. D'Aquila RT, Hughes MD, Johnson VA, et al. Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection. *Ann Intern Med* 1996, 124:1019-30. <http://amedeo.com/lit.php?id=8633815>
8. Eshleman SH, Jackson JB. Nevirapine resistance after single dose prophylaxis. *AIDS Rev* 2002; 4:59-63. <http://amedeo.com/lit.php?id=12152519>
9. Fisac C, Fumero E, Crespo M, et al. Metabolic benefits 24 months after replacing a protease inhibitor with abacavir, efavirenz or nevirapine. *AIDS* 2005, 19:917-25. <http://amedeo.com/lit.php?id=15905672>
10. Fletcher CV, Acosta EP, Cheng H, et al. Competing drug-drug interactions among multidrug antiretroviral regimens used in the treatment of HIV-infected subjects: ACTG 884. *AIDS* 2000, 14:2495-2501. <http://amedeo.com/lit.php?id=11101060>
11. Friedl AC, Ledergerber B, Flepp M, et al. Response to first protease inhibitor- and efavirenz-containing antiretroviral combination therapy. *AIDS* 2001, 15: 1793-800. <http://amedeo.com/lit.php?id=11579241>
12. Fumaz CR, Tuldra A, Ferrer MJ, et al. Quality of life, emotional status, and adherence of HIV-1-infected patients treated with efavirenz versus PI-containing regimens. *J AIDS* 2002, 29:244-53. <http://amedeo.com/lit.php?id=11873073>
13. Gallego L, Barreiro P, del Rio R, et al. Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz. *Clin Infect Dis* 2004, 38:430-2. <http://amedeo.com/lit.php?id=14727217>
14. Garcia F, Knobel H, Sambeat MA, et al. Comparison of twice-daily stavudine plus once- or twice-daily didanosine and nevirapine in early stages of HIV infection: the scan study. *AIDS* 2000, 14:2485-94. <http://amedeo.com/lit.php?id=11101059>
15. GESIDA 26/02 Study Group. Failure of Cetirizine to prevent nevirapine-associated rash: a double-blind placebo-controlled trial for the GESIDA 26/01 Study. *J Acquir Immune Defic Syndr* 2004, 37:1276-1281. <http://amedeo.com/lit.php?id=15385735>
16. Gonzalez de Requena D, Nunez M, Jimenez-Nacher I, Soriano V. Liver toxicity caused by nevirapine. *AIDS* 2002; 16:290-1. <http://amedeo.com/lit.php?id=11807315>
17. Gulick RM, Ribaldo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004, 350:1850-1861. <http://amedeo.com/lit.php?id=15115831>
18. Haas DW, Ribaldo HJ, Kim RB, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004;18:2391-2400. <http://amedeo.com/lit.php?id=15622315>
19. Harris M, Alexander C, O'Shaughnessy M, Montaner JS. Delavirdine increases drug exposure of ritonavir-boosted protease inhibitors. *AIDS* 2002; 16: 798-9.
20. Henry K, Erice A, Tierney C, et al. A randomized, controlled, double-blind study comparing the survival benefit of four different reverse transcriptase inhibitor therapies (three-drug, two-drug, and alternating drug) for the treatment of advanced AIDS. ACTG 193A Study Team. *J AIDS Hum Retrovirol* 1998, 19:339-49. <http://amedeo.com/lit.php?id=9833742>
21. Johnson JA, Li JF, Morris L, et al. Emergence of drug-resistant hiv-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. *J Infect Dis* 2005, 192:16-23. <http://amedeo.com/lit.php?id=15942889>
22. Jourdain G, Ngo-Giang-Huong N, Le Coeur S, et al. Intrapartum exposure to nevirapine and subsequent maternal responses to nevirapine-based antiretroviral therapy. *N Engl J Med* 2004, 351:229-40.
23. Kappelhoff BS, van Leth F, Robinson PA, et al. Are adverse events of nevirapine and efavirenz related to plasma concentrations? *Antivir Ther* 2005, 10:489-98. <http://amedeo.com/lit.php?id=16038474>
24. Launay O, Roudiere L, Boukli N, et al. Assessment of cetirizine, an antihistamine, to prevent cutaneous reactions to nevirapine therapy: results of the viramune-zyrtec double-blind, placebo-controlled trial. *Clin Infect Dis* 2004, 38:e66-72. <http://amedeo.com/lit.php?id=15095233>
25. Lochet P, Peyriere H, Lotthe A, Mauboussin JM, Delmas B, Reynes J. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. *HIV Med* 2003, 4:62-6. <http://amedeo.com/lit.php?id=12534961>
26. Martinez E, Arnaiz JA, Podzamczar D, et al. Substitution of nevirapine, efavirenz or abacavir for protease inhibitors in patients with HIV infection. *N Eng J Med* 2003; 349:1036-46. <http://amedeo.com/lit.php?id=12968087>
27. Martin AM, Nolan D, James I, et al. Predisposition to nevirapine hypersensitivity associated with HLA-DRB1\*0101 and abrogated by low CD4 T-cell counts. *AIDS* 2005, 19:97-9. <http://amedeo.com/lit.php?id=15627041>

28. Marzolini C, Telenti A, Decosterd LA, Greub G, Biollaz J, Buclin T. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001, 15: 71-5. <http://amedeo.com/lit.php?id=11192870>
29. Miller V, Staszewski S, Boucher CAB, Phair JP. Clinical experience with non-nucleoside reverse transcriptase inhibitors. *AIDS* 1997, 11 (suppl A): S157-164.
30. Muro E, Droste JA, Hofstede HT, et al. Nevirapine plasma concentrations are still detectable after more than 2 weeks in the majority of women receiving single-dose nevirapine: implications for intervention studies. *J AIDS* 2005; 39:419-421. <http://amedeo.com/lit.php?id=16010163>
31. Nunez M, Soriano V, Martin-Carbonero L, et al. SENC trial: a randomized, open-label study in HIV-infected naive individuals. *HIV Clin Trials* 2002, 3:186-94.
32. Phillips AN, Pradier C, Lazzarin A, et al. Viral load outcome of non-nucleoside reverse transcriptase inhibitor regimens for 2203 mainly antiretroviral-experienced patients. *AIDS* 2001;15:2385-95. <http://amedeo.com/lit.php?id=11740189>
33. Piketty C, Gerard L, Chazallon C, et al. Virological and immunological impact of non-nucleoside reverse transcriptase inhibitor withdrawal in HIV-infected patients with multiple treatment failures. *AIDS* 2004, 18:1469-71. <http://amedeo.com/lit.php?id=15199325>
34. Podzamczar D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). *Antivir Ther* 2002, 7:81-90.
35. Raboud JM, Rae S, Vella S, et al. Meta-analysis of two randomized controlled trials comparing combined zidovudine and didanosine therapy with combined zidovudine, didanosine, and nevirapine therapy in patients with HIV. *INCAS study team. J AIDS* 1999, 22: 260-6. <http://amedeo.com/lit.php?id=10770346>
36. Raffi F, Reliquet V, Ferre V, et al. The VIRGO study: nevirapine, didanosine and stavudine combination therapy in antiretroviral-naive HIV-1-infected adults. *Antivir Ther* 2000, 5: 267-72.
37. Rahim S, Ortiz O, Maslow M, et al. A case-control study of gynecomastia in HIV-1-infected patients receiving HAART. *AIDS Read* 2004, 14:23-4. <http://amedeo.com/lit.php?id=14959701>
38. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349: 2293-303. <http://amedeo.com/lit.php?id=14668455>
39. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *J Infect Dis* 2005;191:825-9. <http://amedeo.com/lit.php?id=15717255>
40. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349: 2304-15. <http://amedeo.com/lit.php?id=14668456>
41. Sheran M. The NNRTIs efavirenz and nevirapine in the treatment of HIV. *HIV Clin Trials* 2005, 6:158-68.
42. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J AIDS* 2004; 36: 1011-1019. <http://amedeo.com/lit.php?id=15247553>
43. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *NEJM* 1999, 341:1865-73. <http://amedeo.com/lit.php?id=10601505>
44. Storfer S, Leith J, Piliero P, Hall D. Analysis of hepatic events within the 2NN study: controlling for ethnicity and CD4+ count at initiation of nevirapine therapy. Abstract PE9.6/2. 10th EACS 2005. Dublin.
45. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection. *JAMA* 2000, 283: 74-80. <http://amedeo.com/lit.php?id=10632283>
46. Sulkowski MS, Thomas DL, Mehta SH, Chaisson RE, Moore RD. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002, 35:182-9. <http://amedeo.com/lit.php?id=11786975>
47. Torre D, Tambini R, Speranza F. Nevirapine or efavirenz combined with two nucleoside reverse transcriptase inhibitors compared to HAART: a meta-analysis of randomized clinical trials. *HIV Clin Trials* 2001, 2: 113-21. <http://amedeo.com/lit.php?id=11590519>
48. Van der Valk M, Kastelein JJ, Murphy RL, et al. Nevirapine-containing antiretroviral therapy in HIV-1 infected patients results in an anti-atherogenic lipid profile. *AIDS* 2001, 15: 2407-14. <http://amedeo.com/lit.php?id=11740191>
49. Van Heeswijk RP, Veldkamp AI, Mulder JW, et al. The steady-state pharmacokinetics of nevirapine during once daily and twice daily dosing in HIV-1-infected individuals. *AIDS* 2000, 14:F77-82. <http://amedeo.com/lit.php?id=10853971>

50. Van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003, 17:987-99. <http://amedeo.com/lit.php?id=12700448>
51. Van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004, 363:1253-63. <http://amedeo.com/lit.php?id=15094269>
52. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005, 192:958-66. <http://amedeo.com/lit.php?id=16107947>
53. Winston A, Pozniak A, Smith N, et al. Dose escalation or immediate full dose when switching from efavirenz to nevirapine-based highly active antiretroviral therapy in HIV-1-infected individuals? *AIDS* 2004, 18:572-4. <http://amedeo.com/lit.php?id=15090815>
54. Yazdanpanah Y, Sissoko D, Egger M, et al. Clinical efficacy of antiretroviral combination therapy based on protease inhibitors or NNRTIs: indirect comparison of controlled trials. *BMJ* 2004, 328:249. <http://amedeo.com/lit.php?id=14742351>

## Protease inhibitors (PIs)

### Mechanism of action and efficacy

The HIV protease cuts the viral gag-pol polyprotein into its functional subunits. If the protease is inhibited and proteolytic splicing prevented, non-infectious virus particles will result. With the knowledge of the molecular structure of the protease encoded by the virus, the first protease inhibitors were designed in the early nineties; these substances were modified in such a way that they fit exactly into the enzyme active site of the HIV protease (review: Eron 2001).

Since 1995, protease inhibitors have revolutionized the treatment of HIV infection. At least three large studies with clinical endpoints have demonstrated the efficacy of indinavir, zidovudine and zalcitabine (Hammer 1997, Cameron 1998, Stellbrink 2000). Although PIs have been criticized at times due to their frequently high pill burden and side effects (see below), they remain an essential component of HAART. With growing knowledge of the mitochondrial toxicity of nucleoside analogs and through the introduction of easy-to-take PIs, this class of drugs is currently experiencing a renaissance – now even PI-only regimens are being investigated.

As with the NNRTIs, initially, there was competition among pharmaceutical companies to establish which PI had superior efficacy. However, there have (still) only been few comparative randomized studies, which is not just the fault of the pharmaceutical industry, but also the result of restrictive regulations in many countries preventing the conduction of such studies, or at least making them very difficult.

But even in the case of PIs, the differences are not so significant as to completely compromise individual members of this class. Two exceptions that have since been taken off the market are: the hard gel capsule saquinavir and ritonavir on its own. Boosted PI combinations are presumably more effective than unboosted regimens (see below for more details).

Apart from gastrointestinal side effects and high pill burden, all PIs used in long-term therapy encounter problems – to a greater or lesser extent, all are associated with lipodystrophy and dyslipidemia (review: Nolan 2003). Other problems can cause drug interactions, which can sometimes be substantial on ritonavir-boosted regimens. Cardiac arrhythmias (Anson 2005) and sexual dysfunction have also been

attributed to PIs (Schrooten 2001), although the data does not remain unchallenged (Lallemand 2002).

There is a high degree of cross-resistance between protease inhibitors, which was described even before PIs were put on the market (Condra 1995). All PIs are inhibitors of the CYP3A4 system and interact with many other drugs (see “Drug Interactions” chapter). Ritonavir is the strongest inhibitor, saquinavir probably the weakest.

### Individual agents: Special features and problems

**Amprenavir (Agenerase™)** was the fifth PI to enter the European market, in June 2000. Following the licensing of fosamprenavir in 2004 (Telzir™, see below), patients should be switched to Telzir™ (Rodriguez 2004). The 150 mg tablet has already been discontinued, and only the suspension and the pediatric 50 mg tablet are still available.

**Atazanavir (Reyataz™)** was the first once-daily PI to be licensed in 2004. Two Phase II studies (AI424-007 and -008) demonstrated better tolerability in comparison to nelfinavir, although the antiretroviral potency was comparable (Murphy 2003, Sanne 2003). In a Phase III study (AI424-034), atazanavir (with a nuke backbone of AZT+3TC) showed comparable virological efficacy to efavirenz (Squires 2004). Lipid levels were clearly better in the atazanavir arm than in the efavirenz arm. Data from other studies are now available showing that lipids improve when nelfinavir or other PIs are replaced by atazanavir (Wood 2004, Gatell 2005). Boosting of atazanavir with ritonavir does not seem to have negative effects on lipid levels, and is generally recommended, particularly for combinations with NNRTIs or tenofovir, which significantly lower atazanavir levels (Le Tiec 2005). Unfavorable interactions occur particularly in combination with proton pump inhibitors (see “Drug Interactions” chapter).

Atazanavir is slightly less effective than lopinavir in treatment-experienced patients, when it is not boosted (Cohen 2005). This does not seem to be the case if ritonavir is used as a booster, at least when PI resistance is limited (Johnson 2006). The primary resistance mutation for this drug is I50L, which does not impair sensitivity to other PIs, and possibly even increases it (Colonna 2003). On the other hand, there are a number of cross-resistance mutations, and susceptibility to many virus isolates with moderate PI resistance is reduced (Schnell 2003). Atazanavir is still only licensed for treatment-experienced patients. In order to increase its licensure, atazanavir is currently being tested against lopinavir in a large worldwide study on therapy-naïve patients (CASTLE study).

In contrast to other PIs, atazanavir does not have a negative influence on lipid levels (Robinson 2000, Sanne 2003, Cohen 2005, Johnson 2006), which is its main advantage besides the once-daily dosing. It also does not induce insulin resistance (Noor 2004). Whether this will be reflected clinically (with less lipodystrophy), as suggested in some studies (Haerter 2004, Jemsek 2006), has still to be confirmed.

One problem with atazanavir is that more than half the patients experience elevated bilirubin levels, which can reach grade 3-4 in approximately one third of all cases (Squires 2004). Some patients even develop jaundice. The mechanism for this resembles that of Gilbert’s syndrome (and the increased levels with indinavir – do not combine these two drugs!); there is reduced conjugation in the liver. Recently, a

genetic predisposition has been identified (Rotger 2005). Although the hyperbilirubinemia is supposed to be harmless and only few cases of serious hepatic disorders have been described to date (Eholie 2004), liver function should be monitored when on atazanavir, and treatment discontinued in cases of significantly elevated bilirubin (> 5-6 times the upper limit of normal).

**Fosamprenavir (Telzir™ or Lexiva™)**, as a calcium phosphate ester, has better solubility and absorption than amprenavir. This means that a significantly lower number of pills have to be taken. Fosamprenavir was licensed for treatment-naïve and –experienced patients in 2004. The recommended doses are either a) 1400 mg bid (2 pills bid), b) 700 mg bid plus 100 mg ritonavir bid (2 pills bid) or c) 1400 mg plus 200 mg ritonavir once daily (4 pills qd). Once-daily dosing is not recommended for treatment-experienced patients, and, like the unboosted dose, is not licensed in Europe. One advantage of the drug is that there are no restrictions with respect to food intake, and it can be taken on an empty stomach or with a meal.

Three pivotal studies have investigated fosamprenavir: NEAT, SOLO and CONTEXT. In the NEAT Study, unboosted fosamprenavir was slightly more effective virologically and had better tolerability than nelfinavir in treatment-naïve patients (Rodriguez-French 2004). However, a relatively heterogeneous study population and high dropout rates in both arms limited this study. In the SOLO study, boosted once-daily fosamprenavir was about as effective as nelfinavir (Gathe 2004). No resistance was found on boosted fosamprenavir even after 48 weeks (MacManus 2004). In the CONTEXT Study, fosamprenavir was not quite as effective as lopinavir/r in PI-experienced patients; the difference, however, was not significant (Elston 2004). As a potent inducer of amprenavir metabolism, efavirenz can significantly (probably with clinical relevance) lower plasma levels, as can nevirapine. This does not occur when fosamprenavir is boosted with ritonavir (Wire 2002, DeJesus 2004). Beware of the combination with lopinavir as plasma levels (AUC, Cmin) of both drugs are lowered! This unfortunately seems to eliminate what would otherwise have been an interesting salvage option (Kashuba 2005).

**Indinavir (Crixivan™)** is one of the oldest PIs, which was initially very successful in large studies (Gulick 1997, Hammer 1997). Later, indinavir had mixed success, at least when unboosted: in the Atlantic Study, it was about as effective as nevirapine (Van Leeuwen 2003), but in the 006 Study it was clearly weaker than efavirenz (Staszewski 1999). In the double blind, randomized CNAAB3005 Study, indinavir was more effective than abacavir, particularly in patients with high viral load at baseline (Staszewski 2001). In the CHEESE Study and MaxCmin1 studies, the efficacy was comparable to saquinavir-SGC (Cohen-Stuart 1999, Dragstedt 2003). Low protein binding (60 %) seems to allow better CNS penetration than with other PIs (Martin 1999).

There are, however, a number of problems associated with indinavir. Firstly, it causes nephrolithiasis in approximately 5-25 % of patients (Meraviglia 2002), and thus requires good hydration (at least 1.5 liters daily). Unboosted indinavir must be taken three times daily on an empty stomach (Haas 2000), and for this reason, boosting with ritonavir is recommendable, although may increase the rate of side effects (Arnaiz 2004). In the MaxCmin1 Trial, the dropout rate on indinavir was notably higher than among patients receiving saquinavir (Dragstedt 2003). Specific side effects associated with indinavir include mucocutaneous side effects reminis-

cent of retinoid therapy: alopecia, dry skin and lips, and ingrown nails. Many patients may also develop asymptomatic hyperbilirubinemia. Although it seems that the dose and thus toxicity can be reduced in most patients by boosting and monitoring plasma levels, indinavir still only has an inferior role to play.

**Lopinavir/r (Kaletra™)** was licensed in April 2001 and was the first (and so far only) PI with a fixed booster dose of ritonavir. This increases concentrations of lopinavir by more than 100 fold (Sham 1998). It is possible, that by increasing the ritonavir dose, lopinavir levels can be boosted even more, which may be useful in salvage therapy (Flexner 2003).

In treatment-naïve patients in a randomized double-blind study, lopinavir/r was significantly superior to an unboosted regimen with nelfinavir. The proportion of patients with less than 50 copies/ml was 67 versus 52 % after 48 weeks (Walmsley 2002). Lopinavir/r also showed slightly better results than boosted saquinavir (still in the old Fortovase™ formulation) in an open-label randomized (MaxCmin2) trial on a heterogeneous population of treatment-experienced patients. This was particularly true for tolerability, but also with respect to treatment failure (Dragstedt 2005). In this study, however, significantly more patients in the Fortovase™ arm interrupted treatment for personal reasons - in the on-treatment analysis, at least the efficacies of saquinavir/r and lopinavir/r were comparable.

Development of resistance with lopinavir/r first-line therapy is rare, but is theoretically possible (Walmsley 2002, Kagan 2003, Conradie 2004, Friend 2004). Lopinavir/r has a high genetic barrier to resistance, and it is likely that at least 6-8 cumulative PI resistance mutations are necessary for treatment failure (Kempf 2002). The drug has good efficacy in salvage therapy, and is an important medication (see “Salvage Therapy”). However, in two large studies in PI-experienced patients, virological efficacy of lopinavir/r was not significantly higher than that of boosted atazanavir (Johnson 2006) or fosamprenavir (Elston 2004) – although the cohort numbers in these studies were rather small.

A significant problem, in addition to the gastrointestinal side effects (diarrhea, nausea) and lipodystrophy, is the often considerable, dyslipidemia, which is probably more marked than with most other PIs (Walmsley 2002, Calza 2003). A number of interactions should also be considered. The dose must be increased in combination with efavirenz and nevirapine, probably also with concurrent administration of fosamprenavir. Newer studies show that a single daily dose of lopinavir/r is possible, although diarrhea will occur slightly more often (Molina 2004). Once-daily lopinavir/r (800/200) has been licensed in the USA since May 2005.

**Nelfinavir (Viracept™)** was the fourth PI on the market and was for a long time one of the most frequently used PIs. The dose of five capsules twice daily is just as effective as three capsules three times daily. Boosting with ritonavir does not improve the plasma levels (Kurowski 2002).

In the pivotal 511 Study, 61 % of patients on nelfinavir (with AZT+3TC) had a viral load below 50 copies/ml at 48 weeks (Saag 2001). In the open-label, randomized CNAF3007 Study, the decrease in viral load was comparable to abacavir (Matheron 2003).

In comparison to NNRTIs or other PIs, nelfinavir is probably slightly less potent. In the Combine Study, nelfinavir was weaker (not significantly) than nevirapine

(Podzamczar 2002). In ACTG 384 and 364, nelfinavir showed lower efficacy than efavirenz in both treatment-naïve and nuke-experienced patients (Albrecht 2001, Robbins 2003, Shafer 2003). Finally, in the double blind, randomized M98-863 Study, the efficacy of nelfinavir was significantly poorer than that of lopinavir/r – after one year, 52 versus 67 % of patients reached a viral load below 50 copies/ml (Walmsley 2002).

The most important side effect of nelfinavir is diarrhea, which may be considerable. The drug is otherwise very well tolerated. Another positive aspect is the good resistance profile. The D30N primary mutation for nelfinavir reduces viral fitness (Martinez-Picado 1999) and does not influence the efficacy of other PIs. However, this only occurs in a few cases - other mutations that can jeopardize the success of later regimens unfortunately occur frequently (Hertogs 2000).

Nelfinavir is only rarely effective if a PI-containing regimen has failed (Lawrence 1999, Gulick 2000, Hammer 2002). In several studies, such as SPICE and TIDBID, nelfinavir was combined with saquinavir, which then significantly elevated plasma levels (Cohen 1999, Moyle 2000, Chavanet 2001). This led to increased efficacy, at least in patients with prior NRTI therapy. However, such a combination has a high pill burden and is associated with even more diarrhea – it is only accepted by few patients today. A new formulation (nelfinavir 625 mg), that enables a reduction to two capsules bid is being produced by Pfizer and is available in the USA. In Europe, where Roche has the rights, there are obviously production problems, so that the new formulation will not be available there for the time being.

**Ritonavir (Norvir™)** was the first PI for which efficacy was proven on the basis of clinical endpoints (Cameron 1998). However, ritonavir is now obsolete as a single PI, since tolerability is too poor (Katzenstein 2000). As gastrointestinal complaints and perioral paresthesias can be very disturbing, ritonavir is now only given to boost other PIs. The “baby dose” used for this purpose (100 mg bid) is tolerated better.

Ritonavir inhibits its own metabolism via the cytochrome P450 pathway. The potent enzyme induction results in a high potential for interactions; thus, many drugs are contraindicated for concomitant administration with ritonavir. Metabolic disorders probably occur more frequently than with other PIs. Caution should be exercised in the presence of impaired liver function. It is important to inform patients that ritonavir capsules must be stored at cool temperatures, which can often be a problem when traveling.

**Saquinavir** (previously **Invirase™**, **Fortovase™**, now **Invirase 500™**) was, in December 1995, the first PI to be licensed for HIV therapy and is still today one of the few substances whose efficacy has been proven based on clinical end points (Stellbrink 2000). Boosting with ritonavir raises the plasma level sufficiently, as does a simultaneous food intake, so that saquinavir should be taken with meals. Saquinavir is well tolerated – there are hardly any serious side effects. With no serious short-term problems, Saquinavir is an attractive PI for patients who need a boosted PI-regimen. The earlier hard gel (Invirase™) and soft gel (Fortovase™) capsules were replaced in 2005 by Invirase 500™ tablets, which have significantly reduced the number of pills to four a day (Bittner 2005).

It is possible that a lot of data from the time of the Fortovase™ capsules cannot be easily transferable to the new tablets, but should be briefly mentioned here. In the

CHEESE Study, there was no difference between saquinavir soft gel and indinavir (Cohen-Stuart 1999). In the MaxCmin1 Trial, in which saquinavir soft gel as well as indinavir were boosted with ritonavir, both demonstrated similar efficacy, although saquinavir was tolerated better (Dragstedt 2003). In the MaxCmin2 Trial, boosted saquinavir-SGC compared slightly less favorably to lopinavir/r (Dragstedt 2005). In the Staccato trial, after 24 weeks on a once-daily regimen (1,600 saquinavir/100 mg ritonavir) 89 % of all patients achieved a viral load below 50 copies/ml (Ananworanich 2005). With the new Invirase 500™ tablet, saquinavir has once again become an interesting option, due to its good tolerability.

**Tipranavir (Aptivus™)** is the first non-peptide PI, and is also the last PI to be licensed in Europe since July 2005. As the oral bioavailability is only moderate, ritonavir boosting (McCallister 2004) is necessary, whereby 2 x 200 mg (2 x 2 ritonavir) should be used. The plasma level can also be increased by a high fat meal.

Tipranavir shows good efficacy against PI-resistant viruses (Larder 2003). Tipranavir even has a considerable effect in the presence of UPAMs (universal protease inhibitor-associated mutations = L33I/V/F, V82A/F/L/T, I84V, and L90M), as well as mutations that are resistant to all other currently available PIs. However, the efficacy is not limitless – with 3 UPAMs, the sensitivity to tipranavir starts to decline significantly (Hall 2003). In two large Phase III trials (RESIST-1 in the USA and RESIST-2 in Europe) on 1,483 intensively pretreated patients, each of whom had an optimized therapy (optimized background therapy = OBT), tipranavir was better than the comparison PI (Lazzarin 2005). The patients had a viral load of 1,000 copies/ml and at least one primary PI mutation (but not more than 2 mutations on codons 30, 82, 84, and 90). After 24 weeks, 24 % had less than 50 copies/ml (versus 9 % on the comparison PI).

A significant problem of tipranavir, apart from dyslipidemia (grade 3-4 increase in triglycerides: 22 versus 13 % for the comparison arm), which was more serious in the RESIST Study, is the increase in transaminases. This is sometimes substantial (grade 3-4: 7 versus 1 %) and requires careful monitoring of all patients on tipranavir, especially those coinfecting with hepatitis B or C. In addition, several unfavorable interactions also occur (Roszko 2003, Walmsley 2004). The combination with delavirdine is contra-indicated, dDI has to be taken with a several hour time delay, and plasma levels of lopinavir, saquinavir, and amprenavir fall significantly, so that double PI therapy with tipranavir is currently not under consideration. As the abacavir levels also drop, this combination is not recommendable either.

### Why “boosting” PIs?

Ritonavir is a very potent inhibitor of the isoenzyme 3A4, a subunit of the cytochrome P450 hepatic enzyme system. Inhibition of these gastrointestinal and hepatic enzymes allows the most important pharmacokinetic parameters of almost all PIs to be significantly increased, or “boosted” (Kempf 1997): maximum concentration (C<sub>max</sub>), trough levels (C<sub>trough</sub>) and half-life. The interaction between ritonavir and the other PIs simplifies daily regimens by reducing the frequency and number of pills to be taken every day, in many cases independent of food intake. Some PIs can now be used in twice-daily regimens. Current trials are investigating the possibility of once-daily dosing.



Boosting can be effective against resistant viral strains as a result of the elevated drug plasma levels (Condra 2000). Resistances are only rarely observed on boosted PIs, at least in therapy-naïve patients, as the genetic barrier is high. According to some experts, patients with an elevated viral load should receive boosted PIs at the start of therapy. Boosting with ritonavir is usually indicated by addition of an “/r” after the drug name.

Indeed, nelfinavir is the only PI for which boosting with ritonavir is not recommended as plasma levels do not rise significantly (Kurowski 2002). In addition to boosting with ritonavir, boosting with a combination of saquinavir and nelfinavir is possible (Moyle 2000, Stellbrink 2002). In our experience, it works very well, but is no longer practical today due to the large number of pills.

Ritonavir boosting is also associated with risks. There is a high degree of variability in plasma levels among individuals. As well as the trough levels, the peak levels are also elevated, which may lead to more side effects. If in doubt (reduced efficacy, side effects), plasma levels should be measured in all cases of boosting, especially in patients with severe hepatic diseases, because the extent of interaction cannot be predetermined for individual cases. Dose adjustment is often necessary. Apart from boosting with atazanavir, all other booster combinations appear to increase lipid levels (Van der Valk 2003).

**Saquinavir/r** is the most-studied boosted combination. Due to the low oral bioavailability of saquinavir, this combination was tested very early on (detailed review: Plosker 2003). Plasma levels of saquinavir can be increased 20 fold by ritonavir. The new Invirase-500 tablets are licensed in the 1,000/100 bid dose (1,000 mg saquinavir and 100 mg ritonavir twice daily).

**Indinavir/r** has also been well investigated. Good pharmacokinetic data exists on the 2 x 800/100 mg daily dose (Van Heeswijk 1999). In a smaller pilot study, however, results showed nephrolithiasis in 19 of 57 patients (Voigt 2002). The 400/400 mg dose possibly induces less renal side effects. The boosted combination generally has a slightly higher rate of side effects (Arnaiz 2003), probably because boosting of indinavir results in doses that are too high in many patients (Ghosh 2003). The German MIDAS protocol attempted to gradually reduce doses. Preliminary result: It is likely that a dose of 2 x 400/100 mg is often possible.

**Lopinavir/r** is, to date, the only fixed-dose boosted combination therapy available in one capsule (see above). With **fosamprenavir**, **atazanavir**, and **tipranavir**, three further PIs have arrived, through which good plasma levels and even sometimes once-daily dosing can be achieved when boosted.

### Which boosted combination is best?

So far, only a few studies have made direct comparisons between boosted PI regimens. Therefore, currently many experts consider lopinavir/r to be the most effective PI boosting. On closer observation, the available data is not so clear.

In the MaxCmin2 Study, both treatment-naïve and treatment-experienced patients were randomized to receive either saquinavir/r (soft gel) or lopinavir/r. At first glance, saquinavir/r did slightly less well (Dragstedt 2005). After 48 weeks, the proportion of patients in the ITT analysis with less than 50 copies/ml was 65 versus 57 % in favor of lopinavir/r. However, this significance was not detectable in the on-treatment analysis (70 versus 75 %). The explanation is that a relatively large

number of patients in this open-label study discontinued saquinavir/r “of their own accord” (presumably because of the high number of pills). There was therefore no conclusive proof of the virological supremacy of lopinavir/r in this study.

This was also true for the AI424-045 Study, in which lopinavir/r was no better than boosted atazanavir/r in treatment-experienced patients, at least in those patients with few PI resistances (Johnson 2006). In the CONTEXT Study, there was only a trend in favor of lopinavir/r in treatment-experienced patients compared to fosamprenavir/r, at least with the twice-daily dose. The once-daily dose of fosamprenavir/r is likely to be weaker (Elston 2004).

It is with anticipation that the results of the many trials, currently comparing boosted PIs with lopinavir/r in therapy-naïve patients, including atazanavir/r (CASTLE), saquinavir/r (GEMINI), darunavir/r (ARTEMIS), are being awaited. Not forgetting ACTG 5142, in which a NNRTI (efavirenz) is being tested against lopinavir/r. The first results are expected in 2006.

Table 2.3: Current doses of protease inhibitors with ritonavir boosting.

	Dose (mg)	Pills*/day	Comment
Atazanavir/r	1 x 300/100	1 x 3	Only approved for treatment-experienced patients in many countries
Darunavir/r	2 x 600/100	2 x 3	Only available in EAP**
Fosamprenavir/r	2 x 700/100	2 x 2	Should be used instead of amprenavir
Fosamprenavir/r	1 x 1400/200	1 x 4	Only approved for PI-naïve patients in Europe
Indinavir/r	2 x 800/100	2 x 3	High rate of nephrolithiasis
Lopinavir/r	2 x 400/100	2 x 3	Only fixed booster combination
Lopinavir/r	1 x 800/200	1 x 6	Currently only approved in the USA
Saquinavir/r	2 x 1000/100	2 x 3	Officially licensed for boosting
Tipranavir/r	2 x 500/200	2 x 4	Only approved for treatment-experienced patients

\* Number of pills including the ritonavir dose. \*\*EAP = expanded access program

## References on protease inhibitors

- Albrecht M, Bosch RJ, Hammer SM, et al. Nelfinavir, efavirenz, or both after the failure of nucleoside treatment of HIV infection. *New Eng J Med* 2001, 345:398-407. <http://amedeo.com/lit.php?id=11496850>
- Ananworanich J, Hill A, Siangphoe U, et al. A prospective study of efficacy and safety of once-daily saquinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors in treatment-naïve Thai patients. *Antivir Ther* 2005, 10:761-7. <http://amedeo.com/lit.php?id=16218176>
- Anson BD, Weaver JG, Ackerman MJ, et al. Blockade of HERG channels by HIV protease inhibitors. *Lancet* 2005, 365:682-6. <http://amedeo.com/lit.php?id=15721475>
- Arnaiz JA, Mallolas J, Podzamczar D, et al. Continued indinavir versus switching to indinavir/ritonavir in HIV-infected patients with suppressed viral load. *AIDS* 2003, 17:831-40. <http://amedeo.com/lit.php?id=12660530>
- Bittner B, Riek M, Holmes B, Grange S. Saquinavir 500 mg film-coated tablets demonstrate bioequivalence to saquinavir 200 mg hard capsules when boosted with twice-daily ritonavir in healthy volunteers. *Antivir Ther* 2005, 10:803-10. <http://amedeo.com/lit.php?id=16312177>
- Calza L, Manfredi R, Farneti B, Chiodo F. Incidence of hyperlipidaemia in a cohort of 212 HIV-infected patients receiving a protease inhibitor-based antiretroviral therapy. *Int J Antimicrob Agents* 2003, 22:54-59. <http://amedeo.com/lit.php?id=12842328>

7. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998, 351:543-9. <http://amedeo.com/lit.php?id=9492772>
8. Chavanet P, Piroth L, Grappin M, et al. Randomized salvage therapy with saquinavir-ritonavir versus saquinavir-nelfinavir for highly protease inhibitor-experienced HIV-infected patients. *HIV Clinical Trials* 2001, 2:408-412. <http://amedeo.com/lit.php?id=11673815>
9. Cohen C, Nieto-Cisneros L, Zala C, et al. Comparison of atazanavir with lopinavir/ritonavir in patients with prior protease inhibitor failure: a randomized multinational trial. *Curr Med Res Opin* 2005, 21:1683-92. <http://amedeo.com/lit.php?id=16238909>
10. Cohen Stuart JW, Schuurman R, Burger DM, et al. Randomized trial comparing saquinavir soft gelatin capsules versus indinavir as part of triple therapy (CHEESE study). *AIDS* 1999, 13: F53-8. <http://amedeo.com/lit.php?id=10357371>
11. Colonna RJ, Thiry A, Limoli K, Parkin N. Activities of atazanavir (BMS-232632) against a large panel of HIV type 1 clinical isolates resistant to one or more approved protease inhibitors. *Antimicrob Agents Chemother* 2003, 47:1324-33. <http://amedeo.com/lit.php?id=12654666>
12. Condra JH, Petropoulos CJ, Ziermann R, et al. Drug resistance and predicted virologic responses to HIV type 1 protease inhibitor therapy. *J Infect Dis* 2000, 182: 758-65. <http://amedeo.com/lit.php?id=10950769>
13. Condra JH, Schleif WA, Blahy OM, et al. In vivo emergence of HIV-1 variants resistant to multiple protease inhibitors. *Nature* 1995, 374:569-71. <http://amedeo.com/lit.php?id=7700387>
14. Conradie F, Sanne I, Venter W, et al. Failure of lopinavir-ritonavir (Kaletra)-containing regimen in an antiretroviral-naive patient. *AIDS* 2004, 18:1084-5. <http://amedeo.com/lit.php?id=15096819>
15. Conway B. Initial therapy with protease inhibitor-sparing regimens: evaluation of nevirapine and delavirdine. *Clin Infect Dis*. 2000, Suppl 2:S130-4. <http://amedeo.com/lit.php?id=10860897>
16. Corbett AH, Eron JJ, Fiscus SA, Rezk NL, Kashuba AD. The pharmacokinetics, safety, and initial virologic response of a triple-protease inhibitor salvage regimen containing amprenavir, saquinavir, and ritonavir. *JAIDS* 2004, 36:921-928. <http://amedeo.com/lit.php?id=15220698>
17. Deeks SG, Grant RM, Beatty GW, et al. Activity of a ritonavir plus saquinavir-containing regimen in patients with virologic evidence of indinavir or ritonavir failure. *AIDS* 1998, 12: F97-102. <http://amedeo.com/lit.php?id=9677159>
18. DeJesus E, Piliro P, Summers K, et al. Evaluation of the pharmacokinetic drug interaction between fosamprenavir (FPV), FPV plus ritonavir, and nevirapine in HIV-infected patients (APV10014). Abstract A447, 44<sup>th</sup> ICAAC 2004, Washington.
19. Dragstedt UB, Gerstoft J, Pedersen C, et al. Randomised trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human HIV type-1 infected patients: the MaxCmin1 trial. *J Inf Dis* 2003, 188:635-42. <http://amedeo.com/lit.php?id=12934178>
20. Dragstedt UB, Gerstoft J, Youle M, et al. A randomized trial to evaluate lopinavir/ritonavir versus saquinavir/ritonavir in HIV-1-infected patients: the MaxCmin2 trial. *Antivir Ther* 2005, 10:735-43. <http://amedeo.com/lit.php?id=16218173>
21. Eholie SP, Lacombe K, Serfaty L, et al. Acute hepatic cytolysis in an HIV-infected patient taking atazanavir. *AIDS* 2004, 18:1610-1.
22. Elston RC, Yates P, Tisdale M, et al. GW433908 (908)/ritonavir (r): 48-week results in PI-experienced subjects: A retrospective analysis of virological response based on baseline genotype and phenotype. Abstract MoOrB1055, XV Int AIDS Conf 2004; Bangkok.
23. Eron JJ JR. HIV-1 protease inhibitors. *Clin Infect Dis* 2000, 30 Suppl 2: S160-70. <http://amedeo.com/lit.php?id=10860901>
24. Flexner C, Chiu YL, Foit C, et al. Steady state pharmacokinetics and short-term virologic response of two lopinavir/ritonavir (LPV/r) high-dose regimens in multiple antiretroviral-experienced subjects (study 049). Abstract 843, 2nd IAS 2003, Paris.
25. Friend J, Parkin N, Liegler T, et al. Isolated lopinavir resistance after virological rebound of a ritonavir/lopinavir-based regimen. *AIDS* 2004, 18:1965-6.
26. Gatell JM, Salmon-Ceron D, Lazzarin A, et al. Efficacy of atazanavir based HAART in patients switched from a stable PI or boosted PI treatment. Planned week 24 analysis of a phase IIIb 48 week multicenter, open-label, randomized, prospective trial. The SWAN study. Abstract WePe6.3C15, 3<sup>rd</sup> IAS 2005, Rio.
27. Gathe JC Jr, Iye P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS* 2004, 18:1529-37. <http://amedeo.com/lit.php?id=15238771>
28. Ghosn J, Lamotte C, Ait-Mohand H, et al. Efficacy of a twice-daily antiretroviral regimen containing 100 mg ritonavir/400 mg indinavir in HIV-infected patients. *AIDS* 2003, 17:209-14. <http://amedeo.com/lit.php?id=12545081>

29. Gulick RM, Hu XJ, Fiscus SA, et al. Randomized study of saquinavir with ritonavir or nelfinavir together with delavirdine, adefovir or both in HIV-infected adults with virologic failure on indinavir: ACTG 359. *J Inf Dis* 2000, 182:1375-1384. <http://amedeo.com/lit.php?id=11023461>
30. Gulick RM, Mellors JW, Havir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with HIV infection and prior antiretroviral therapy. *N Engl J Med* 1997, 337: 734-9. <http://amedeo.com/lit.php?id=92872228>
31. Haas DW, Arathoon E, Thompson MA, et al. Comparative studies of two-times-daily versus three-times-daily indinavir in combination with zidovudine and lamivudine. *AIDS* 2000, 14: 1973-8. <http://amedeo.com/lit.php?id=10997402>
32. Haerter G, Manfras BJ, Mueller M, et al. Regression of lipodystrophy in HIV-infected patients under therapy with the new protease inhibitor atazanavir. *AIDS* 2004, 18:952-5. <http://amedeo.com/lit.php?id=15060446>
33. Hall D, McCallister S, Neubacher D, et al. Characterisation of treatment-emergent resistance mutations in two Phase II studies of tipranavir. *Antiviral Therapy* 8: S16, 2003.
34. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. ACTG 320. *N Engl J Med* 1997, 337:725-33. <http://amedeo.com/lit.php?id=9287227>
35. Hammer SM, Vaida F, Bennett KK, et al. Dual vs single protease inhibitor therapy following antiretroviral treatment failure: a randomized trial. *JAMA* 2002;288:169-80. <http://amedeo.com/lit.php?id=12095381>
36. Hertogs K, Bloor S, Kemp SD, et al. Phenotypic and genotypic analysis of clinical HIV-1 isolates reveals extensive protease inhibitor cross-resistance: a survey of over 6000 samples. *AIDS* 2000, 14:1203-1210. <http://amedeo.com/lit.php?id=10894285>
37. Jemsek JG, Arathoon E, Arlotti M, et al. Body fat and other metabolic effects of atazanavir and efavirenz, each administered in combination with zidovudine plus lamivudine, in antiretroviral-naive HIV-infected patients. *CID* 2006, 42:273-80. <http://amedeo.com/lit.php?id=16355341>
38. Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. *AIDS* 2006, 20:711-718. <http://amedeo.com/lit.php?id=16514301>
39. Kagan RM, Shenderovich M, Ramnarayan K, Heseltine PNR. Emergence of a novel lopinavir resistance mutation at codon 47 correlates with ARV utilization. *Antivir Ther* 2003, 8:S54.
40. Kashuba AD, Tierney C, Downey GF, et al. Combining fosamprenavir with lopinavir/ritonavir substantially reduces amprenavir and lopinavir exposure: ACTG protocol A5143 results. *AIDS* 2005, 19:145-52.
41. Katzenstein TL, Kirk O, Pedersen C, et al. The danish protease inhibitor study: a randomized study comparing the virological efficacy of 3 PI-containing regimens for the treatment of HIV type 1 infection. *J Infect Dis* 2000, 182: 744-50. <http://amedeo.com/lit.php?id=10950767>
42. Kempf DJ, Isaacson JD, King MS, et al. Analysis of the virological response with respect to baseline viral phenotype and genotype in protease inhibitor-experienced HIV-1-infected patients receiving lopinavir/ritonavir therapy. *Antiviral Therapy* 2002, 7:165-174. <http://amedeo.com/lit.php?id=12487383>
43. Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the HIV protease by coadministration with ritonavir. *Antimicrob Agents Chemother* 1997, 41:654-60. <http://amedeo.com/lit.php?id=9056009>
44. Kurowski M, Kaeser B, Sawyer A, Popescu M, Mrozkiewicz A. Low-dose ritonavir moderately enhances nelfinavir exposure. *Clin Pharmacol Ther* 2002, 72:123-32. <http://amedeo.com/lit.php?id=12189359>
45. Lallemand F, Salhi Y, Linard F, Giami A, Rozenbaum W. Sexual dysfunction in 156 ambulatory HIV-infected men receiving HAART combinations with and without protease inhibitors. *J AIDS* 2002, 30: 187-90. <http://amedeo.com/lit.php?id=12045681>
46. Larder BA, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. *AIDS* 2000, 14:1943-8. <http://amedeo.com/lit.php?id=10997398>
47. Lawrence J, Schapiro J, Winters M, et al. Clinical resistance patterns and responses to two sequential protease inhibitor regimens in saquinavir and reverse transcriptase inhibitor experienced persons. *J Inf Dis* 1999, 179:1356-1364. <http://amedeo.com/lit.php?id=10228055>
48. Lazzarin A, Mukwaya G, Clumek N, et al. Tipranavir/ritonavir (TPV/r) demonstrates superior treatment response to lopinavir/r, amprenavir/r or saquinavir/r in PI-experienced patients from the TPV RESIST-1 and RESIST-2 trials. Abstract WePe6.3C07, 3rd IAS 2005, Rio de Janeiro.
49. MacManus S, Yates PJ, Elston RC, et al. GW433908/ritonavir once daily in antiretroviral therapy-naive HIV-infected patients: absence of protease resistance at 48 weeks. *AIDS* 2004, 18:651-5. <http://amedeo.com/lit.php?id=15090770>

50. Martin C, Sonnerborg A, Svensson JO, Stahle L. Indinavir-based treatment of HIV-1 infected patients: efficacy in the central nervous system. *AIDS* 1999, 13: 1227-32. <http://amedeo.com/lit.php?id=10416527>
51. Martinez-Picado X, Savara A, Sutton L, et al. Replicative fitness of protease inhibitor-resistant mutants of HIV-1. *J Virol* 1999, 73: 3744-3752.
52. Matheron S, Descamps D, Boue F, et al. Triple nucleoside combination zidovudine/lamivudine/abacavir versus zidovudine/lamivudine/ nelfinavir as first-line therapy in HIV-1-infected adults: a randomized trial. *Antivir Ther* 2003, 8:163-71. <http://amedeo.com/lit.php?id=12741629>
53. McCallister S, Valdez H, Curry K, et al. A 14-day dose-response study of the efficacy, safety, and pharmacokinetics of the nonpeptidic protease inhibitor tipranavir in treatment-naive HIV-1-infected patients. *J AIDS* 2004, 35:376-82. <http://amedeo.com/lit.php?id=15097154>
54. Meraviglia P, Angeli E, Del Sorbo F, et al. Risk factors for indinavir-related renal colic in HIV patients: predictive value of indinavir dose/body mass index. *AIDS* 2002, 16:2089-2093. <http://amedeo.com/lit.php?id=12370513>
55. Moyle G, Pozniak A, Opravil M, et al. The SPICE study: 48-week activity of combinations of saquinavir soft gelatin and nelfinavir with and without nucleoside analogues. *J Acquir Immune Defic Syndr* 2000, 23: 128-37. <http://amedeo.com/lit.php?id=10737427>
56. Murphy RL, Sanne I, Cahn P, et al. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS* 2003, 17:2603-14. <http://amedeo.com/lit.php?id=14685054>
57. Nolan D. Metabolic complications associated with HIV protease inhibitor therapy. *Drugs* 2003, 63:2555-74. <http://amedeo.com/lit.php?id=14636077>
58. Noor MA, Parker RA, O'mara E, et al. The effects of HIV protease inhibitors atazanavir and lopinavir/ritonavir on insulin sensitivity in HIV-seronegative healthy adults. *AIDS* 2004, 18:2137-2144. <http://amedeo.com/lit.php?id=15577646>
59. Plosker GL, Scott LJ. Saquinavir: a review of its use in boosted regimens for treating HIV infection. *Drugs* 2003, 63:1299-324. <http://amedeo.com/lit.php?id=12790697>
60. Podzamczar D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). *Antivir Ther* 2002, 7:81-90. <http://amedeo.com/lit.php?id=12212928>
61. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003, 349: 2293-303. <http://amedeo.com/lit.php?id=14668455>
62. Robinson BS, Riccardi KA, Gong YF, et al. BMS-232632, a highly potent HIV protease inhibitor that can be used in combination with other available antiretroviral agents. *Antimicrob Agents Chemother* 2000, 44:2093-2099. Original-Artikel: <http://hiv.net/link.php?id=200>
63. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J AIDS* 2004, 35:22-32. <http://amedeo.com/lit.php?id=14707788>
64. Rotger M, Taffe P, Bleiber B, et al. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. *J Infect Dis* 2005, 192:1381-6. <http://amedeo.com/lit.php?id=16170755>
65. Roszko PJ, Curry K, Brazina B, et al. Standard doses of efavirenz (EFV), zidovudine (ZDV), tenofovir (TDF), and didanosine (ddl) may be given with tipranavir/ritonavir (TPV/r). Abstract 865, 2nd IAS 2003, Paris.
66. Saag MS, Tebas P, Sension M, et al. Randomized, double-blind comparison of two nelfinavir doses plus nucleosides in HIV-infected patients (Agouron study 511). *AIDS* 2001, 15:1971-8. <http://amedeo.com/lit.php?id=11600825>
67. Sanne I, Piliero P, Squires K, et al. Results of a phase 2 clinical trial at 48 weeks (AI424-007): a dose-ranging, safety, and efficacy comparative trial of atazanavir at three doses in combination with didanosine and stavudine in antiretroviral-naive subjects. *J AIDS* 2003, 32:18-29. <http://amedeo.com/lit.php?id=12514410>
68. Schnell T, Schmidt B, Moschik G, et al. Distinct cross-resistance profiles of the new protease inhibitors atazanavir, lopinavir, and tipranavir in a panel of clinical samples. *AIDS* 2003, 17:1258-61. <http://amedeo.com/lit.php?id=12819531>
69. Schrooten W, Colebunders R, Youle M, et al. Sexual dysfunction associated with protease inhibitor containing HAART. *AIDS* 2001, 15: 1019-23. <http://amedeo.com/lit.php?id=11399984>
70. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003, 349: 2304-15. <http://amedeo.com/lit.php?id=14668456>

71. Sham HL, Kempf DJ, Molla A, et al. ABT-378, a highly potent inhibitor of the HIV protease. *Antimicrob Agents Chemother* 1998, 42:3218-24. <http://amedeo.com/lit.php?id=9835517>
72. Squires K, Lazzarin A, Gatell JM, et al. Comparison of once-daily atazanavir with efavirenz, each in combination with fixed-dose zidovudine and lamivudine, as initial therapy for patients infected with HIV. *J AIDS* 2004, 36: 1011-1019. <http://amedeo.com/lit.php?id=15247553>
73. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral naïve HIV-infected adults: a randomized equivalence trial. *JAMA* 2001, 285: 1155-1163. <http://amedeo.com/lit.php?id=11231744>
74. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *Study 006 Team. N Engl J Med* 1999, 341:1865-73. <http://amedeo.com/lit.php?id=10601505>
75. Stellbrink HJ, Hawkins DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients. *Clin Drug Invest* 2000, 20:295-307.
76. Stellbrink HJ, van Lunzen J, Westby M, et al. Effects of interleukin-2 plus highly active antiretroviral therapy on HIV-1 replication and proviral DNA (COSMIC trial). *AIDS* 2002, 16:1479-87. <http://amedeo.com/lit.php?id=12131185>
77. Van der Valk, Reiss P. Lipid profiles associated with antiretroviral drug choices. *Curr Opin Infect Dis* 2003, 16: 19-23. <http://amedeo.com/lit.php?id=12821825>
78. Van Heeswijk RP, Veldkamp AI, Hoetelmans RM, et al. The steady-state plasma pharmacokinetics of indinavir alone and in combination with a low dose of ritonavir in twice daily dosing regimens in HIV-1-infected individuals. *AIDS* 1999, 13: F95-9. <http://amedeo.com/lit.php?id=10513637>
79. Van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003, 17:987-99. <http://amedeo.com/lit.php?id=12700448>
80. Voigt E, Wickesberg A, Wasmuth JC, et al. First-line ritonavir/indinavir 100/800 mg twice daily plus nucleoside reverse transcriptase inhibitors in a German multicentre study: 48-week results. *HIV Med* 2002, 3:277-282. <http://amedeo.com/lit.php?id=12444946>
81. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med* 2002, 346:2039-46. <http://amedeo.com/lit.php?id=12087139>
82. Walmsley S, Leith J, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir (TPV/r) alone or in combination with saquinavir (SQV), amprenavir (APV), or lopinavir (LPV): Interim analysis of B1182.51. Abstract WeOrB1236, XV Int AIDS Conf 2004, Bangkok.
83. Wire MB, Ballou C, Preston SL, et al. Pharmacokinetics and safety of GW433908 and ritonavir, with and without efavirenz, in healthy volunteers. *AIDS* 2004, 18:897-907. <http://amedeo.com/lit.php?id=15060437>
84. Wood R, Phanuphak P, Cahn P, et al. Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or atazanavir. *J AIDS* 2004, 36:684-692. <http://amedeo.com/lit.php?id=15167287>

## Entry inhibitors

There are three crucial steps for entry of HIV into the CD4+ T-cell:

1. Binding of HIV to the CD4 receptor (“attachment” – target of attachment inhibitors),
2. Binding to coreceptors (target of coreceptor antagonists), and finally
3. Fusion of virus and cell (target of fusion inhibitors).

Every step of HIV entry can theoretically be inhibited. All three drug classes, namely attachment inhibitors, coreceptor antagonists and fusion inhibitors are currently summarized as entry inhibitors. In May 2003, T-20 – the first drug of this class – was licensed in Europe and the US. Numerous other drugs are in the pipeline, but will not be available within the next two years. These are discussed in the HAART 2006/2007 chapter.

**T-20 (Enfurvitide, Fuzeon™)** is the prototype of the fusion inhibitors. It is a relatively large peptide comprised of 36 amino acids, and therefore, like insulin, needs to be administered by subcutaneous injection (Review: Oldfield 2005). It binds to an intermediate structure of the HIV gp41-protein, which appears during fusion of HIV with the target cell. T-20 was licensed in Europe and the US in May 2003 for the treatment of HIV-1 infection in antiretroviral-experienced adults and children over 6 years of age. It is preferable to treat patients within clinical studies, so that clinical experience with this new drug can be collected.

Initially, HIV patients were given T-20 monotherapy intravenously. Antiviral activity was dose-dependent, and at the higher dose of 100 mg bid, the viral load was reduced by almost 2 logs (Kilby 1998). The first study on 78 highly treatment-experienced patients who received subcutaneous application of T-20 in addition to stable HAART – either via an insulin pump or twice daily subcutaneously – also showed positive dose-dependent effects (Kilby 2002). However, maximal suppression was lower at 1.6 logs. In the T20-205 study, 70 patients, mostly PI-experienced, received 2 x 50 mg T-20 subcutaneously daily for 48 weeks (Lalezari 2000). After 48 weeks, an effect on viral load was still evident in one third of patients, but it became apparent that T-20 was of more benefit to those who received other additional new drugs for their HAART regimen. Finally, after the first Phase II study (T20-206) it became clear that the simple addition of T-20 as “monotherapy” was not very beneficial (Lalezari 2002).

Two Phase III studies finally led to the licensing of T-20. TORO 1 (“T-20 versus Optimized Regimen Only”) enrolled 491 extensively pretreated patients in North America and Brazil, most with multiresistant viruses. In TORO 2, 504 patients in Europe and Australia were enrolled. Patients in both studies, on an optimized HAART regimen, either received 90 mg T-20 bid subcutaneously or none at all (Lalezari 2003, Lazzarin 2003). In TORO-1, the reduction in viral load was 0.94 logs better with T-20; in TORO-2 this difference was 0.78 logs (Nelson 2005). The impact on viral load was still apparent after 96 weeks (Arasteh 2004).

The success of T-20 therapy should be monitored early on, particularly in view of the cost. Patients without a decrease in viral load of at least one log after 8-12 weeks will not benefit on T-20, and can be spared the required twice-daily injections. It is also not recommended to inject double the dose of T-20 just once a day: although 1 x 180 mg has the same bioequivalence (as measured by AUC) to the standard 2 x 90 mg dose, a recent study showed a trend towards a lesser decrease in viral load with the 180 mg dose that was clearly associated with lower trough levels (Thompson 2006).

A new occurrence in the TORO studies was the increased frequency of lymphadenopathy and bacterial pneumonia under T-20 (6.7/100 versus 0.6/100 patient years) (Trottier 2005). Septicemia also occurred more often on T-20, but the difference was not significant. The reason for the increased rate of infections has remained unclear, but binding of T-20 to granulocytes has been suspected. Substantial side effects remain almost obligatory (98 % in the TORO studies), and with increasing duration of therapy, severe local skin reactions can sometimes occur at the injection site. These can be particularly painful, and result every so often in interruption of therapy: 4.4 % of cases in the TORO studies. In our experience of everyday clinical treatment, therapy is interrupted more frequently due to the skin problems – see the

section on “Side Effects” for the possibilities of dealing with this. Local side effects can possibly be reduced by using a bioinjection system, in which T-20 is pressed into the skin (Harris 2006).

Resistance mutations develop relatively rapidly on T-20, but seem to reduce viral fitness (Lu 2002, Menzo 2004). Receptor tropism of the virus seems to be less significant than initially thought. Many more seem to have changes to a short sequence on the gp41 gene, causing reduced susceptibility to T-20; this requires only simple point mutations (Mink 2005). In contrast, viruses resistant to conventional HAART (NRTIs, NNRTIs, PIs) are susceptible (Greenberg 2003). As T-20 is a relatively large peptide, it induces antibody production. However, this does not seem to impair efficacy (Walmsley 2003). More disturbing, is the fact that, in a large TDM study, there were very big differences between individuals, and extremely low plasma levels were usually measured (Stocker 2006).

In summary: patients with a well-controlled viral load or who still have options with “classical” HAART do not require T-20. For salvage therapy, however, the drug seems to be very valuable. Although there are still no data from studies with clinical endpoints, patients are likely to benefit clinically from this drug. Mathematical analyses of the TORO studies have shown survival gains of 1.5 years compared to optimized HAART (Hornberger 2003). The price remains an important aspect of T-20, and HAART costs twice as much with the addition of T-20. The company claims that it is one of the most complicated drugs it has ever manufactured. This is unlikely to change even if an improved formulation becomes available – the company is currently working on pegylation of T-20, which would allow weekly dosing.

## References on T-20

1. Arasteh K, Lazzarin A, Clotet B, et al. TORO: 96 week virological and immunological response and safety evaluation of enfuvirtide with an optimized background. Abstract MoOrB1058, XV Int AIDS Conf 2004, Bangkok.
2. Greenberg ML, Melby T, Sista P, et al. Baseline and on-treatment susceptibility to enfuvirtide seen in TORO 1 and 2 to 24 weeks. Abstract 141, 10th CROI 2003, Boston. <http://www.retroconference.org/2003/Abstract/Abstract.aspx?AbstractID=1687>
3. Harris M, Joy R, Larsen G, et al. Enfuvirtide plasma levels and injection site reactions using a needle-free gas-powered injection system (Biojector). AIDS 2006, 20:719-23. <http://amedeo.com/lit.php?id=16514302>
4. Hornberger J, Green J. Clinical prognosis of enfuvirtide in combination with an optimized background regimen among categories of baseline CD4+ cell count and HIV antiretroviral resistance. Abstract 478, 2nd IAS 2003, Paris.
5. Kilby JM, Hopkins S, Venetta TM, et al. Potent suppression of HIV-1 replication in humans by T-20, a peptide inhibitor of gp41-mediated virus entry. Nat Med 1998, 4:1302-1307. <http://amedeo.com/lit.php?id=9809555>
6. Kilby JM, Lalezari JP, Eron JJ, et al. The safety, plasma pharmacokinetics, and antiviral activity of subcutaneous enfuvirtide (T-20), a peptide inhibitor of gp41-mediated virus fusion, in HIV-infected adults. AIDS Res Hum Retroviruses 2002, 18:685-93. <http://amedeo.com/lit.php?id=12167274>
7. Lalezari J, Cohen C, Eron J, and the T20-205 study group. Forty eight week analysis of patients receiving T-20 as a component of multidrug salvage therapy. Abstract LbPp116, XIII Int AIDS Conf 2000, Durban, South Africa.
8. Lalezari J, DeJesus E, Northfelt D, et al. A week 48 assessment of a randomized, controlled, open-label phase II trial (T20-206) evaluating 3 doses of T-20 in PI-experienced, NNRTI-naïve patients infected with HIV-1. Abstract 418, 9th CROI 2002, Seattle, USA. <http://63.126.3.84/2002/Abstract/13592.htm>
9. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. N Engl J Med 2003, 348:2175-85. <http://amedeo.com/lit.php?id=12637625>



10. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003, 348:2186-95. <http://amedeo.com/lit.php?id=12773645>
11. Lu J, Sista P, Cammack N, Kuritzkes D, et al. Fitness of HIV-1 clinical isolates resistant to T-20 (enfuvirtide). *Antiviral therapy* 2002, 7:S56
12. Menzo S, Castagna A, Monchetti A, et al. Resistance and replicative capacity of HIV-1 strains selected in vivo by long-term enfuvirtide treatment. *New Microbiol* 2004, 27:51-61. <http://amedeo.com/lit.php?id=15646065>
13. Mink M, Mosier SM, Janumpalli S, et al. Impact of human immunodeficiency virus type 1 gp41 amino acid substitutions selected during enfuvirtide treatment on gp41 binding and antiviral potency of enfuvirtide in vitro. *J Virol* 2005, 79:12447-54. <http://amedeo.com/lit.php?id=16160172>
14. Nelson M, Arasteh K, Clotet B, et al. Durable efficacy of enfuvirtide over 48 weeks in heavily treatment-experienced HIV-1-infected patients in the T-20 versus optimized background regimen only 1 and 2 clinical trials. *J AIDS* 2005, 40:404-12. <http://amedeo.com/lit.php?id=16280694>
15. Oldfield V, Keating GM, Plosker G. Enfuvirtide: A Review of its use in the management of HIV Infection. *Drugs* 2005, 65:1139-60.
16. Stocker H, Kloft C, Plock N, et al. Pharmacokinetics of enfuvirtide in patients treated in typical routine clinical settings. *Antimicrob Agents Chemother* 2006, 50:667-73. <http://amedeo.com/lit.php?id=16436725>
17. Thompson M, DeJesus E, Richmond G, et al. Pharmacokinetics, pharmacodynamics and safety of once-daily versus twice-daily dosing with enfuvirtide in HIV-infected subjects. *AIDS* 2006, 20:397-404. <http://amedeo.com/lit.php?id=16439873>
18. Trottier B, Walmsley S, Reynes J, et al. Safety of enfuvirtide in combination with an optimized background of antiretrovirals in treatment-experienced HIV-1-infected adults over 48 weeks. *JAIDS* 2005, 40:413-21. <http://amedeo.com/lit.php?id=16280695>
19. Walmsley S, Henry K, Katlama C, et al. Lack of influence of gp41 antibodies that cross-react with enfuvirtide on the efficacy and safety of enfuvirtide in TORO 1 and TORO 2 Phase III trials. Abstract 558, 10th CROI 2003, Boston.

### 3. ART 2006/2007: The horizon and beyond

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Although more than two dozen different products are now available for the treatment of HIV infection, there is a growing need for new drugs. This is not just true for patients with multiresistant viruses awaiting new treatment options. Significant problems related to long-term toxicity and adherence are anticipated with therapies that will presumably need to span whole decades, as eradication of HIV is currently not possible. As a result, there is an urgent need for new drugs that are easier to take, with high genetic barriers to the development of resistance and above all less toxic. To eventually reach the goal of eradication, new drugs need to be more potent than those available today. The following overview of substances that could make it to the clinic based on current data (beginning of 2006) does not claim to be complete.

#### Refurbished old drugs

Several currently available drugs are under further development, the most important goals being the reduction of pill burden, easier dosing and less side effects. Three such preparations to have recently entered the market are Invirase 500<sup>TM</sup>, Truvada<sup>TM</sup> and Kivexa<sup>TM</sup>. New improvements are being developed; licensing applications for some of these are already in progress. Gilead and BMS are working on a combination pill of FTC, tenofovir and efavirenz. However, it will be some time before this so far one-off co-operation bears fruit. Experience in Africa has shown that it is not difficult to produce combination preparations, many of which have provided very encouraging results (Laurent 2004).

**Kaletra<sup>TM</sup> (Meltrex) tablets** – although a lot of data is still not available, the manufacturer Abbott expects to have a new tablet (200 mg lopinavir, 50 mg ritonavir) by autumn 2006 to replace the current soft capsules. This will allow pill reduction to 2 tablets bid and also eliminate the need for refrigeration. In the US, the new formulation of FDA was licensed in October 2005, following data from a total of 141 healthy volunteers that showed the pharmacokinetic profiles of the tablet and capsule to be almost identical. In addition, the bioavailability seems to be affected less when taken together with food (Awni 2005). The size of the tablet, produced by melt extrusion technology (“Meltrex”), is equivalent to that of the capsule. The tolerability appears to be better, and the interactions with efavirenz are less (Awni 2005, Klein 2005). Equally pleasing: antacids have no negative effects on the pharmacokinetics of the tablets (Klein 2006). Large randomized studies are currently underway to further compare the tablets with the soft capsules.

**Nelfinavir 625 mg** – this new formulation was approved in the US in April 2003. It reduces the nelfinavir dose to 2 tablets bid. One study has shown that this formulation is better tolerated, particularly with respect to gastrointestinal side effects – despite the fact that plasma levels are around 30 % higher than with the previous nelfinavir formulation (Johnson 2003, Kaeser 2003). In Europe, where nelfinavir is produced and sold by Roche instead of Pfizer, the 625 mg tablet is not available due to production problems.

**Zerit PRC™** (PRC = “prolonged release capsule”, in the US: XR = “extended release”) is a capsulated once-daily formulation of d4T. The formulation is stable, does not accumulate and seems to cause less polyneuropathy (Baril 2002). d4T XR was approved in Europe in October 2002. However, it is still (in January 2006) not available. There are currently other attempts underway to improve d4T through minor modifications to its molecular structure (Haraguchi 2003, Dutschman 2004).

## References

1. Awani W, Chiu Y-L, Zhu T, et al. Significantly reduced food effect and pharmacokinetic variability with a novel lopinavir/ritonavir tablet formulation. Abstract WeOa0206, 3rd IAS 2005, Rio de Janeiro.
2. Baril JG, Pollard RB, Raffi FM, et al. Stavudine extended/prolonged release (XR/PRC) vs. stavudine immediate release in combination with lamivudine and efavirenz: 48 week efficacy and safety. Abstract LbPeB9014, 14th Int AIDS Conf 2002, Barcelona.
3. Dutschman GE, Grill SP, Gullen EA, et al. Novel 4'-substituted stavudine analog with improved anti-HIV activity and decreased cytotoxicity. *Antimicrob Agents Chemother* 2004, 48:1640-6. <http://amedeo.com/lit.php?id=15105115>
4. Haraguchi K, Takeda S, Tanaka H, et al. Synthesis of a highly active new anti-HIV agent 2',3'-didehydro-3'-deoxy-4'-ethynylthymidine. *Bioorg Med Chem Lett* 2003, 13:3775-7. <http://amedeo.com/lit.php?id=14552777>
5. Johnson M, Nieto-Cisneros L, Horban A, et al. Viracept (Nelfinavir) 625 mg film-coated tablets: investigation of safety and gastrointestinal tolerability of this new formulation in comparison with 250 mg film-coated tablets (Viracept) in HIV patients. Abstract 548, 2nd IAS 2003, Paris.
6. Kaeser B, Akintola DJ, Saifulanwar A, et al. Improved gastrointestinal tolerability of Roche nelfinavir 625 mg film-coated tablets. Abstract 6.4, 4th Int Worksh Clin Pharma HIV Ther 2003, Cannes.
7. Klein C, Zhu T, Chui YL, et al. The effects of efavirenz on the lopinavir/ritonavir pharmacokinetics from a new tablet formulation. Abstract PE4.3/2, 10th EACS 2005, Dublin.
8. Klein C, Chiu YL, Cai Y, et al. Lack of effect of acid-reducing agents on the pharmacokinetics of lopinavir/ritonavir tablet. Abstract 578, 13<sup>th</sup> CROI 2006, Denver.
9. Laurent C, Kouanfack C, Koulla-Shiro S, et al. Effectiveness and safety of a generic fixed-dose combination of nevirapine, stavudine, and lamivudine in HIV-1-infected adults in Cameroon: open-label multicentre trial. *Lancet* 2004, 364:29-34. <http://amedeo.com/lit.php?id=15234853>

## New nucleoside analogs

Since the development of DAPD and of dextelucitabine (reverset) came to a halt, hopes are now limited that there will be new nucleoside analogs on the market in the near future.

**SPD-754 (Oxara or AVX-754)** is a heterocyclic cytidine analog that was sold by Shire Biochem to Avexa at the beginning of 2005. The substance bears a close chemical resemblance to 3TC (Taylor 2000, Bethell 2002). SPD-754 has *in vitro* activity against a broad spectrum of TAMs, and up to 5 nucleoside mutations do not significantly impair its activity (Gu 2006). A first placebo-controlled study in 63 HIV-infected patients treated with SPD-754 monotherapy showed decreases in viral load of between 1.2 and 1.7 logs after 10 days depending on the dose – good potency for a nucleoside analog (Cahn 2003). The drug has been well tolerated and has very good oral bioavailability (Francis 2003).

What about long-term toxicity? In monkeys, there were minor skin problems, usually hyperpigmentation, after 52 weeks of exposure. SPD-754 was thus significantly less toxic than its racemate BCH-10652, which caused severe degenerative dermatopathy in all exposed monkeys (Locas 2004). 3TC and FTC significantly and competitively lower intracellular levels of SPD-754. Combination with other cytidine analogs such as 3TC and FTC could therefore pose a problem (Bethell 2004).

Avexa is currently planning phase IIb studies. SPD-754 is expected to come onto the market in 2009.

**Elvucitabine** (or **ACH-126,443**) is a nucleoside analog developed by Achillion Pharmaceuticals. It is an enantiomer of dexelvucitabine, with the chemical name beta-L-D4FC, and is also effective against HIV and HBV. In vitro studies show potency even in the presence of numerous nucleoside resistance mutations, and viruses with completely unique resistances, such as M184I or the so far unknown mutant D237E, are selected for (Fabrycki 2003). It is also of interest as it seems to have low mitochondrial toxicity, and because of its extremely long half-life of up to 150 hours (Dunkle 2001, Colucci 2005). Phase II studies are underway in HIV-infected patients and in patients with hepatitis B. A small, double-blind study showed a reduction in viral load of between 0.7 and 0.8 logs after 28 days in HIV patients with the M184V mutation. However, this study had to be prematurely terminated, as 6/56 patients developed leukopenia on a dose of 100 mg elvucitabine (Dunkle 2003). Several patients also developed rashes. It is currently being deliberated which dose would retain sufficient activity while at the same time being less toxic – this may require only once-weekly dosing (Stypinski 2004, Colucci 2005).

**Phosphazide (Nicavir)** is a nucleoside analog that was developed (and is already marketed) in Russia, which is very similar to AZT. After 12 weeks of phosphazide monotherapy (400 mg), viral load in a small group of patients dropped by a median 0.7 logs. Since phosphazide is a prodrug of AZT, it requires an additional activation step. The D67N mutation seems to reduce efficacy (Machado 1999). A small study has shown potency in combination with ddI and nevirapine (Kravtchenko 2000), another with ddI and saquinavir (Sitdykova 2003). It is still hard to see the advantage over AZT – although better tolerability had been presumed, this has not been proven.

**Racivir** is a cytidine analog produced by Pharmasset. It is a mixture of FTC and its enantiomer. Possibly, both enantiomers have different resistance profiles so that, theoretically, the development of resistance is impeded (Hurwitz 2005). It has shown good antiviral activity in combination with d4T and efavirenz after two weeks (Herzmann 2005). Whether racivir will make it to the clinic after this Phase I/II study, and what the main advantage is over FTC remains to be seen. The data from the Phase II study should become available in 2006.

**Stampidine** is a nucleoside analog developed by the American Parker Hughes Institute. It resembles d4T and is apparently 100 times more potent than AZT in vitro (Uckun 2002). It also has activity against HIV mutants with up to 5 TAMs. Considerable efficacy was demonstrated in cats infected with feline immunodeficiency virus. This attracted much attention on the internet, but whether these positive results can be replicated in humans remains to be seen (Uckun 2003). In recent years, it has been discussed also as a potential microbicide (D'Cruz 2004), but supposedly studies on HIV patients are currently being prepared (Uckun 2005).

**KP-1461** from Koronis Pharmaceuticals is an oral precursor of KP1212, a nucleoside analog that still clearly shows potency against numerous NRTI resistances. The method of action (selective viral mutagenesis) distinguishes it from the classical nucleoside analogs that induce a chain break (Harris 2005). There is no cross-resistance with other NRTIs and also no mitochondrial toxicity. This very exciting

substance was tolerated well by healthy volunteers in Phase Ia studies, and, in October 2005, the first study on HIV-infected patients began.

**MIV-210**, produced by Medivir, is a precursor of the guanosine analog FLG, that is also effective against HBV and is potent for viruses with numerous NRTI resistance mutations (multiple TAMs, as well as T69 insertions), at least in vitro (Zhang 2002). In 2003, a co-operation between Medivir and GSK was arranged, from which GSK has since retired – the development of MIV-210 should, however, continue to go ahead. A Phase II study on HIV-infected patients began in September 2005. As similar (fluoridated) substances such as lodenosine were, above all, hepatotoxic, the tolerability is being closely observed.

**Dioxolanthymidine (DOT)** is a new thymidine analog – one of the few new substances in this subgroup. Dioxolane appeared to be relatively good in preclinical trials (Chung 2005, Liang 2006), however, clinical studies have to show the potential of DOT. Phase I studies are underway.

Out of sight, out of mind: the following NRTIs are not being pursued:

- Adefovir dipivoxil (bis-POM PMEAs) from Gilead, low activity against HIV, nephrotoxicity
- FddA (Beta-fluoro-ddA, Lodenosine™) from US Bioscience, development stopped in 1999 due to severe liver and kidney damage
- dOTC from Biochem Pharma, toxicity in monkeys
- Lobucavir from BMS, carcinogenicity
- GS 7340 from Gilead, stopped at the beginning of 2004 due to changes in the eye lenses. Development may possibly be resumed ?
- SPD-756 (BCH-13520) and SPD-761
- MIV-310 (Alovudin, FLT) from Boehringer, stopped in March 2005 due to a disappointing Phase II study.
- Dixelvucitabine (DFC or Reverset) from Incyte, stopped in 2006 due to several cases of pancreatitis

## References

1. Bethell R, Adams J, De Muys J et al. Pharmacological evaluation of a dual deoxycytidine analogue combination: 3TC and SPD754. Abstract 138, 11th CROI 2004, San Francisco. <http://www.retroconference.org/2004/cd/Abstract/138.htm>
2. Bethell RC, Allard B, De Muys JM, et al. BCH-13520, a new heterosubstituted nucleoside analogue, is an effective inhibitor of drug-resistant HIV-1. Abstract 386, 9th CROI 2002, Seattle. <http://63.126.3.84/2002/Abstract/13340.htm>
3. Cahn P, Lange J, Cassetti I, et al. Anti HIV-1 activity of SPD754 a new NRTI: results of a 10 day monotherapy study in treatment naive HIV patients. Abstract LB15, 2nd IAS 2003, Paris.
4. Chung KC, Yadav V, Rapp K, Chong Y, Schinazi R. Dioxolane thymine nucleoside is active against a variety of NRTI-resistant mutants. Abstract 554, 12th CROI 2005, Boston.
5. Colucci P, Pottage J, Robison H, et al. The different clinical pharmacology of elvucitabine (beta-L-Fd4C) enables the drug to be given in a safe and effective manner with innovative drug dosing. Abstract LB-27, 45th ICAAC 2005, Washington.
6. D'Cruz OJ, Uckun FM. Stampidine is a potential non-spericidal broad-spectrum anti-HIV microbicide. *Fertil Steril* 2004, 1:831-41. <http://amedeo.com/lit.php?id=15019817>
7. Dunkle LM, Gathe JC, Pedevillano DE, et al. Elvucitabine: potent antiviral activity demonstrated in multidrug-resistant HIV infection. *Antiviral Therapy* 2003, 8:S5.

8. Dunkle LM, Oshana1 SC, Cheng YC, et al. ACH-126,443: a new nucleoside analog with potent activity against wild type and resistant HIV-1 and a promising pharmacokinetic and mitochondrial safety profile. Abstract 303, 8th CROI 2001, Chicago.  
<http://www.retroconference.org/2001/abstracts/abstracts/abstracts/303.htm>
9. Fabrycki J, Zhou Y, Wearne J, et al. In vitro induction of HIV variants with reduced susceptibility to elvicitabine (ACH-126,443,beta-L-Fd4C). *Antiviral Therapy* 2003, 8:S8.
10. Francis RJ, Lanclos L, Shiveley L, Sawyer J. Pharmacokinetics of SPD-754, a new cytidine analog in healthy volunteers. Abstract 528, 2nd IAS 2003, Paris.
11. Gu Z, Allard B, de Muys JM, et al. In vitro antiretroviral activity and in vitro toxicity profile of SPD754, a new deoxycytidine nucleoside reverse transcriptase inhibitor for treatment of human immunodeficiency virus infection. *Antimicrob Agents Chemother* 2006, 50:625-31.
12. Harris KS, Brabant W, Styrchak S, Gall A, Daifuku R. KP-1212/1461, a nucleoside designed for the treatment of HIV by viral mutagenesis. *Antiviral Res* 2005, 67:1-9.  
<http://amedeo.com/lit.php?id=15890415>
13. Herzmann C, Arasteh K, Murphy RL, et al. Safety, pharmacokinetics, and efficacy of (+/-)-beta-2',3'-dideoxy-5-fluoro-3'-thiacytidine with efavirenz and stavudine in antiretroviral-naive HIV-infected patients. *Antimicrob Agents Chemother* 2005, 49:2828-33. <http://amedeo.com/lit.php?id=15980356>
14. Hurwitz SJ, Otto MJ, Schinazi RF. Comparative pharmacokinetics of Racivir, (+/-)-beta-2',3'-dideoxy-5-fluoro-3'-thiacytidine in rats, rabbits, dogs, monkeys and HIV-infected humans. *Antivir Chem Chemother* 2005, 16:117-27. <http://amedeo.com/lit.php?id=15889534>
15. Katlama C, Ghosn J, Tubiana R, et al. MIV-310 reduces HIV viral load in patients failing multiple antiretroviral therapy: results from a 4-week phase II study. *AIDS* 2004, 18:1299-304.  
<http://amedeo.com/lit.php?id=15362662>
16. Kim EY, Vrang L, Oberg B, Merigan TC. Anti-HIV type 1 activity of 3'-fluoro-3'-deoxythymidine for several different multidrug-resistant mutants. *AIDS Res Hum Retroviruses* 2001, 17:401-7.  
<http://amedeo.com/lit.php?id=11282008>
17. Kravtchenko AV, Salamov GG, Serebrovskaya LV, et al. The first experience of HAART with phosphazid + didanosine + nevirapine in HIV-infected patients in Russia. Abstract 3, 5th Int Conf Drug Therapy 2000, Glasgow, Scotland.
18. Liang Y, Narayanasamy J, Schinazi RF, Chu CK. Phosphoramidate and phosphate prodrugs of (-)-beta-d-(2R,4R)-dioxolane-thymine: Synthesis, anti-HIV activity and stability studies. *Bioorg Med Chem* 2006, 14:2178-89.
19. Locas C, Ching S, Damment S. Safety profile of SPD754 in cynomolgus monkeys treated for 52 weeks, Abstract 527, 11th CROI 2004, San Francisco.  
<http://www.retroconference.org/2004/cd/Abstract/527.htm>
20. Machado J, Tsoukas C, Salomon H, et al. Antiviral activity and resistance profile of phosphazid - a novel prodrug of AZT. Abstract 594, 6th CROI 1999, Chicago.  
<http://www.retroconference.org/99/abstracts/594.htm>
21. Murakami E, Ray AS, Schinazi RF, Anderson KS. Investigating the effects of stereochemistry on incorporation and removal of 5-fluorocytidine analogs by mitochondrial DNA polymerase gamma: comparison of D- and L-D4FC-TP. *Antiviral Res* 2004, 62:57-64.
22. Murphy RL, Schürmann D, Kravec I, et al. Pharmacokinetics, safety and antiviral activity of the nucleoside reversion following single doses in HIV-1 infected patients. Abstract 545, 2nd IAS 2003, Paris.
23. Sitydkova YR, Serebrovskaya LV, Kravchenko AV. Immune reconstitution on treatment of HIV-infected patients with phosphazid, didanosine and saquinavir/ritonavir once daily in russia. Abstract 2.7/1. 9th EACS 2003, Warsaw, Poland.
24. Stypinski D, Pottage Jr CC, Gustavson LM, Gorski HA, Lavigne J, Ducharme MP. Optimization of the therapeutic index of elvicitabine through PK/PD modeling. Abstract 5.5, 5th Int Worksh Clin Pharm HIV Ther 2004, Rom.
25. Taylor DL, Ahmed PS, Tyms AS, et al. Drug resistance and drug combination features of the HIV inhibitor, BCH-10652 [(+/-)-2'-deoxy-3'-oxa-4'-thiocytidine, dOTC]. *Antivir Chem Chemother* 2000, 11:291-301. <http://amedeo.com/lit.php?id=10950391>
26. Uckun F, Venkatachalam T, Tibbles H, Erbeck D. Stampidine exhibits potent antiretroviral activity in chronically FIV-infected cats at nontoxic dose levels. Abstract TuPe6.1B14, 3rd IAS 2005, Rio de Janeiro.
27. Uckun FM, Chen CL, Samuel P, et al. In vivo antiretroviral activity of stampidine in chronically feline immunodeficiency virus-infected cats. *Antimicrob Agents Chemother* 2003; 47:1233-40.  
<http://amedeo.com/lit.php?id=12654652>
28. Uckun FM, Pendergrass S, Venkatachalam TK, Qazi S, Richman D. Stampidine is a potent inhibitor of zidovudine- and nucleoside analog reverse transcriptase inhibitor-resistant primary clinical HIV type 1 isolates with thymidine analog mutations. *Antimicrob Agents Chemother* 2002, 46:3613-3616.  
<http://amedeo.com/lit.php?id=12384373>
29. Zhang H, Öberg B, Harmenberg J, et al. Inhibition of multiple drug-resistant (MDR) HIV-1 by 3'-fluoro-2',3'-dideoxyguanosine (FLG). Abstract H-182, 42nd ICAAC 2002, San Diego.

## New NNRTIs

More than with any other drug class, me-too-drugs are not needed here. Many drugs have already been abandoned; the road to approval is especially long and hard for NNRTIs, even though they are relatively cheap to develop. Since efavirenz was licensed in 1998, no NNRTI has made it onto the market – despite the urgent need for NNRTIs in view of increasing resistance. This not only affects the pretreated patients: in 2002, almost 10 % of patients in Europe with an acute HIV infection had viruses with at least one NNRTI resistance mutation (Wensing 2005). The most significant problem in development is the proof of action in Phase II/III studies. The crucial hurdle is the correct design of these trials: because the single substitution of a NNRTI into a failed regime is ethically not allowed, the remaining ART always has to be optimized, whereby the options meanwhile are often so effective that the effect of the new NNRTI cannot be determined. The latest example of this dilemma was capravirine, that was curtailed in July 2005, following the disastrous results of a Phase II study (Pesano 2005).

**Etravirine (TMC 125)**, developed by Tibotec, has possibly the best chance. As a diarylpyrimidine (DAPY) analog and a second-generation NNRTI, it works well against the wild-types, the resistant mutants, and, in particular, against the classical NNRTI mutations such as K103N and Y181C. The genetic resistance barrier is higher than that of other NNRTIs. This appears to be because, by changing its confirmation, etravirine can bind very flexibly to the HIV-1 reverse transcriptase (Vingerhoets 2005). Mutations of the enzyme binding site therefore hardly affect the binding and therefore the potency of this NNRTI (Das 2004). In Phase I/II studies, etravirine lowered viral load by an average of 2.0 logs in treatment-naïve patients after only one week (Gruzdev 2003), and still by 0.9 logs in the presence of NNRTI mutations (Gazzard 2003, Sankatsing 2003). In C233, a large Phase II trial on 199 patients with NNRTI- and PI-mutations, who have previously been intensively treated, the viral load was approximately one log less than with placebo after 24 weeks (Grossmann 2005). However, the overall effect decreased with resistance to an increasing number of NNRTIs. Even so, in the presence of 3 mutations, the drop caused by etravirine was still 0.7 logs (Vingerhoets 2006).

Etravirine has so far been well tolerated, although the typical problems of efavirenz and NNRTIs (dizziness, rash) are to be expected. In the C233 trial, 20 % of patients developed a skin rash and some had to stop etravirine because of it. Etravirine, at a dose of 800 mg (2 x 200 mg tablets bid), is currently being investigated together with the protease inhibitor darunavir in Phase III studies (DUET). In this combination, there does not appear to be any interactions (Boffito 2006). However, the level of etravirine sinks significantly when combined with tipranavir (Schöller 2006).

**Rilpivirine (TMC 278)** first appeared in February 2005. Like etravirine, the substance is also a DAPY-NNRTI (Janssen 2005). Rilpivirine is effective against most NNRTI-resistant viruses. In three placebo-controlled dose-finding studies (up to 150 mg over 14 days) the substance was well tolerated (de Bethune 2005). An early Phase IIa study on therapy-naïve patients receiving monotherapy for 7 days produced an average decrease in the viral load of 1.2 logs. In addition, there was no dose-dependent effect between 25 and 150 mg (Goebel 2005). A considerable ad-

vantage of rilpivirine is its very long half-life (40 hours). In combination with lopinavir, the level is significantly increased, necessitating dose adjustment (Hoetelmans 2005).

**GW5634** is a second-generation benzophenone NNRTI, resulting from its predecessors GW8248 and GW8635, both of which had poor oral bioavailability. GW5634 is the prodrug of GW8248, which has good in vitro activity against NNRTI resistant viruses (Freeman 2003, Romines 2003, Hazen 2003). However, individual resistance mutations have been detected (V106I, P236L, E138KL), indicating that GW5634 will not be invincible. In summer 2005, the first in vivo data on GW5634 were published. In total, 46 HIV patients with NNRTI mutations received various doses for 7 days. The viral load was reduced by 1.2–1.6 logs, a respectable result for a NNRTI (Becker 2005).

**BIRL 355 BS** is a second generation NNRTI from Boehringer. It also seems to have a good and wide efficacy against resistant viruses (Coulombe 2005). However, in the presence of the mutations Y188L and Y181C/G190A the effect is limited (Wardrop 2005). In Germany, a Phase IIa study is planned for spring 2006.

**Calanolide A** is an NNRTI, which has been in development since 1997 by Sarawak MediChem Pharmaceuticals. The substance has an unusually natural origin – it was extracted from plants that grow in the Malayan rainforest. Most importantly, calanolide A appears to have an effect on the Y181C mutation, as well as on K103N (Quan 1999). Healthy volunteers tolerated the drug well (Creagh 2001). In a placebo-controlled trial on HIV-infected patients, the virus load was reduced by 0.8 logs after 14 days (Shereer 2000). According to the firm's website, Phase II/III studies were planned for 2004/5 (<http://www.sarawak-medicem.com/cal/dev.htm>), but as the website has not been updated for a long time, there is doubt as to whether this substance will achieve anything.

The following NNRTIs are no longer being developed:

- Ateviridine from Upjohn, the company prioritized development of delavirdine (the right decision?)
- DPC 083 (BMS-561390) – development stopped in May 2003 due to unsatisfactory PK and safety data
- DPC 961 – suicide thoughts in healthy volunteers; DPC 963
- Emivirine (EMV, MKC-442, Coactinone) – quite far developed by Triangle, but too weak
- GW420867X – from GSK, classical me-too drug
- GW8248 – from GSK, poor bioavailability
- HBY-097 from Hoechst-Bayer, unfavorable side effects
- Loviride from Janssen Pharmaceuticals, too weak in (at that time, relatively advanced) clinical trials (CAESAR Study)
- MIV-150 from Medivir/Chiron, poor bioavailability, being developed further as a microbicide
- PNU142721 from Pharmacia & Upjohn, too similar to efavirenz (me-too)



- TMC120 (dapivirine) from Tibotec, poor oral bioavailability
- Capravirine (AG1549) from Pfizer, probably too weak, Pfizer returned the rights to Shionogi in July 2005. The future is uncertain.

## References

1. Bu HZ, Pool WF, Wu EY, Raber SR, Amantea MA, Shetty BV. Metabolism and excretion of capravirine, a new non-nucleoside reverse transcriptase inhibitor, alone and in combination with ritonavir in healthy volunteers. *Drug Metab Dispos* 2004, 32:689-98. <http://hiv.net/link.php?id=15205383>
2. Burnette M, Marr H, Owens B, Wheelan P, Moore K. Interspecies pharmacokinetics and scaling of GW8248, a novel non-nucleoside HIV reverse transcriptase inhibitor, and its prodrug GW5634. Abstract F-1837, 43rd ICAAC 2003, Chicago.
3. Schaller LT, Burnetter T, Cowan J, et al. Prodrug strategies to deliver novel HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) GW8248 and GW8635. Abstract 872, 43rd ICAAC 2003, Chicago.
4. Becker S, Lalezari J, Walworth C, et al. Antiviral activity and safety of GW695634, a novel next generation NNRTI, in NNRTI-resistant HIV-1 infected patients. Abstract WePe6.2C03, 3rd IAS 2005, Rio de Janeiro, Brazil.
5. Boffito M, Winston A, Fletcher C, et al. Pharmacokinetics and ART response to TMC114/r and TMC125 combination in patients with high-level viral resistance. Abstract 575c, 13th CROI 2006, Denver.
6. Coulombe R, Fink D, Landry S, et al. Crystallographic study with BILR 355 BS, a novel non-nucleoside reverse transcriptase inhibitor (NNRTI) with a broad anti HIV-1 profile. Abstract WePp0105, 3rd IAS 2005, Rio de Janeiro.
7. Creagh T, Ruckle JL, Tolbert DT, et al. Safety and pharmacokinetics of single doses of (+)-calanolide a, a novel, naturally occurring nonnucleoside reverse transcriptase inhibitor, in healthy, HIV-negative human subjects. *Antimicrob Agents Chemother* 2001, 45:1379-86. Originalartikel: <http://aac.asm.org/cgi/content/full/45/5/1379?view=full&pmid=11302799>
8. Das K, Clark AD Jr, Lewi PJ, et al. Roles of conformational and positional adaptability in structure-based design of TMC125-R165335 (etravirine) and related non-nucleoside reverse transcriptase inhibitors that are highly potent and effective against wild-type and drug-resistant HIV-1 variants. *J Med Chem* 2004, 47: 2550-60. <http://amedeo.com/lit.php?id=15115397>
9. de Béthune M-P, Andries K, Azijn H, et al. TMC278, a new potent NNRTI, with an increased barrier to resistance and good pharmacokinetic profile. Abstract 556, 12th CROI 2005, Boston.
10. Freeman G, Romines K, Chanet J, et al. Novel benzophenone non-nucleoside reverse transcriptase inhibitors with unique drug resistance profiles. Abstract 538, 2nd IAS 2003, Paris. *Antiviral Therapy* 8: S328.
11. Fujiwara T, Sato A, el-Farrash M, et al. S-1153 inhibits replication of known drug-resistant strains of HIV-1. *Antimicrob Agents Chemother* 1998, 42:1340-5. Original-Artikel <http://hiv.net/link.php?id=1995>
12. Gazzard BG, Pozniak AL, Rosenbaum W, et al. An open-label assessment of TMC 125—a new, next-generation NNRTI, for 7 days in HIV-1 infected individuals with NNRTI resistance. *AIDS* 2003, 17:F49-54. <http://amedeo.com/lit.php?id=14685068>
13. Gewurz BE, Jacobs M, Proper JA, Dahl TA, Fujiwara T, Dezube BJ. Capravirine, a nonnucleoside reverse-transcriptase inhibitor in patients infected with HIV-1: a phase 1 study. *J Infect Dis* 2004, 190:1957-1961. <http://hiv.net/link.php?id=15529260>
14. Goebel F, Yakovlev A, Pozniak A, et al. TMC278: Potent anti-HIV activity in antiretroviral therapy-naïve patients. Abstract 160, 12th CROI 2005, Boston.
15. Grossman HA, Hicks C, Nadler J, et al. Efficacy and tolerability of TMC125 in HIV patients with NNRTI and PI resistance at 24 weeks: TMC125-c223. Abstract H-416c, 45th ICAAC 2005, Washington.
16. Gruzdev B, Rakhmanova A, Doubovskaya E, et al. A randomized, double-blind, placebo-controlled trial of TMC125 as 7-day monotherapy in antiretroviral naïve, HIV-1 infected subjects. *AIDS* 2003, 17: 2487-94. <http://amedeo.com/lit.php?id=14600520>
17. Hazen RJ, Harvey R, Ferris R, et al. Characterization of the anti-HIV-1 activity of GW8248 in combination with other anti-retroviral drugs and in vitro selection for resistance. Abstract 445, 43rd ICAAC 2003, Chicago.
18. Hoetelmans R, van Heeswijk R, Kestens D, et al. Pharmacokinetic interaction between TMC278, an investigational non-nucleoside reverse transcriptase inhibitor (NNRTI), and lopinavir/ritonavir (LPV/r) in healthy volunteers. Abstract PE4.3/1, 10th EACS 2005, Dublin.
19. Janssen PA, Lewi PJ, Arnold E, et al. In search of a novel anti-HIV drug: multidisciplinary coordination in the discovery of 4-[[4-[[4-[(1E)-2-cyanoethenyl]-2,6-dimethylphenyl]amino]-2- pyri-

midinyl]amino]benzotrile (R278474, rilpivirine). *J Med Chem* 2005, 48:1901-9.  
<http://amedeo.com/lit.php?id=15771434>

20. Pesano R, Piraino S, Hawley P, et al. 24-week safety, tolerability, and efficacy of capravirine as add-on therapy to nelfinavir and 2 nucleoside reverse transcriptase inhibitors in patients failing a NNRTI-based regimen. Abstract 555, 12th CROI 2005, Boston.
21. Quan Y, Motakis D, Buckheit R Jr, et al. Sensitivity and resistance to (+)-calanolide A of wild-type and mutated forms of HIV-1 reverse transcriptase. *Antiviral Therapy* 1999, 4:203-9.  
<http://amedeo.com/lit.php?id=10723499>
22. Romines K, St Clair M, Hazen R, et al. Antiviral characterization of GW8248, a novel benzophenone non-nucleoside reverse transcriptase inhibitor. Abstract 535, 2nd IAS 2003, Paris.
23. Sankatsing SU, Weverling GJ, Peeters M, et al. TMC125 exerts similar initial antiviral potency as a five-drug, triple class antiretroviral regimen. *AIDS* 2003, 17:2623-7.  
<http://amedeo.com/lit.php?id=14685056>
24. Schöller M, Kraft M, Hoetelmans R, et al. Significant decrease in TMC125 exposures when co-administered with tipranavir boosted with ritonavir in healthy subjects. Abstract 583, 13th CROI 2006, Denver.
25. Sherer R, Dutta B, Anderson R, et al. A phase 1B study of (+)-calanolide A in HIV-1-infected, antiretroviral therapy-naive patients. Abstract 508, 7th CROI 2000, San Francisco.
26. Vingerhoets J, Azijn H, Franssen E, et al. TMC125 displays a high genetic barrier to the development of resistance: evidence from in vitro selection experiments. *J Virol* 2005, 79:12773-82.  
<http://amedeo.com/lit.php?id=16188980>
27. Vingerhoets J, Peeters M, Corbett C, et al. Impact of baseline resistance on the virologic response to TMC125 in patients with extensive NNRTI and PI resistance: analysis of study TMC125-C223. Abstract 154, 13th CROI 2006, Denver.
28. Wardrop E, Tremblay S, L. Bourgon L, et al. In vitro selection of resistance and characterization of HIV subtype sensitivity to the non-nucleoside reverse transcriptase inhibitor BILR 355 BS. Abstract 1091, 45th ICAAC, Washington.
29. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005, 192:958-66.  
<http://amedeo.com/lit.php?id=16107947>

## New protease inhibitors (PIs)

Even with the PIs, many substances have been lost along the way. Following the licensing of tipranavir in 2005 and perhaps later this year, darunavir (TMC 114), not much can be expected from this group in the mid-term. This is also due to the immense demands on new PIs in view of the increasingly large competition within this group.

**Darunavir (TMC 114, Prezista™)** is a nonpeptidic PI, originally developed by the Belgian company Virco/Tibotec (now bought by Johnson & Johnson). Due to its impressive potency towards PI-resistant viruses (Koh 2003), darunavir is currently one of the most interesting drug in HIV therapy. The binding affinity for resistant mutants is less reduced than with traditional PIs (King 2004). Following the initial encouraging clinical results (Arasteh 2003), the two large worldwide Phase IIb POWER studies, have come to the forefront of attention (Katlama 2005). In POWER I (US) and 2 (Europe) nearly 600 pretreated patients (pretreatment with three classes and an average of 11 drugs) were included. Several ritonavir-boosted darunavir doses were tested against a boosted comparison PI. Despite considerable resistance at baseline, in 47 % of the patients in the 600 mg group (600 mg bid together with 100 mg bid ritonavir) the viral load sank to less than 50 copies/ml after 24 weeks – a significantly improved result in comparison to the control PI (14 %), and a success that has so far not been seen in a patient group with such limited options. The potency of darunavir is, of course, not endless. The first incidences of

resistance mutations have already been reported: namely V321, I47V, and I54M (De Meyer 2006).

Darunavir is well tolerated apart from moderate gastrointestinal side effects. Dyslipidemia and raised liver enzymes, that are associated with the main PI-concurrence tipranavir, do not appear to be important here. Combination with lopinavir is not ideal, as the plasma level of darunavir is reduced. The comparative studies that are currently underway with lopinavir on therapy-naïve (C211) and on pretreated (C214) patients are very exciting, although data are still not available. Darunavir will enter the expanded-use program in spring 2006, and the licensing application should also be entered in 2006.

**Breacanavir (GW640385X or VX-385)** is a PI resulting from a collaboration between Vertex and GSK, similarly to amprenavir and fosamprenavir. At present, breacanavir is in Phase IIb (STRIVE study). Doses up to 800 mg were well tolerated (Ford 2005). Potency seems to be good even in PI-resistant viruses (Ward 2005). Although it is chemically very similar to amprenavir, *in vitro* data suggest that there will hardly be any cross-resistance (Florance 2004). However, the activity of breacanavir is reduced in the presence of the I54L/M+I84V mutation, and with A28S (Yates 2004).

**AG-001859** is an allophenylnorstatin-containing PI from Pfizer, currently being investigated in Phase I studies. *In vitro* data shows that this substance has antiviral activity even in the presence of multiple primary and secondary PI mutations (Hammond 2004).

**SM-309515** is a new PI from Sumitomo Pharmaceuticals, and has apparently entered Phase I studies. Earlier versions failed due to the short half-life, and attempts are now being made to improve this (Mimoto 2003). Pharmacokinetic data in dogs seemed to be comparable to atazanavir. The drug remained effective against mutations such as S37N, I47V, R57K, and I84V. Conversely, sensitivity to all other PIs remained despite resistance against SM-309515. Ritonavir boosting is now being tested in humans.

Out of sight, out of mind – development of the following PIs has been stopped:

- DPC 684 – cardiotoxic, apparently with a narrow therapeutic range
- DPC 681 – bought by BMS, which does not seem interested in further development
- GS 9005 (previously GS 4338) – from Gilead
- JE-2147 (AG1776, KNI-764) – from Pfizer, apparently stopped (nothing new since 1999)
- KNI-272 (Kynostatin), poor PK data
- Mozenavir (DMP-450) – development stopped by Gilead in 2002 as there were no advantages to other PIs
- RO033-4649 – from Roche, probably too similar to saquinavir
- SC-52151 and SC-55389A – poor bioavailability
- TMC 126 – Tibotec is concentrating on TMC 114

## References

1. Arasteh K, Clumeck N, Pozniak A, et al. Antiretroviral activity, safety and pharmacokinetics of TMC114, a next-generation HIV-1 protease inhibitor in multiple PI experienced patients. Abstract LB 16, 2nd IAS 2003, Paris. <http://www.aegis.com/conferences/2ndIASHIVPT/LB16.html>
2. Katlama C, Carvalho MI, Cooper D, et al. TMC 114/r out performs investigator selected PI(s) in three class-experienced patients: week 24 primary analysis of POWER 1 (TMC 114-C213). Abstract WeOaLB0102, 3rd IAS 2005, Rio de Janeiro.
3. Katlama C, Berger D, Bellos N, et al. Efficacy of TMC114/r in 3-class experienced patients with limited treatment options: 24-week planned interim analysis of 2 96-week multinational dose-finding trials. Abstract 164LB, 3rd IAS 2005, Rio de Janeiro.
4. Ford S, Reddy S, Anderson M, Murray S, Ng-Cashin J, Johnson M. 640385, a novel HIV-1 protease inhibitor: safety and pharmacokinetics following repeat administration with and without ritonavir in healthy subjects. Abstract 563, 12th CROI 2005, Boston.
5. Florance A, Elston R, Johnson M, Spreen W, St Clair M. Phenotypic and genotypic resistance to a new protease inhibitor, in HIV-1 virus samples from subjects failing amprenavir. *Antiviral Therapy* 2004, 9:S15.
6. Hammond J, Jackson L, Graham J, et al. Antiviral activity and resistance profile of AG-001859, a novel HIV-1 protease inhibitor with potent activity against protease inhibitor-resistant strains of HIV. *Antiviral Therapy* 2004; 9:S17
7. King NM, Prabu-Jeyabalan M, Nalivaika EA, et al. Structural and thermodynamic basis for the binding of TMC114, a next-generation human immunodeficiency virus type 1 protease inhibitor. *J Virol* 2004, 78:12012-21. <http://amedeo.com/lit.php?id=15479840>
8. Koh Y, Nakata H, Maeda K, et al. Novel bis-tetrahydrofuranylethane-containing nonpeptidic protease inhibitor (PI) UIC-94017 (TMC114) with potent activity against multi-PI-resistant HIV in vitro. *Antimicrob Agents Chemother* 2003; 47: 3123-3129. <http://aac.asm.org/cgi/content/abstract/47/10/3123>
9. De Meyer S, Hill A, De Baere I, et al. Effect of baseline susceptibility and on-treatment mutation on TMC-114 and control PI efficacy: preliminary analysis of data from PI-experienced patients from POWER 1 and POWER 2. Abstract 157, 13th CROI 2006, Denver.
10. Mimoto T, Nojima S, Terashima K, et al. SM-309515: a novel and promising HIV protease inhibitor with favourable pharmacokinetics and resistance profiles. Abstract 873, 43rd ICAAC 2003, Chicago.
11. Ward D, Lalezari J, Thompson M et al. Preliminary antiviral activity and safety of 640385/ritonavir in HIV-infected patients (study hpr10006): an 8-week interim analysis. Abstract H-412. 45th ICAAC 2005, Washington.
12. Yates P, Hazen R, St Clair M, Boone L, Elston R. In vitro selection and characterization of resistance to the new HIV protease inhibitor GW640385. *Antiviral Therapy* 2004, 9:S16.

## Entry inhibitors

There are three crucial steps for entry of HIV into the CD4+ T-cell:

1. binding of HIV via the gp120 envelope protein to the CD4 receptor (“attachment” – target of attachment inhibitors),
2. binding to coreceptors (target of coreceptor antagonists) via conformational changes, and finally
3. fusion of virus and cell (target of fusion inhibitors).

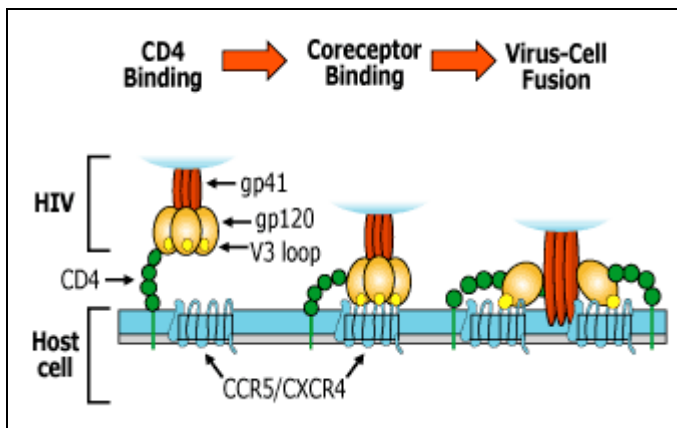


Figure 1: The three main steps of HIV entry into the cell (from: Moore JP, Doms RW. The entry of entry inhibitors: a fusion of science and medicine. PNAS 2003, 100:10598-602).

Although biochemically very heterogeneous, attachment inhibitors, coreceptor antagonists and fusion inhibitors are at present grouped together as entry inhibitors. Even if the antiviral effects of most of the drugs are not overwhelming, the concept is intriguing and entry inhibitors could open up new possibilities for the treatment of HIV infection in the coming years. On the other hand, a lot of the data does not go beyond basic science at this stage, and many of the drugs discussed below may eventually disappear. Most significantly, coreceptor antagonists had to bear several bitter setbacks in 2005.

### Attachment inhibitors

This group is very heterogeneous, so it is not possible to speak of a single drug class. Since the beginning of the nineties, there have been a number of investigations into soluble CD4 molecules that prevent the attachment of HIV to the CD4+ cell (Daar 1990, Schooley 1990). But, after attaining disappointing results, this approach was abandoned for several years. With the growing knowledge of the mechanism of HIV entry into the cell, as well as following the success of T-20 as the first entry inhibitor, the development of attachment inhibitors has been reinvigorated. However, most drugs are not yet far advanced, often have problematic PK data and are therefore still in the proof-of-concept stage. Most attachment inhibitors act on the interaction between the viral protein gp120 and the CD4 receptor. In contrast to coreceptor antagonists, the activity of attachment inhibitors seems to be independent of coreceptor tropism (Trkola 1998).

**Pro-542** (or recombinant CD4-IgG2) is a soluble antibody-like tetravalent fusion protein developed by Progenics, which prevents attachment of HIV to CD4+ T-lymphocytes by binding to gp120. Phase I studies have shown good tolerability, and viral load decreased even after a single infusion at 10 mg/kg – although only marginally (Jacobson 2000). In another study, Pro-542 was given at a higher dose of 25 mg/kg as an infusion in 12 HIV-infected patients (Jacobson 2004). The average decrease in viral load was 0.5 logs, and this effect was maintained over 4-6 weeks.

Surprisingly, activity was greater in more advanced HIV infection. X4-tropic viruses (see below) were just as susceptible as R5-tropic strains. This substance was well tolerated after a single infusion. Pro-542 has also been tested in children (Shearer 2000). In the SCID mouse model, Pro-542 has shown remarkable efficacy (Franti 2002). Phase II studies are underway.

**BMS-488,043** is an early attachment inhibitor from BMS, which binds very specifically and reversibly to HIV gp120 and thereby prevents attachment of HIV to the CD4+ cell. It has replaced BMS-806, with which sufficient inhibition concentrations could not be reached. In early 2004, the first results in HIV-infected patients were published (Hanna 2004). Patients received either 800 mg or 1800 mg, both twice daily, or placebo. Viral load after 7 days of monotherapy dropped in both dose groups by a median 0.72 or 0.96 logs. In 7/12 patients in the 800 mg group, viral load was reduced by more than one log; in the 1800 mg dose group this proportion was 8/12 patients. The substance was well tolerated in this study. However, pill burden is still high – the formulation requires further improvement.

**TNX-355** (previously “Hu5A8”) is a monoclonal antibody that binds to the CD4 receptor and thereby prevents the entry of HIV. It is currently being developed by Tanox Biosystem (Houston, Texas). The mechanism of action has not been clearly explained. In contrast to other attachment inhibitors, TNX-355 does not seem to prevent binding of gp120 to CD4, but rather the conformational changes and thereby the binding of gp120 to CCR5 and CXCR4. Some experts therefore describe it as a coreceptor antagonist. It can only be administered intravenously. Following the initial early data (Jacobsen 2004, Kuritzke 2004), provisional data from a placebo-controlled Phase II trial were very encouraging (Norris 2005). In this study, extensively pretreated patients received TNX-355 as an infusion every two weeks for a year in two different doses (10 mg/kg or 15 mg/kg) or placebo in addition to an optimized ART regime. Intermediate analysis has shown a long-lasting decrease in the viral load of approximately one log after 24 weeks in both verum arms of the study.

## References

1. Daar ES, Li XL, Moudgil T, Ho DD. High concentrations of recombinant soluble CD4 are required to neutralize primary human immunodeficiency virus type 1 isolates. *Proc Natl Acad Sci U S A* 1990, 87:6574-6578. <http://amedeo.com/lit.php?id=2395859>
2. Franti M, O'Neill T, Maddon P, et al. PRO 542 (CD4-IgG2) has a profound impact on HIV-1 replication in the Hu-PBL-SCID mouse model. Abstract 401, 9th CROI 2002, Seattle, USA. <http://63.126.3.84/2002/Abstract/13664.htm>
3. Hanna G, Lalezari L, Hellinger J, et al. Antiviral activity, safety, and tolerability of a novel, oral small-molecule HIV-1 attachment inhibitor, BMS-488043, in HIV-1-infected subjects a novel, oral small-molecule HIV-1 attachment inhibitor, BMS-488043, in HIV-1-infected subjects. Abstract 141, 11th CROI, 2004, San Francisco.
4. Jacobson JM, Israel RJ, Lowy I, et al. Treatment of advanced human immunodeficiency virus type 1 disease with the viral entry inhibitor PRO 542. *Antimicrob Agents Chemother* 2004, 48:423-9. <http://amedeo.com/lit.php?id=14742190>
5. Jacobson JM, Kuritzkes DR, Godofsky E, et al. Phase 1b study of the anti-CD4 monoclonal antibody TNX-355 in HIV-infected subjects: safety and antiretroviral activity of multiple doses. Abstract 536, 11th CROI 2004, San Francisco.
6. Jacobson JM, Lowy I, Fletcher CV, et al. Single-dose safety, pharmacology, and antiviral activity of the HIV type 1 entry inhibitor PRO 542 in HIV-infected adults. *J Infect Dis* 2000, 182:326-329. <http://amedeo.com/lit.php?id=10882617>
7. Kuritzkes DR, Jacobson J, Powderly WG, et al. Antiretroviral activity of the anti-CD4 monoclonal antibody TNX-355 in patients infected with HIV type 1. *J Infect Dis* 2004, 189:286-91. <http://amedeo.com/lit.php?id=14722894>

8. Norris D, Morales J, Gathe J, et al. TNX-355 in combination with optimized background regimen (OBR) exhibits greater antiviral activity than OBR alone in HIV treatment experienced patients. Abstract H-LB2-26, 45th ICAAC 2005, Washington.
9. Schooley RT, Merigan TC, Gaut P, et al. Recombinant soluble CD4 therapy in patients with the acquired immunodeficiency syndrome (AIDS) and AIDS-related complex. *Ann Intern Med.* 1990, 112:247-253. <http://amedeo.com/lit.php?id=2297203>
10. Shearer W, Israel R, Starr S, et al., for the PACTG Protocol 351 Study Team. Recombinant CD4-IgG2 in HIV type 1-infected children: phase 1/2 study. *J Infect Dis* 2000, 182:1774-1779. <http://amedeo.com/lit.php?id=11069253>
11. Trkola A, Ketas T, Kewalramani VN, et al. Neutralization sensitivity of human immunodeficiency virus type 1 primary isolates to antibodies and CD4-based reagents is independent of coreceptor usage. *J Virol* 1998, 72:1876-85. <http://amedeo.com/lit.php?id=9499039>

## Coreceptor antagonists

In addition to CD4 receptors, HIV also requires so-called coreceptors to enter the target cell. The two most important ones, CXCR4 and CCR5, were discovered in the middle of the 1990s. These receptors, of which there are probably more than 200 in total, are named after the natural chemokines that usually bind to them. Their nomenclature is derived from the amino acid sequence. For CCR5 receptors these are the “CC-chemokine” MIP and RANTES, for CXCR4-receptors it is the “CXC-chemokine” SDF-1.

HIV-variants use either the CCR5- or the CXCR4-receptors for entry into the target cell. According to their receptor tropism, HIV variants are termed R5 if they use CCR5 as a coreceptor, whereas viruses with a preference for CXCR4 are termed X4-viruses. R5 viruses are viruses that predominantly infect macrophages (previously: “M-trope” viruses); X4 viruses mainly infect T cells (previously: “T-trope” viruses). In most patients, R5 viruses are found in the early stages of infection; the significantly more virulent X4 viruses, which are probably able to infect a wider spectrum of cell types, first occur in the later stages. The change in the tropism is frequently a consequence of illness progression (Connor 1997, Scarkatti 1997, Xiao 1998). It is still not clear why this happens after several years of infection, although the tropism shift only needs a few small mutations. However, it is probable that R5 viruses are less virulent overall and are therefore not recognized so well by the immune system. X4 viruses are significantly more virulent, but because of their low glycosylation more immunogenic. They are neutralized better by the immune system and it is likely, therefore, that they only become apparent when there is a significant immune deficiency. In an analysis of a large cohort, approximately 80 % of all viruses showed CCR5 tropism, i.e., were R5 viruses. The receptor tropism correlated clearly with the stage of the infection. The higher the CD4+ T-cell count and the lower the viral load, the more R5 viruses tended to be present (Moyle 2005, Brumme 2005). In contrast, X4 viruses are almost exclusively found in advanced stages of the disease: when the CD4+ count is > 500/μl, they are only found in 6 %; at < 25 CD4+ T-cells/μl, in more than 50 % of patients (Brumme 2005). In addition, X4 viruses almost always occur in X4/R5-mixed populations, and an exclusive X4 virus population is very rare. A further study in treatment experienced patients found significantly more viruses with CXCR4 tropism (Demarest 2004).

CCR5- and CXCR4-antagonists can be distinguished according to their specificity for one of the two coreceptors. They block the respective coreceptor similarly to the natural chemokine, which they partially resemble chemically. The development of

CCR5 antagonists (some of which have “-viroc” at the end of their names) is significantly more advanced than for CXCR4 antagonists. This is mainly because the blockade of CCR5, at least theoretically, has less clinical consequences. Individuals with a congenital CCR5 receptor defect are healthy. With CXCR4, it is not so certain. A congenital, harmless defect in humans is not known, and in trials on animals, CXCR4 blockade had far-reaching consequences.

However, CCR5 antagonists are not without problems. Recently, this drug group, which was as good as on the market a few months ago, experienced a few setbacks. Subsequently, the development of aplaviroc (CCR5 antagonist from GSK) was stopped in 2005 due to several cases of severe, life-threatening hepatotoxicity (<http://www.gsk.com/ControllerServlet?appld=4&pagel=402&newsid=667>).

In contrast, a Phase III study on vicriviroc in therapy-naïve patients was ended prematurely due to poor efficacy (Greaves 2006). As usual: the more one learns about a drug class, the more questions arise. The most important are:

*Is the hepatotoxicity of aplaviroc a class problem?* In October 2005, the development of aplaviroc was stopped by GSK as some patients developed severe and unexpected hepatotoxicity (Steel 2005). Since then, all CCR5 antagonists have been under close observation with regard to possible hepatic damage. So far, no negative data has been received on vicriviroc, but, in December 2005, Pfizer reported one case of hepatic failure with subsequent liver transplant in a patient on maraviroc. However, the patient, who was from Thailand, had also received hepatotoxic isozide and the entire clinical management of this case was very questionable. Interim result: there is no clear evidence to suggest that all CCR5 antagonists are hepatotoxic, but vigilance is required.

*Which patients would be candidates for CCR5 antagonists?* Initially it would seem that only patients with R5-tropic viruses would qualify. Although past studies have unanimously demonstrated that the proportion of X4-tropic viruses is fairly small, at around 20 % overall (Brumme 2005, Moyle 2005), it seems that particularly patients with advanced HIV infection and extensive prior therapy would consequently hardly benefit from CCR5 antagonists. In ACTG 5211, a Phase IIb study on vicriviroc in 368 pretreated patients, only 48 % had R5-tropic viruses, 48 % of the patients had X4/R5 combinations, and 4 % X4-tropic viruses (Wilkin 2006). This means that CCR5 antagonists should probably be given earlier on in the course of the disease. In the salvage situation, their role remains unclear.

*Will the expected X4 shift induced by CCR5 antagonists harm patients?* It is known that X4 viruses are associated with rapid CD4+ T-cell decline and disease progression (Connor 2000, Scarkatti 1997, Xiao 1998). Although complex phylogenetic studies have demonstrated that X4-tropic viruses emerging under treatment with CCR5 antagonists are probably selected from pre-existing pools and do not develop as a result of a switch in receptor usage (Lewis 2004), the consequences of the X4 selection for the patient remain uncertain.



*What are the immunological consequences of CCR5 antagonists?* Patients with in-born coreceptor defects are healthy. Nevertheless, it is feared that blockade of these receptors could have negative consequences. Moreover, the action of coupling to the receptor could possibly induce an autoimmune reaction. So far, neither problem has been observed in monkey models (Peters 2005).

*Does the tropism have to be tested in each patient prior to therapy?* Finally, an important problem is how to test for viral tropism. ViroLogic is currently the only laboratory conducting this complex test, which requires living cells. Nobody knows how accurate this test really is and what the presence of dual tropic viral populations comprised of both R5 and X4 strains signifies.

*Does cross resistance exist between the CCR5 antagonists?* Because the coreceptor antagonists all bind similarly to the receptor, there is a theoretical risk of classical predominant cross resistance. Although according to several laboratory trials, the problem seems to be minimal (Door 2005, Westby 2005), this has still to be confirmed in clinical studies.

**Maraviroc (UK 427,857)**, a CCR5 antagonist from Pfizer, is currently the most promising of its kind. Data from the first studies have recently been published in *Nature Medicine* (Fätkenheuer 2005). In a randomized double blind trial, 63 patients with R5-tropic viruses were given various doses of maraviroc. After 10-15 days, an average reduction in viral load of 1.6 logs was observed in patients who received at least 100 mg bid. The drug has so far been well-tolerated. This was also the case in 54 healthy volunteers, who took maraviroc 100 or 300 mg bid for four weeks (Russell 2003). Maraviroc is not effective against X4 viruses. Several Phase III studies are currently underway on therapy-naïve and pretreated patients. However, there has already been one small setback: one arm of the trial on once-daily doses proved that in therapy-naïve patients maraviroc was worse in comparison to efavirenz and had to be stopped.

**Vicriviroc (SCH-D, or 417690)** is a CCR5 antagonist from Schering-Plough with oral bioavailability. Its binding affinity for the CCR5 coreceptor is greater than that of its predecessor SCH-C (Stritzki 2005). Vicriviroc is already in Phase III studies. In the Phase I studies, the highest dose of 50 mg daily induced an average drop in the viral load of 1.62 logs (Schürmann 2004). The substance has so far been well tolerated. Arrhythmia (QT elongation), which occurred under the earlier version SCH-C, was not observed (Sansone 2005). Data from a Phase II study on therapy-naïve patients has recently shed doubt on the long-term effects of vicriviroc (Greaves 2006). In this trial, vicriviroc in various doses was compared to efavirenz (all patients also received AZT and 3TC). After an average observation period of 31 weeks, an independent data monitoring board decided to prematurely end the trial. Therapy failure (> 50 copies/ml) was observed at this stage in 2 out of 24 patients (8 %) on efavirenz, in 13/23 (57 %) on 25 mg vicriviroc, in 10/22 (45 %) on 50 mg vicriviroc, and in 5/23 (22 %) on 75 mg vicriviroc. The observation that the rate of therapy failure at the higher doses was relatively low, provides hope that the problem with vicriviroc is purely one of dosage. Studies in treatment-experienced

patients and in patients with HCV coinfection are continuing, although they have not yet been published.

**Pro-140** is a CCR5 antagonist from Progenics, which acts as a monoclonal antibody (Trkola 2001). It appears to act synergistically with other CCR5 antagonists (Murga 2005). In animal studies (SCID mouse model), single doses of the drug achieved significant and dose-dependent reductions in viral load without evidence of rebound under treatment (Franti 2002). In vitro data suggests good tolerability, as the normal function of CCR5 receptors is apparently not disturbed, at least not at the doses that are required for inhibition of HIV replication (Gardner 2003). In summer 2005, the first clinical data were published – 20 healthy volunteers, who had received a single i.v. dose, tolerated the antibody well, and dose-dependent concentrations were measured (Olson 2005). The long-lasting effect of pro-140 was surprising. The CCR5 receptors were blocked for more than 60 days in some cases. Consequently, the probands are to be observed for longer than was planned (Olson 2006).

**TAK-652** is a CCR5 antagonist from the Japanese firm Takeda. It has good oral bioavailability (Baba 2005). In vitro it shows synergistic effects with T-20 (Tremblay 2005).

**AK-602** is a CCR5 antagonist that was developed by several companies at the same time (other names: ONO4128 or GW873140). The drug should already be in Phase II trials (Nakata 2005).

**AMD 070** is a CXCR4 receptor antagonist. This receptor is mainly used by R4-tropic SI strains, that are found at later stages of infection and are associated with a rapid decline in T helper cells (van Rij 2002). AMD 070 is not effective against R5-tropic viruses. The drug has good oral bioavailability, and initial studies in humans are underway (Schols 2003). Healthy volunteers tolerated AMD 070 well, but developed leukocytosis. It is already being discussed in hematology circles whether AMD 070 could be used as a leukocyte growth factor, similar to G-CSF. Plasma levels were higher than the EC90 of HIV, as determined in vitro (Stone 2004) – activity after oral dosing is therefore likely. The strategy for double entry inhibition, i.e. the combination with a CCR5 antagonist, will certainly be intriguing. The first in vitro data testing this hypothesis is now available (Schols 2004, Nakata 2005). It remains to be seen whether CD4+ cells can carry out their function in the presence of such a double blockade.

**KRH-3955 and KRH-3140** are two new CXCR4 antagonists, that have been shown to be effective at least in mice (Tanaka 2006).

## References

1. Baba M, Takashima K, Miyake H, et al. TAK-652 inhibits CCR5-mediated human immunodeficiency virus type 1 infection in vitro and has favorable pharmacokinetics in humans. *Antimicrob Agents Chemother* 2005, 49:4584-91. <http://amedeo.com/lit.php?id=16251299>
2. Brumme ZL, Goodrich J, Mayer HB, et al. Molecular and clinical epidemiology of CXCR4-using HIV-1 in a large population of antiretroviral-naïve individuals. *J Infect Dis* 2005, 192:466-74. <http://amedeo.com/lit.php?id=15995960>
3. Connor RI, Sheridan KE, Ceradini D, Choe S, Landau NR. Change in coreceptor use coreceptor use correlates with disease progression in HIV-1-infected individuals. *J Exp Med*. 1997, 185:621-8. <http://amedeo.com/lit.php?id=9034141>
4. Demarest J, Bonny T, Vavro C, et al. HIV-1 co-receptor tropism in treatment naïve and experienced subjects. Abstract H-1136, 44th ICAAC 2004, Washington.

5. Dorr PK, Todd K, Irvine R, et al. Site-directed mutagenesis studies of CCR5 reveal differences in the interactions between the receptor and various CCR5 antagonists. Abstract H-411. 45th ICAAC 2005, Washington.
6. Este JA. TAK-779 (Takeda). *Curr Opin Investig Drugs* 2001; 2:354-6. <http://amedeo.com/lit.php?id=11575704>
7. Fatkenheuer G, Pozniak AL, Johnson MA, et al. Efficacy of short-term monotherapy with maraviroc, a new CCR5 antagonist, in patients infected with HIV-1. *Nat Med* 2005, 11:1170-2. <http://amedeo.com/lit.php?id=16205738>
8. Franti M, O'Neill T, Maddon P, et al. PRO 542 (CD4-IgG2) has a profound impact on HIV-1 replication in the Hu-PBL-SCID mouse model. Abstract 401, 9th CROI 2002, Seattle, USA. <http://63.126.3.84/2002/Abstract/13664.htm>
9. Gardner J, Cohen M, Rosenfield SI, Nagashima KA, Maddon PJ, Olson WC. Immunotoxicology of PRO 140: a humanized anti-CCR5 monoclonal antibody for HIV-1 therapy. Abstract 876, Abstract 444, 43rd ICAAC 2003, Chicago.
10. Greaves W, Landovitz R, Fatkenheuer G, et al. Late virologic breakthrough in treatment naive patients on a regimen of Combivir + vicriviroc. Abstract 161LB, 13th CROI 2006, Denver.
11. Lewis ME, van der Ryst E, Youle M, et al. Phylogenetic analysis and co-receptor tropism of HIV-1 envelope sequences from two patients with emergence of CXCR4 using virus following treatment with the CCR5 antagonist UK427,857. Abstract H584-b, 44th ICAAC 2004, Washington.
12. Moyle GJ, Wildfire A, Mandalia S, et al. Epidemiology and predictive factors for chemokine receptor use in HIV-1 infection. *J Infect Dis* 2005, 191:866-72. <http://amedeo.com/lit.php?id=15717260>
13. Murga J, Olson W, Pevear D, et al. Antiviral synergy between the CCR5 mAb PRO 140 and small-molecule CCR5 antagonists. Abstract TuOa0206, 3rd IAS 2005, Rio de Janeiro.
14. Nakata H, Koh Y, Maeda K, et al. Greater synergistic anti-HIV effects upon combinations of a CCR5 inhibitor AK602/ONO4128/GW873140 with CXCR4 inhibitors than with other anti-HIV drugs. Abstract 543. 12th CROI 2005, Boston.
15. Olson W, Doshan H, Zhan C et al. First-in-humans trial of PRO 140, a humanized CCR5 monoclonal antibody for HIV-1 therapy. Abstract WePe6.2C04, 3rd IAS 2005, Rio de Janeiro.
16. Olson WC, Doshan H, Zhan C. Prolonged coating of CCR5 lymphocytes by PRO 140, a humanized CCR5 monoclonal antibody for HIV-1 therapy. Abstract 515, 13th CROI 2006, Denver.
17. Peters C, Kawabata T, Syntin P, et al. Assessment of immunotoxic potential of maraviroc (UK-427,857) in cynomolgus monkeys. Abstract 1100, 45th ICAAC, Washington.
18. Russell D, Bakhtyari A, Jazrawi RP, et al. Multiple dose study to investigate the safety of UK-427,857 (100mg or 300mg) BID for 28 days in healthy males and females. Abstract 874, 43rd ICAAC 2003, Chicago.
19. Sansone A, Kraan M, Long MJ, et al. QTc interval analysis of SCH 417690, a novel CCR5 inhibitor. Abstract 1095, 45th ICAAC, Washington.
20. Scarlatti G, Tresoldi E, Bjornal A, et al. In vivo evolution of HIV-1 co-receptor usage and sensitivity to chemokine-mediated suppression. *Nat Med* 1997, 3:1259-65. <http://amedeo.com/lit.php?id=9359702>
21. Schols D, Claes S, Hatse S, et al. Anti-HIV activity profile of AMD070, an orally bioavailable CXCR4 antagonist H. Abstract 563, 10th CROI 2003, Boston. <http://www.retroconference.org/2003/Abstract/Abstract.aspx?AbstractID=887>
22. Schols D, Vermeire K, Hatse S, et al. On vitro anti-HIV activity profile of AMD887, a novel CCR5 antagonist, in combination with the CXCR4 inhibitor AMD070. Abstract 539, 11th CROI 2004, San Francisco.
23. Schürmann D, Rouzier R, Nourgarede R. SCH D: Antiviral activity of a CCR5 receptor antagonist. Abstract 140LB, 11th CROI 2004, San Francisco.
24. Steel HM. Special presentation on aplaviroc-related hepatotoxicity. 10th EACS 2005, Dublin. Special presentation.
25. Stone N, Dunaway S, Flexner C, et al. Biologic activity of an orally bioavailable CXCR4 antagonist in human subjects. Abstract TuPeB4475, XV Int AIDS Conf, Bangkok.
26. Strizki JM, Tremblay C, Xu S, et al. Discovery and characterization of vicriviroc (SCH 417690), a CCR5 antagonist with potent activity against human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2005, 49:4911-9. <http://amedeo.com/lit.php?id=16304152>
27. Tanaka Y, Okuma K, Tanaka R, et al. Development of novel orally bioavailable CXCR4 antagonist, KRH-3955 and KRH-3140: binding specificity, pharmacokinetics and anti-HIV activity in vivo and in vitro. Abstract 49 LB, 13th CROI 2006, Denver.
28. Tremblay CL, Giguél F, Chou TC, et al. TAK-652, a novel small molecule inhibitor of CCR5 has favorable anti-HIV interactions with other antiretrovirals in vitro. Abstract 542, 12th CROI 2005, Boston.

29. Trkola A, Ketas TJ, Nagashima KA, et al. Potent, broad-spectrum inhibition of HIV type 1 by the CCR5 monoclonal antibody PRO 140. *J Virol* 2001, 75:579-88. Original-Artikel: <http://jvi.asm.org/cgi/content/full/75/2/579?view=full&pmid=11134270>
30. van Rij RP, Visser JA, Naarding M, et al. In vivo evolution of X4 HIV-1 variants in the natural course of infection coincides with reduced sensitivity to CXCR4 antagonists. Abstract 395, 9th CROI 2002, Seattle, USA. <http://63.126.3.84/2002/Abstract/12981.htm>
31. Westby M, Smith-Burchnell C, Hamilton D, et al. Structurally related HIV co-receptor antagonists bind to similar regions of CCR5 but have differential activities against UK-427,857-resistant primary isolates. Abstract 96, 12th CROI 2005.
32. Wilkin T, Su Z, Kuritzkes D, et al. Co-receptor tropism in patients screening for ACTG 5211, a phase 2 study of vicriviroc, a CCR5 Inhibitor. Abstract 655, 13th CROI 2006, Denver.
33. Xiao L, Rudolph DL, Owen SM, Spira TJ, Lal RB. Adaptation to promiscuous usage of CC and CXC-chemokine coreceptors in vivo correlates with HIV-1 disease progression. *AIDS* 1998, 12: F137-43. <http://amedeo.com/lit.php?id=9764773>

## Fusion inhibitors

(For T-20, see above)

Although the fusion inhibitor T-20 was the first entry inhibitor, there has been little development in this field. The development of T-1249, which was both well tolerated and effective against T-20-resistant virus isolates, was stopped in early 2004. The official reason was that the manufacturing process was too complicated. The real reason was probably different. The success of T-20 has been too modest so far, and T-1249 would have required daily subcutaneous injection. This is unappealing for many patients and clinicians – expectations in the HAART era are high. It therefore now seems unlikely that another drug will make it to licensing in the next years. It still needs to be demonstrated whether small molecular fusion inhibitors, a new group of fusion inhibitors with oral bioavailability, are effective (Jiang 2004 + 2005).

**T-649** is a T-1249 analog that binds to the HR2-region of gp41, like T-20. However, the binding site seems to overlap only partially with that of T-20 (Derdeyn 2001). Combination of T-20 and T-649 can possibly prevent or delay development of resistance. However, mechanisms for T-649 resistance have also been discovered (Heil 2002), and the future of this drug is in doubt.

**FP-21399** is being developed by Lexigen (previously Fuji ImmunoPharmaceutical) as a fusion inhibitor. A single dose shows good tolerability, with the most frequent side effects being discoloration of skin and urine. However, the initial viral load data was not convincing – only 2 out of 13 patients had a decrease in viral load of at least 1 log after 4 weeks (Dezube 2000). Since then, not much has been heard and it is uncertain whether FP-21399 will be developed further. Indeed, on the company's website, it looks as if Lexigen would like to dispose of this drug.

**TR-290999** and **TR-291144** are two new generation fusion inhibitors, that were developed by Trimers in cooperation with Roche (Delmedico 2006). According to studies on monkeys, the potency, duration of action and pharmacokinetics of these peptides are much improved in comparison to T-20. Although administration is still by injection, it may be possible to limit this to once a week. The data from human investigations are not yet available.

Out of sight, out of mind: terminated entry inhibitors:

- AMD 3100 (CXCR4A) from AnorMed, due to cardiotoxicity
- BMS 806 (attachment inhibitor), replaced with BMS 488,043
- T-1249 (fusion inhibitor) from Roche/Trimeris, little prospect of success
- SCH-C (CCR5A) from Schering-Plough, due to arrhythmia
- TAK-779, TAK-220 (CCR5A) from Takeda, replaced with TAK-652
- Aplaviroc (CCR5A) from GSK, due to hepatotoxicity

## References

1. Delmedico M, Bray B, Cammack N, et al. Next generation HIV peptide fusion inhibitor candidates achieve potent, durable suppression of virus replication in vitro and improved pharmacokinetic properties. Abstract 48, 13th CROI 2006, Denver.
2. Derdeyn C, Decker J, Sfakians J, et al. Sensitivity of HIV-1 to fusion inhibitors is modulated by coreceptor specificity and involves distinct regions of gp41. Abstract 75, 1st IAS 2001, Buenos Aires, Argentina.
3. Dezube BJ, Dahl TA, Wong TK, et al. A fusion inhibitor (FP-21399) for the treatment of HIV infection: a phase I study. *J Infect Dis* 2000, 182: 607-10. <http://amedeo.com/lit.php?id=10915097>
4. Heil M, Decker J, Sfakianos J, et al. Analysis of patient-derived HIV-1 isolates suggests a novel mechanism for decreased sensitivity to inhibition by T-20 and T-649. Abstract 392, 9th CROI 2002, Seattle. <http://63.126.3.84/2002/Abstract/13373.htm>
5. Jiang S, Lu H, Liu S, Zhao Q, He Y, Debnath AK. N-substituted pyrrole derivatives as novel human immunodeficiency virus type 1 entry inhibitors that interfere with the gp41 six-helix bundle formation and block virus fusion. *Antimicrob Agents Chemother* 2004, 48:4349-59.
6. Jiang S, Lu H, Liu S, et al. Small molecule HIV entry inhibitors targeting gp41. Abstract TuOa0201. 3rd IAS 2005, Rio de Janeiro.

## Integrase inhibitors

Integrase, along with reverse transcriptase and protease, is one of the three key enzymes in the HIV replication cycle. This enzyme is involved in the integration of viral DNA into the host genome, and is essential for the proliferation of HIV (Nair 2002). Integrase inhibitors are occasionally falsely classified as entry inhibitors. However, unlike the latter, they do not prevent entry of the virus into the cell. Although there is probably no integrase in human cells, the development of new drugs is proving difficult and slow, as the effects observed in the laboratory cannot be converted into antiviral effects at present (see Pommier 2005 for a comprehensive review). The position at which integrase is effectively inhibited was first discovered in 2000 (Hazuda 2000). Since 2005, clinical studies have, for the first time, started to make progress, and the scepticism that was present in the last edition of this text, has been withdrawn: integrase inhibitors will come, and will probably play an important role in the therapy of HIV.

**MK-0518** is an integrase inhibitor from MSD, and possibly the most exciting experimental drug of all at present in the treatment of HIV. MK-0518 is the successor of L-870810, the first integrase inhibitor, which showed antiviral activity in HIV-infected patients (Little 2005), but had to be withdrawn due to hepatotoxicity in beagles. So far, this toxicity has not been associated with MK-0518, and the drug appears to be well tolerated. MK-0518 has a wide range of efficacy for R5- and X4-tropic viruses, as well as inhibiting the replication of HIV-2. Resistance mutations

appear to reduce the viral fitness. The data from a placebo-controlled Phase II study are extremely impressive (Grinzstein 2006): 116 patients with a long pre-treatment history (median 10 years, in which approximately 30 % of the patients had no more treatment options left open to them) received 200-600 mg MK-0518 bid. After 8 weeks, 63-67 % of the patients on MK-0518 had attained a viral load of less than 50 copies/ml, compared to 8 % in the placebo group. This is a truly exceptional result for such a pre-treated patient group, in which at least one third received virtually a monotherapy of MK-0518. The plasma levels of the drug were significantly elevated by atazanavir. The results of the Phase III studies that are currently underway on extensively pre-treated patients, are being awaited with baited breath.

**GS 9137 (JTK-303)** is an integrase inhibitor produced by Gilead, and is biochemically similar to the quinolone antibiotics (Sato 2006). Single doses of GS 9137 had oral bioavailability, were safe and well tolerated (Kawaguchi 2006). In vitro, a synergy existed with other medicines (Matsuzaki 2006). In a preliminary study on 40 HIV-infected patients (therapy naïve and pre-treated), the viral load sank by approximately 2 logs after 10 days of monotherapy (DeJesus 2006). When boosted with 100 mg of ritonavir, GS 9137 can be given as a once daily dose. In the first half of 2006, a Phase II study will investigate boosted once daily doses (20, 50 and 125 mg).

## Maturation inhibitors

The so-called maturation inhibitors inhibit HIV replication in a very late phase of the HIV reproduction cycle, i.e., by the budding or maturation of new virions. As is the case for integrase inhibitors, 2005 can be counted as the introductory year: this was the first time a preparation was proven to have an antiviral effect on HIV-infected patients.

**PA-457** is a derivative of betulinic acid, which is isolated as triterpene carbonic acid from birch bark. Produced by the biotechnology firm Panacos, PA-457 inhibits HIV replication in a very late phase of the HIV reproduction cycle, i.e. the budding or maturation of new virions (Li 2003). PA-457 inhibits the transition of the capsid precursor (p25) into the mature capsid protein (p24). This prevents the production of infectious viruses. Because of its novel method of action, it is also effective against resistant viruses. Following the publication of the first results of a small study on HIV patients at the start of 2005 (Martin 2005), the data of a Phase IIa placebo-controlled trial were published in autumn 2005, in which patients received an oral once daily monotherapy of PA-457 for 10 days (Beatty 2005). In the highest dosage group (200 mg) a reduction in viral load of 1.03 logs was reached; in the 100 mg group it was just 0.48 logs. However, some patients had no significant reduction in the viral load. Fortunately, the drug has a long half-life, and a once daily dose will definitely be possible. PA-457 has so far been well tolerated. Resistance has not yet been observed in humans, although the laboratory data seem to show that a single mutation in the gag region produces resistance. Resistant mutants are probably less capable of reproducing than the wild-type viruses (Adamson 2006). PA-457 also works synergistically with other antiviral drugs (Kilgore 2006).

**UK-201844** is a maturation inhibitor from Pfizer. It was discovered after the screening of more than one million drugs (Blair 2006). The method of action seems

to lie in the interaction with gp160, which leads to the production of non-infectious virus.

Maturation inhibitors are, without a doubt, an interesting class of new drugs. They now have to traverse the stony path of Phase IIb/Phase III studies. Whether a prototype for this class, such as PA-457, will make it as far as the clinic, is still completely unclear. It is also already exciting to see that, not just in theory, but in practice too, HIV can be attacked from a new angle. On the other hand, HIV will probably find ways to overcome the effect of this drug, too...

## References

1. Adamson C, Salzwedel K, Castillo A, et al. Viral resistance to PA-457, a novel inhibitor of HIV-1 maturation. Abstract 156, 13th CROI 2006, Denver.
2. Beatty G, Jacobson J, Lalezari J, et al. Safety and Antiviral Activity of PA-457, the First-In-Class Maturation Inhibitor, in a 10-Day Monotherapy Study in HIV-1 Infected Patients. Abstract Abstract H-416D, 45th ICAAC 2005, Washington.
3. Blair W, Cao J, Jackson L, et al. Execution of a high throughput HIV-1 replication screen and the identification of a novel small molecule inhibitor that targets HIV-1 envelop maturation. Abstract 50LB, 13th CROI 2006, Denver.
4. DeJesus E, Berger D, Markowitz M, et al. The HIV integrase inhibitor GS-9137 (JTK-303) exhibits potent antiviral activity in treatment-naïve and experienced patients. Abstract 160LB, 13th CROI 2006, Denver.
5. Grinsztejn B, Nguyen BY, Katlama C, et al. Potent antiretroviral effect of MK-0518, a novel HIV-1 integrase inhibitor, in patients with triple-class resistant virus. Abstract 159LB, 13th CROI 2006, Denver.
6. Hazuda DJ, Felock P, Witmer M, et al. Inhibitors of strand transfer that prevent integration and inhibit HIV-1 replication in cells. *Science* 2000, 287:646-50.
7. Kawaguchi I, Ishikawa T, Ishibashi M, Irie S, Kakee A. Safety and pharmacokinetics of single oral dose of JTK-303/GS 9137, a novel HIV integrase inhibitor, in HIV healthy volunteers. Abstract 580, 13th CROI 2006, Denver.
8. Kilgore N, Reddick M, Zuiderhof M, et al. The first-in-class maturation inhibitor, PA-457, is a potent inhibitor of HIV-1 drug-resistant isolates and acts synergistically with approved HIV drugs in vitro. Abstract 509, 13th CROI 2006, Denver.
9. Li F, Goila-Gaur R, Salzwedel K, et al. PA-457: a potent HIV inhibitor that disrupts core condensation by targeting a late step in Gag processing. *Proc Natl Acad Sci U S A* 2003, 100:13555-60.
10. Little S, Drusano G, Schooley R, et al. Antiretroviral effect of L-000870810, a novel HIV-1 integrase inhibitor, in HIV-1-infected patients. Abstract 161, 12th CROI 2005, Boston.
11. Martin D, and others. The safety, tolerability, and pharmacokinetics of multiple oral doses of pa-457, the first-in-class HIV maturation inhibitor, in healthy volunteers. Abstract 551. 12th CROI 2005, Boston.
12. Martin D, Jacobson J, Schurmann D, et al. PA-457, the first-in-class maturation inhibitor, exhibits antiviral activity following a single oral dose in HIV-1-infected patients. Abstract 159, 12th CROI 2005, Boston.
13. Matsuzaki Y, Watanabe W, Yamataka K, et al. JTK-303/GS 9137, a novel small-molecule inhibitor of HIV-1 integrase: anti-HIV activity profile and pharmacokinetics in animals. Abstract 508, 13th CROI 2006, Denver.
14. Nair V. HIV integrase as a target for antiviral chemotherapy. *Rev Med Virol* 2002, 12:179-93.
15. Pommier Y, Johnson AA, Marchand C. Integrase inhibitors to treat HIV/AIDS. *Nat Rev Drug Discov* 2005, 4:236-48. 15729361
16. Sato M, Motomura T, Aramaki H, et al. Novel HIV-1 integrase inhibitors derived from quinolone antibiotics. *J Med Chem* 2006, 49:1506-8. <http://amedeo.com/lit.php?id=16509568>

## Immunotherapy and its relevance in clinical practice

In recent years, in addition to “conventional” ART, immunomodulatory treatment strategies have been investigated to an increasing extent (reviews in: Mitsuyasu 2002, Sereti et al 2001). All of these therapies still lack proof of clinical benefit. Some approaches are nevertheless addressed briefly below.

### Interleukin-2 (Proleukin™)

Interleukin-2 (IL-2, aldesleukin, Proleukin™) is a cytokine that is produced by activated T cells and which induces proliferation and cytokine production in T cells, B cells and NK cells (review in: Paredes 2002). It has been employed in oncology for years. IL-2 was already investigated in the early nineties, either intravenously or as a continuous infusion in HIV-infected patients (Wood 1993, Carr 1998). It is now usually administered subcutaneously. There are a few reports of the use of IL-2 in acute infection (Dybul 2002), but most studies have been in chronically infected patients.

The most important effect of IL-2 in HIV medicine is the increase in CD4+ and CD8 T cells, which may be quite impressive in individual cases (Kovacs 1996). Several randomized studies have consistently demonstrated significant increases in CD4+ T-cells with varying subcutaneous regimens. After administration of IL-2, CD45RO memory cells initially increase, followed by naïve CD45RA T cells (Chun 1999, Carcelain 2003). The life span of CD4+ and CD8 T cells may also be lengthened.

IL-2 is usually given at doses of 2 x 4.5 million I.E. subcutaneously over 5 days, in cycles 6-8 weeks apart (Davey 2000, Losso 2000, Abrams 2002, Lelezari 2000, Hengge 1998). Daily low-dose treatment has also been investigated (review in: Smith 2001). Viral load was usually unaffected by IL-2. The main results of several large, randomized studies are summarized in the following table.

The combination of IL-2 with HAART has so far been relatively safely proven in all of the larger studies. Nevertheless: the drug has considerable side effects. The main dose-limiting effects are fever, chills, and in some cases severe influenza-like symptoms such as muscular pains. The side effects are a consequence of the release of cytokines due to IL-2 and usually improve 2-3 days after the final dose. It may be helpful to take paracetamol as well as rest and ingestion of electrolyte solutions. However, it is usually not possible to be completely free of side effects, which tend to be worse than with interferon. Pegylated interleukin-2 is somewhat weaker and is also not tolerated any better (Carr 1998). Combination with prednisone is of no benefit (Tavel 2003).

Unfortunately, the activation of T cells has no influence on viral reservoirs. Although it was initially hoped that IL-2 could be used to purge virus in the reservoirs and thereby “wash out” latently infected cells from the body (Chun 1999), it is now clear that this does not occur. In the COSMIC Study, 56 patients with more than 350 CD4+ T-cells/ $\mu$ l on HAART were randomized to receive IL-2 or placebo. Although IL-2 led to a normalization of CD4+ T-cell count in significantly more patients, IL-2 did not influence viral replication, proviral DNA or latently infected cells (Stellbrink 1998+2002). In contrast, a study from a French working group (Levy 2005+2006) reported positive effects of IL-2 when given in combination



with therapeutic vaccines (the vaccines ALVAC 1433 and HIV-LIPO-6T were used). The 177 patients who received this immunotherapy were able to interrupt their ART for significantly longer than the 89 patients without immunotherapy – over an observation period of 15 months, they needed approximately 40 % less ART.

Table 3.1: Larger, randomized IL-2 studies on HIV patients.

Study	n	Patients (CD4 median at baseline)	Doses of Interleukin-2 (MIU)	Main results (In each case with versus without IL-2)
ANRS 079 Levy 2001	118	PI-naïve (CD4 200- 550)	2 x 5 for 5 days 10 cycles	Median CD4 increase (865 versus 240 after 74 weeks) No difference in VL
ACTG 328 Mitsuyasu 2001	174	HAART (CD4 264)	1 x 7.5 for 5 days every 8 weeks	Median CD4 increase (614 versus 396 after 84 weeks)
CPCRA 059 Abrams 2002	511	HAART (> 300 CD4)	2 x 1.5-7.5 for 5 days every 8 weeks	CD4 increase in the IL-2 arms higher by 251 at month 12, no dif- ference in viral load
Lalezari 2002	115	HAART (< 300 CD4)	1 x 1.2 daily	No significant difference in CD4, but in NK and naïve CD4 at 6 months
ANRS 082 Katlama 2002	72	HAART (< 200 CD4)	2 x 4.5 for 5 days every 6 weeks	Median CD4 increase (51 versus 11 after 24 weeks)
Davey 2000	82	HAART (CD4 2-500)	2 x 7.5 for 5 days every 6 weeks	Median CD4 increase (384 versus 64 after 52 weeks) VL -0.28 vs 0.09 log (p=0.03)
ACTG 248 Vogler 2004	115	ART (CD4 3-700)	1 x 1.0 daily	No significant difference

VL = viral load, MIU = Million International Units

Most studies have now shown that CD4+ T-cell nadir is predictive for CD4+ T-cell increases under IL-2 (Markowitz 2003). In other words: the greater the impairment of the immune system, the less likely it is to benefit from IL-2 therapy. The source of the CD4+ T-cell increases under IL-2 is also a subject of some discussion. Some authors suspect that the increase is more due to peripheral expansion than to increased thymus output (Lu 2003), others have assigned greater importance to the thymus (Carcelain 2003).

One question that so far remains unanswered: are the CD4+ T-cells generated by IL-2 of the same quality as “normal” CD4+ T-lymphocytes? The immune response to specific antigens such as tetanus, gp120, hepatitis A or B seem to remain unaffected by IL-2 (Valdez 2003). The most important question remains unanswered today – do the increases in CD4+ T-cell count really prevent AIDS? Do patients really benefit clinically from these difficult IL-2 treatments? Little is also known about the long-term use of IL-2 – the longest study performed to date lasted three years (Gougeon 2001). Two newer studies have recently shed a bit more light on the area (Vento 2006): both suspect IL-2, above all, of causing reduced cell turn-

over of the infection or even cell death (Kovacz 2005, Sereti 2005). This obviously only applies to naïve T-cells and not to memory cells.

Answers to these questions on long-term side effects and above all on clinical benefit were expected from ESPRIT and SILCAAT, the two ongoing multinational studies. But, due to the very low number of clinical events (death, AIDS), it is unlikely that either of these studies will provide definitive answers. Besides, both studies are struggling with organization problems and the fact that, due to the side effects, less and less patients are prepared to accept IL-2 treatment for longer periods.

ESPRIT (<http://www.espritstudy.org>) is a randomized study in which around 4,000 patients with at least 300 CD4+ T-cells/ $\mu$ l are being treated with IL-2 or not in addition to antiretroviral therapy (Emery 2002). In the summer of 2003, the first preliminary data was published (Weiss 2003). By this time, 1,929 patients had been randomized. The interim analysis included 1,394 patients: after three cycles, 64 % of patients in the IL-2 arm experienced treatment success, defined as CD4+ T-cell increases of at least 200/ $\mu$ l. A higher CD4+ T-cell nadir, higher CD4+ T-cells at baseline and younger age were associated with treatment success, as expected. Enrolment has now been completed.

SILCAAT had a similar concept, but enrolled patients with 50-299 CD4+ T-cells/ $\mu$ l and a viral load of < 10,000 copies/ml. Patients received a total of 6 cycles of 2 x 4.5 MIU IL-2 subcutaneously over 5 days every 8 weeks. After enrolment of 1,957 patients in 137 centers in 11 countries, the study was stopped in October 2002, as it was simply too expensive for the manufacturer. After major protests, SILCAAT is now continuing with a simplified design. First results have recently been published (Levy 2003): in 449 patients, who have now been followed for one year, the median CD4+ T-cell increase was 123/ $\mu$ l – which is definitely a considerable gain for this group of immunocompromised patients. This gain was again greater in patients with better CD4+ T-cells at baseline, as in ESPRIT. Data from the SILCAAT therefore also seems to indicate that even IL-2 has limited effects for reconstituting the immune system once it has been destroyed.

Summary: despite SILCAAT and ESPRIT, IL-2 therapy must be viewed sceptically based on available data. In our view, there are only a few patients who should potentially be considered for therapy with IL-2. These are patients with no immunological response, patients whose CD4+ T-cell counts remain low despite good viral suppression over longer periods of time (Crespo 2006). However, even in these patients one should question the use of IL-2, given the fact that in the setting of severe immunodeficiency, opportunistic infections occur rarely - as long as the viral load is suppressed.

### **Hydroxyurea (Litalir™, Droxia™)**

Hydroxyurea is an old chemotherapeutic agent with relatively low toxicity which is still being used today in hematology (mostly in chronic myelogenous leukemia). It inhibits DNA synthesis via the ribonucleotide reductase, and leads to an intracellular shortage of deoxynucleotide triphosphates. A synergistic effect on HIV replication in combination with ddI was demonstrated in 1994 (Lori 1994).

A Swiss study, in which 144 patients were treated with hydroxyurea (HU) or placebo in addition to d4T+ddI, attracted attention in 1998 (Rutschmann 1998). After

12 weeks, 54 versus 28 % in the placebo group demonstrated a viral load below 200 copies/ml. Was this the discovery of a new cheaper option for HIV treatment? In the light of these seemingly exciting results, even the fact that the CD4+ T-cell increase in the hydroxyurea group was only 28 versus 107 cells/ $\mu$ l in the placebo group was of minor interest. However, hydroxyurea became even more fashionable after publication of the “Berlin Patient”: a patient, who had been treated with hydroxyurea in addition to indinavir and ddI during acute infection, had stopped all therapy after a few months and subsequently showed no detectable plasma viremia (Liszewicz 1999). Was this unexpected outcome due to hydroxyurea? Several smaller studies from the US and Argentina seemed to confirm these positive results, seen primarily in combination with ddI (Hellinger 2000, Lori 1999, Rodriguez 2000). Many treating physicians added the drug to ART, and even children received hydroxyurea. Many already dreamed of a cheap combination of ddI+HU for Africa.

These initial hopes subsided quite rapidly. Although hydroxyurea is usually well tolerated, the combination with ddI and d4T in particular is obviously problematic. Data from early 2000 reported an additive toxic effect, with a frequency of polyneuropathy of almost 30 per 100 patient years (Moore 2000).

The ACTG 5025 Study (Havliř 2001), in which hydroxyurea was evaluated as a “stabilizer” of successful therapy (stable undetectable viral load), led to the demise of hydroxyurea in HIV therapy. Three deaths occurred on the combination of ddI+d4T (+IDV) due to pancreatitis, all in the hydroxyurea group, and there was a significantly high rate of treatment failure (mainly due to toxicity). The risk of pancreatitis on ddI seems to be four times higher in combination with hydroxyurea (Moore 2001). Randomized studies also failed to show an effect in primary infection: obviously, further Berlin patients cannot simply be “reproduced” (Zala 2002).

Newer data possibly show an effect after all. In 69 patients – with treatment failure under a PI and naïve for efavirenz/ABC – the combination of d4T+ddI+ABC+efavirenz in a randomized study from France had astonishing results. After one year, 55 % on hydroxyurea versus 21 % were below 50 copies/ml (Lafeuillade 2002). But should such data be considered after all that has happened with this drug in the past? Since 2004, at least three more controlled studies were published, showing toxicity but no positive effects (Blanckenberg 2004, Stebbing 2004, Swindells 2005)). In our opinion: hydroxyurea should not be used anymore for antiretroviral therapy outside of clinical studies, even if, after the more recent Italian studies, lower doses are supposed to be better than higher ones (Loir 2005). In addition, such studies should have relevant objectives. At present, there are none in sight.

### **Interferon**

The antiretroviral effect of interferon has been known for years (Milvan 1996). The effect of 3 million I.E. daily s.c. is about 0.5-1 log (Haas 2000). Higher dosing may increase this effect further (Hatzakis 2001). An in-depth investigation of the antiviral activity of interferon was initially not conducted because of the subcutaneous delivery route and its not insignificant side effects. However, there have recently been indications that the drug may be useful for salvage therapy. Pegylated interferons now allow for weekly administration, and improved efficacy with the pegylated drug is anticipated, in analogy to the studies in the setting of hepatitis C

infection. Studies on this are underway. Schering-Plough in particular is currently involved in trying to license the product. However, there have been setbacks, as with IL-2, and a pivotal multinational study in highly treatment-experienced patients was aborted in October 2002 due to insufficient recruitment.

### **Other immunotherapies**

The prototype of therapeutic vaccination already suffered disaster years ago. Remune™, developed by a team headed by Jonas Salk, is a therapeutic vaccine comprised of an envelope-depleted (gp120) virus which, although indeed immunogenic, does not seem to provide any clinical benefit (i.e., prolongation of life and delay of disease progression). A large trial was interrupted prematurely in May 1999 as no benefit had been demonstrated for study participants. More than 2,500 patients had taken part for a mean of 89 weeks in this multinational study, which was designed to evaluate the addition of Remune™ to HAART. As well as the lack of clinical benefit, not even advantages with respect to CD4+ T-cell count or viral load could be shown (Kahn 2000). Remune™ is now probably obsolete, even though there have recently been dubious reports, from Thailand, claiming that some effect exists.

**G-CSF and GM-CSF** – the cytokines G-CSF (granulocyte colony-stimulating factor) and GM-CSF (granulocyte-macrophage colony-stimulating factor) have frequently been used in HIV patients. G-CSF is available as filgrastim, pegfilgrastim and lenogastim; GM-CSF is available as sargramostim or molgramostin.

G-CSF is licensed for treatment of prolonged neutropenia in patients with advanced HIV infection to reduce the risk of bacterial infections. Treatment with G-CSF can be particularly useful in patients on chemotherapy or myelosuppressive drugs such as ganciclovir or AZT. G-CSF significantly reduces bacterial infections in neutropenic HIV patients. In a large randomized study, 258 neutropenic HIV patients (neutrophils 750-1,000/μl) with CD4+ T-cell levels below 200/μl were either treated for 24 weeks with G-CSF (3 times/week) or not. The rate of severe neutropenia was only 2 versus 22 % in the control group (Kuritzkes 1998). The incidence of bacterial infections was reduced by 31 %, and the number of inpatient days was reduced by 45 %. There was no effect on viral load. In patients with CMV retinitis, G-CSF was also shown to have significant survival benefit, although the mechanisms remained unclear (Davidson 2002).

GM-CSF showed a slight effect on viral load in three double-blind, randomized studies (Angel 2000, Skowron 1999, Brites 2000); however, in one study in patients with uncontrolled infection there was a slight increase (Jacobsen 2003). No effect was observed under G-CSF (Aladdin 2000). GM-CSF seems to prevent significant loss of CD4+ cells during longer treatment interruptions (Fagard 2003). However, such approaches cannot be recommended outside of clinical studies. The side effects and significant cost of G-CSF and GM-CSF should also be considered. Whether any clinical benefit exists remains unclear.

**Cyclosporin A (Sandimmune™)** – Immune activation may lead to increased HIV replication, and an attractive treatment hypothesis has been to suppress the immune system in an attempt to slow down viral replication. This is the rationale behind studies investigating the use of cyclosporin A (Calabrese 2002, Rizzarda 2002). The drug is normally used for prophylaxis of transplant rejection after allogenic organ transplantation. In one study to date, 28 HIV-infected patients were recruited to

receive cyclosporin A 4 mg/kg or placebo daily for 12 weeks, with or without antiretroviral therapy (two nucleoside analogs; Calabrese 2002). The results are easily summarized: cyclosporin A had no effect on CD4+ or CD8+ T-cell count, nor on expression of activation markers such as CD38 or HLA-DR. Cyclosporin A therefore probably has no future in the therapy of chronically infected HIV patients. Whether, and how, cyclosporin A might improve treatment of acute HIV infection needs to be clarified in further studies. Use of both immunosuppressants (CsA) and immunostimulants (IL-2) in this setting shows the clear discrepancy between scientific knowledge and hope.

**Mycophenol (Cellcept™)** - the theoretical concept is similar to that of hydroxyurea and cyclosporin A. Mycophenol inhibits inosine monophosphate (IMP) dehydrogenase and is normally used for prophylaxis of acute transplant rejection in patients with allogenic kidney, heart or liver transplantations, as well as for some autoimmune diseases. Inhibition of lymphocyte proliferation and the subsequent reduction of target cells should theoretically inhibit replication of HIV. Initial reports seem to demonstrate an effect on viral load at least in some patients (Margolis 2002, Press 2002). Whether this will be confirmed by randomized trials seems uncertain. The first data suggest that this is unlikely (Sankatsing 2004, Margolis 2006).

**Cannabinoids** have no effect. A controlled, prospective, randomized study, in which patients could either smoke marijuana or receive TCH (dronabinol, Marinol™) or placebo in addition to HAART, showed no effects on lymphocyte subpopulations or lymphocyte function after three weeks (Bredt 2002). THC, which is metabolized via the cytochrome P450 system, also had no detrimental effects on viral load or plasma levels of protease inhibitors (Abrams 2003).

**Corticosteroids** have been and continue to be used and propagated by some HIV clinicians again and again. However, such treatment does not stand the test of controlled studies. In a placebo-controlled study with 0.5 mg prednisone/kg over 8 weeks, there were no effects on CD4+ T-cells or viral load (McComsey 2001). In ACTG 349, 24 patients were treated with 40 mg prednisone daily or not in a double-blind randomized design (Wallis 2003). After 8 weeks, there was a trend towards higher levels of CD4+ cells in the prednisone arm (> 40 %, p = 0.08), but there were no effects on activation markers or apoptosis. Two patients on prednisone developed necrosis of the femoral head. This study should advise caution before the use of steroids for “immunological” reasons is considered.

**Murabutide** is a synthetic muramyldipeptide with a variety of effects on the immune system. It can raise unspecific resistance to infection, induce anti-inflammatory cytokines and growth factors, and strengthen the anti-viral effects of cytokines such as IL-2 or interferon. In HIV patients, a team in France has used it mainly as an immune modulator, although only in small studies, and at the most, with moderate effect (Amiel 2002, Bahr 2003).

**Interleukin-12** stimulates T lymphocytes and NK cells to generate a Th1-type immune response. In a randomized Phase I study with rhIL-12 100 ng/kg 2 x/week, the drug was well tolerated but had no effect on lymphocyte subpopulations, antigen-specific immune response or viral load (Jacobson 2002). Further development is therefore uncertain. The same would appear to be true for interleukin-10 (Angel 2000). In the age of highly effective antiretroviral therapies, such experimental therapies have to meet ever-increasing standards.

**Interleukin-15** is a pleotropic, multifunctional interleukin that acts on NK- and CD8+ T-cells (Ahmad 2005). It is not yet clear whether the preclinical data can be applied to humans (d'Ettorre 2006).

## References

- Abrams DI, Bebchuk JD, Denning ET, et al. Randomized, open-label study of the impact of two doses of subcutaneous recombinant interleukin-2 on viral burden in patients with HIV-1 infection and CD4+ cell counts of  $\geq 300/\text{mm}^3$ : CPCRA 059. *J AIDS* 2002; 29: 221-31. <http://amedeo.com/lit.php?id=11873071>
- Abrams DI, Hilton JF, Leiser RJ, et al. Short-term effects of cannabinoids in patients with HIV-1 infection: a randomized, placebo-controlled clinical trial. *Ann Intern Med* 2003; 139:258-66. <http://amedeo.com/lit.php?id=12965981>
- Ahmad A, Ahmad R, Iannello A, et al. IL-15 and HIV infection: lessons for immunotherapy and vaccination. *Curr HIV Res* 2005, 3:261-70.
- Aladdin H, Ullum H, Katzenstein T, et al. Immunological and virological changes in antiretroviral naive HIV infected patients randomized to G-CSF or placebo simultaneously with initiation of HAART. *Scand J Immunol* 2000, 51:520-5. <http://amedeo.com/lit.php?id=10792845>
- Amiel C, De La Tribonniere X, Vidal V, et al. Clinical tolerance and immunologic effects after single or repeated administrations of the synthetic immunomodulator murabutide in HIV-1-infected patients. *J AIDS* 2002, 30:294-305.
- Angel JB, High K, Rhame F, et al. Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. Leukine/HIV Study Group. *AIDS* 2000, 14:387-95. <http://amedeo.com/lit.php?id=10770541>
- Angel JB, Jacobson MA, Skolnik PR, A multicenter, randomized, double-blind, placebo-controlled trial of recombinant human interleukin-10 in HIV-infected subjects. *AIDS* 2000; 14:2503-8. <http://amedeo.com/lit.php?id=11101061>
- Bahr GM, De La Tribonniere X, et al. Clinical and immunological effects of a 6 week immunotherapy cycle with murabutide in HIV-1 patients with unsuccessful long-term antiretroviral treatment. *J Antimicrob Chemother* 2003, 51:1377-88. <http://amedeo.com/lit.php?id=12716777>
- Blanckenberg DH, Wood R, Horban A, et al. Evaluation of nevirapine and/or hydroxyurea with nucleoside reverse transcriptase inhibitors in treatment-naive HIV-1-infected subjects. *AIDS* 2004, 18:631-40. <http://amedeo.com/lit.php?id=15090768>
- Bredt BM, Higuera-Alhino D, Shade SB, et al. Short-term effects of cannabinoids on immune phenotype and function in HIV-1-infected patients. *J Clin Pharmacol* 2002; 42:82S-89S. <http://amedeo.com/lit.php?id=12412840>
- Brites C, Gilbert MJ, Pedral-Sampaio D, et al. A randomized, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor and nucleoside analogue therapy in AIDS. *J Infect Dis* 2000, 182: 1531-5. <http://amedeo.com/lit.php?id=11023477>
- Calabrese LH, Lederman MM, Spritzler J, et al. Placebo-controlled trial of Cyclosporin-A in HIV-1 disease: Implications for solid organ transplantation. *J Acquir Immune Defic Syndr* 2002, 29:359-362. <http://amedeo.com/lit.php?id=11917239>
- Carcelain G, Saint-Mezard P, Altes HK, et al. IL-2 therapy and thymic production of naive CD4 T cells in HIV-infected patients with severe CD4 lymphopenia. *AIDS* 2003;17:841-50. <http://amedeo.com/lit.php?id=12660531>
- Carr A, Emery S, Lloyd A, et al. Outpatient continuous intravenous interleukin-2 or subcutaneous, polyethylene glycol-modified interleukin-2 in HIV-infected patients: a randomized, controlled, multicenter study. *J Infect Dis* 1998; 178: 992-9. <http://amedeo.com/lit.php?id=9806026>
- Chun TW, Engel D, Mizell SB, et al. Effect of interleukin-2 on the pool of latently infected, resting CD4+ T cells in HIV-1-infected patients receiving HAART. *Nat Med* 1999, 5:651-5. <http://amedeo.com/lit.php?id=10371503>
- Crespo M, Caragol I, Falcó V, et al. Efficacy of recombinant interleukin-2 in patients with advanced HIV-1 infection and blunted immune response to HAART. Abstract 494, 13th CROI 2006, Denver.
- Davey RT JR, Murphy RL, Graziano FM, et al. Immunologic and virologic effects of subcutaneous interleukin 2 in combination with ART: A randomized controlled trial. *JAMA* 2000, 284: 183-9. <http://amedeo.com/lit.php?id=10889591>
- Davidson M, Min YI, Holbrook JT, et al. Use of filgrastim as adjuvant therapy in patients with AIDS-related cytomegalovirus retinitis. *AIDS* 2002, 16: 757-65. <http://amedeo.com/lit.php?id=11964532>

19. d'Ettorre G, Andreotti M, Carnevalini M, et al. Interleukin-15 enhances the secretion of IFN-gamma and CC chemokines by natural killer cells from HIV viremic and aviremic patients. *Immunol Lett* 2006, 103:192-5.
20. Dybul M, Hidalgo B, Chun TW, et al. Pilot study of the effects of intermittent interleukin-2 on HIV-specific immune responses in patients treated during recently acquired HIV infection. *J Infect Dis* 2002; 185: 61-8. <http://amedeo.com/lit.php?id=11756982>
21. Emery S, Abrams DI, Cooper DA, et al. The evaluation of subcutaneous proleukin (interleukin-2) in a randomized international trial: rationale, design, and methods of ESPRIT. *Control Clin Trials* 2002; 23:198-220. <http://amedeo.com/lit.php?id=11943448>
22. Fagard C, Le Braz M, Gunthard H, A controlled trial of granulocyte macrophage-colony stimulating factor during interruption of HAART. *AIDS* 2003, 17:1487-92.
23. Gougeon ML, Rouzioux C, Liberman I, et al. Immunological and virological effects of long term IL-2 therapy in HIV-1-infected patients. *AIDS* 2001, 15:1729-31. Abstract: <http://amedeo.com/lit.php?id=11546950><http://amedeo.com/lit.php?id=11546950>
24. Haas DW, Lavelle J, Nadler JP, et al. A randomized trial of interferon alpha therapy for HIV type 1 infection. *AIDS Res Hum Retrovir* 2000, 16:183-90. <http://amedeo.com/lit.php?id=10710206>
25. Hatzakis A, Gargalianos P, Kiosses V, et al. Low-dose IFN-alpha monotherapy in treatment-naive individuals with HIV-1 infection: evidence of potent suppression of viral replication. *J Interferon Cytokine Res* 2001, 21:861-9. <http://amedeo.com/lit.php?id=11710999>
26. Havlir DV, Gilbert PB, Bennett K, et al. Effects of treatment intensification with hydroxyurea in HIV-infected patients with virologic suppression. *AIDS* 2001; 15: 1379-88. <http://amedeo.com/lit.php?id=11504959>
27. Hellinger JA, Iwane MK, Smith JJ, et al. A randomized study of the safety and antiretroviral activity of hydroxyurea combined with didanosine in persons infected with HIV type 1. *J Infect Dis* 2000, 181: 540-7. <http://amedeo.com/lit.php?id=10669337>
28. Hengge UR, Goos M, Esser S, et al. Randomized, controlled phase II trial of subcutaneous interleukin-2 in combination with HAART in HIV patients. *AIDS* 1998; 12: F225-34. <http://amedeo.com/lit.php?id=9863864>
29. Jacobson JM, Lederman MM, Spritzler J, et al. Granulocyte-macrophage colony-stimulating factor induces modest increases in plasma human immunodeficiency virus (HIV) type 1 RNA levels and cd4+ lymphocyte counts in patients with uncontrolled HIV infection. *J Infect Dis* 2003; 188: 1804-14. <http://amedeo.com/lit.php?id=14673758>
30. Jacobson MA, Spritzler J, Landay A, et al. A Phase I, placebo-controlled trial of multi-dose recombinant human interleukin-12 in patients with HIV infection. *AIDS* 2002; 16:1147-54. <http://amedeo.com/lit.php?id=12004273>
31. Kahn JO, Cherng DW, Mayer K, Murray H, Lagakos S. Evaluation of HIV-1 immunogen, an immunologic modifier, administered to patients infected with HIV having 300 to 549 x 10(6)/L CD4 cell counts: A randomized controlled trial. *JAMA* 2000, 284:2193-202. <http://amedeo.com/lit.php?id=11056590>
32. Katlama C, Carcelain G, Duivivier C, et al. Interleukin-2 accelerates CD4 cell reconstitution in HIV-infected patients with severe immunosuppression despite highly active antiretroviral therapy: the ILSTIM study - ANRS 082. *AIDS* 2002; 16: 2027-34. <http://amedeo.com/lit.php?id=12370501>
33. Kovacs JA, Lempicki RA, Sidorov IA, et al. Induction of prolonged survival of CD4+ T lymphocytes by intermittent IL-2 therapy in HIV-infected patients. *J Clin Invest* 2005; 115: 2139-2148.
34. Kovacs JA, Vogel S, Albert JM, et al. Controlled trial of interleukin-2 infusions in patients infected with the HIV. *N Engl J Med*. 1996, 335:1350-6. <http://amedeo.com/lit.php?id=8857018>
35. Kuritzkes DR, Parenti D, Ward DJ, et al. Filgrastim prevents severe neutropenia and reduces infective morbidity in patients with advanced HIV infection: results of a randomized, multicenter, controlled trial. *AIDS* 1998, 12:65-74. <http://amedeo.com/lit.php?id=9456256>
36. Lafeuillade A, Hittinger G, Chadapaud S, et al. The HYDILE trial: efficacy and tolerance of a quadruple combination of reverse transcriptase inhibitors versus the same regimen plus hydroxyurea or hydroxyurea and interleukin-2 in HIV-infected patients failing PI-based combinations. *HIV Clin Trials* 2002, 3:263-71. <http://amedeo.com/lit.php?id=12187499>
37. Lalezari JP, Beal JA, Ruane PJ, et al. Low-dose daily subcutaneous interleukin-2 in combination with HAART in HIV+ patients: a randomized controlled trial. *HIV Clin Trials* 2000, 1:1-15. <http://amedeo.com/lit.php?id=11590500>
38. Levy Y, Capitant C, Lascaux AS, et al. Effect of subcutaneous IL-2 therapy combined with HAART in HIV-infected patients: results of the ANRS 079 randomized trial. Abstract 344, 8th CROI 2001, Chicago. <http://www.retroconference.org/2001/abstracts/abstracts/344.htm>
39. Levy Y, Durier C, Lascaux AS, et al. Sustained control of viremia following therapeutic immunization in chronically HIV-1-infected individuals. *AIDS* 2006, 20:405-413. <http://amedeo.com/lit.php?id=16439874>

40. Levy Y, Gahery-Segard H, Durier C, et al. Immunological and virological efficacy of a therapeutic immunization combined with interleukin-2 in chronically HIV-1 infected patients. *AIDS* 2005, 19:279-86. <http://amedeo.com/lit.php?id=15718838>
41. Levy Y, Mitsuyasu R, Tambusi G, et al. CD4 count increases in patients with CD4 counts of 50-300 treated with intermittent IL-2: immunologic results from the study of IL-2 in combination with active antiretroviral therapy (SILCAAT) trial; Abstract F14/3, 9th EACS 2003, Warsaw
42. Lisiewicz J, Foli A, Wainberg M, Lori F. Hydroxyurea in the treatment of HIV infection: clinical efficacy and safety concerns. *Drug Saf* 2003; 26:605-24. <http://amedeo.com/lit.php?id=12814330>
43. Lisiewicz J, Rosenberg E, Lieberman J, et al. Control of HIV despite the discontinuation of antiretroviral therapy. *N Engl J Med* 1999, 340:1683-4.
44. Lori F, Foli A, Groff A, et al. Optimal suppression of HIV replication by low-dose hydroxyurea through the combination of antiviral and cytostatic ('virostatic') mechanisms. *AIDS* 2005, 19:1173-81. <http://amedeo.com/lit.php?id=15990570>
45. Lori F, Jessen H, Lieberman J, et al. Treatment of HIV infection with hydroxyurea, didanosine, and a protease inhibitor before seroconversion is associated with normalized immune parameters and limited viral reservoir. *J Infect Dis* 1999, 180: 1827-32. <http://amedeo.com/lit.php?id=10558937>
46. Lori F, Malykh A, Cara A, et al. Hydroxyurea as an inhibitor of HIV-type 1 replication. *Science* 1994, 266:801-5. <http://amedeo.com/lit.php?id=7973634>
47. Lusso MH, Belloso WH, Emery S, et al. A randomized, controlled, phase II trial comparing escalating doses of subcutaneous interleukin-2 plus antiretrovirals versus antiretrovirals alone in HIV-infected patients with CD4+ cell counts  $\geq 350/\text{mm}^3$ . *J Infect Dis* 2000, 181:1614-21. <http://amedeo.com/lit.php?id=10823761>
48. Lu AC, Jones EC, Chow C, et al. Brief Report: Increases in CD4+ T lymphocytes occur without increases in thymic size in hiv-infected subjects receiving interleukin-2 therapy. *J AIDS* 2003; 34:299-303. <http://amedeo.com/lit.php?id=14600575>
49. Margolis D, Mukherjee L, Hogg E, et al. A phase I/II randomized, double-blind, placebo-controlled pilot study of b-D-2,6-diaminopurine dioxolane vs DAPD + mycophenolate mofetil in treatment-experienced Subjects (ACTG 5165). Abstract 517, 13th CROI 2006, Denver.
50. Margolis DM, Kewn S, Coull JJ, et al. The addition of mycophenolate mofetil to antiretroviral therapy including abacavir is associated with depletion of intracellular deoxyguanosine triphosphate and a decrease in plasma HIV-1 RNA. *J Acquir Immune Defic Syndr* 2002, 31:45-9. <http://amedeo.com/lit.php?id=12352149>
51. Markowitz N, Bebchuk JD, Abrams DI. Nadir CD4+ T cell count predicts response to subcutaneous recombinant interleukin-2. *Clin Infect Dis* 2003; 37:e115-20. <http://amedeo.com/lit.php?id=14523786>
52. McComsey GA, Whalen CC, Mawhorter SD, et al. Placebo-controlled trial of prednisone in advanced HIV-1 infection. *AIDS* 2001;15:321-7.
53. Mildvan D, Bassiakos Y, Zucker ML, et al. Synergy, activity and tolerability of zidovudine and interferon-alpha in patients with symptomatic HIV-1 infection: ACTG 068. *Antivir Ther* 1996; 1: 77-88. <http://amedeo.com/lit.php?id=11321183>
54. Mitsuyasu R, Pollard R, Gelman R, Weng D. Prospective randomized controlled phase II study of highly active antiretroviral therapy with continuous IV or subcutaneous interleukin-2 in HIV-infected patients with CD4+ counts of 50-350 cells/mm<sup>3</sup>: ACTG 328--final results at 84 weeks. Abstract 17, 8th CROI 2001, Chicago. <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/17.htm>
55. Mitsuyasu R. Immune therapy: non-HAART management of HIV-infected patients. *J Infect Dis* 2002, 185 (Suppl 2): S115-22. <http://amedeo.com/lit.php?id=12001032>
56. Moore RD, Keruly JC, Chaisson RE. Incidence of pancreatitis in HIV-infected patients receiving nucleoside reverse transcriptase inhibitor drugs. *AIDS* 2001, 15:617-20.
57. Moore RD, Wong WM, Keruly JC, McArthur JC. Incidence of neuropathy in HIV-infected patients on monotherapy versus those on combination therapy with didanosine, stavudine and hydroxyurea. *AIDS* 2000, 14: 273-8. <http://amedeo.com/lit.php?id=10716503>
58. Paredes R, Lopez Benaldo de Quiros JC, Fernandez-Cruz E, Clotet B, Lane HC. The potential role of interleukin-2 in patients with HIV infection. *AIDS Rev* 2002; 4:36-40.
59. Press N, Kimel G, Harris M, et al. Case series assessing the safety of mycophenolate as part of multi-drug rescue treatment regimens. *HIV Clin Trials* 2002, 3:17-20. <http://amedeo.com/lit.php?id=11819181>
60. Rizzardi GP, Harari A, Capiluppi B, et al. Treatment of primary HIV-1 infection with cyclosporin A coupled with HAART. *J Clin Invest* 2002, 109:681-688. <http://amedeo.com/lit.php?id=11877476>
61. Rodriguez CG, Vila J, Capurro AF. Combination therapy with hydroxyurea versus without hydroxyurea as first line treatment options for antiretroviral-naive patients. *HIV Clin Trials* 2000, 1:1-8. <http://amedeo.com/lit.php?id=11590492>



62. Rutschmann OT, Opravil M, Iten A, et al. A placebo-controlled trial of didanosine plus stavudine, with and without hydroxyurea, for HIV infection. *The Swiss HIV Cohort Study. AIDS* 1998, 12: F71-7. <http://amedeo.com/lit.php?id=9631134>
63. Rutschmann OT, Opravil M, Iten A, et al. Didanosine plus stavudine with or without hydroxyurea in HIV-1-infected patients: 1 year follow-up. *Antivir Ther* 1998, 3 (Suppl 4): 65-7. <http://amedeo.com/lit.php?id=10723515>
64. Sankatsing SU, Jurriaans S, van Swieten P, et al. Highly active antiretroviral therapy with or without mycophenolate mofetil in treatment-naive HIV-1 patients. *AIDS* 2004, 18:1925-31. <http://amedeo.com/lit.php?id=15353978>
65. Sereti I, Imamichi H, Natarajan V, et al. In vivo expansion of CD4+CD45RO-CD25+ T cells expressing foxP3 in IL-2-treated HIV-infected patients. *J Clin Invest* 2005; 115: 1839-1847.
66. Sereti I, Lane HC. Immunopathogenesis of HIV: implications for immune-based therapies. *Clin Infect Dis* 2001, 32: 1738-55. <http://amedeo.com/lit.php?id=11360217>
67. Skowron G, Stein D, Drusano G, et al. The safety and efficacy of granulocyte-macrophage colony-stimulating factor (Sargramostim) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial. *J Infect Dis* 1999, 180:1064-71. <http://amedeo.com/lit.php?id=10479132>
68. Smith KA. Low-dose daily interleukin-2 immunotherapy: accelerating immune restoration and expanding HIV-specific T-cell immunity without toxicity. *AIDS* 2001, 15 Suppl 2: S28-35.. <http://amedeo.com/lit.php?id=11424974>
69. Stebbing J, Nelson M, Orkin C, et al. A randomized trial to investigate the recycling of stavudine and didanosine with and without hydroxyurea in salvage therapy (RESTART). *J Antimicrob Chemother* 2004, 53:501-5. <http://amedeo.com/lit.php?id=14762056>
70. Stellbrink HJ, Hufert FT, Tenner-Racz K, et al. Kinetics of productive and latent HIV infection in lymphatic tissue and peripheral blood during triple-drug combination therapy with or without additional interleukin-2. *Antivir Ther* 1998, 3: 209-14. <http://amedeo.com/lit.php?id=10682140>
71. Stellbrink HJ, van Lunzen J, Westby M, et al. Effects of interleukin-2 plus highly active antiretroviral therapy on HIV-1 replication and proviral DNA (COSMIC trial). *AIDS* 2002, 16:1479-87. <http://amedeo.com/lit.php?id=12131185>
72. Swindells S, Cohen CJ, Berger DS, et al. Abacavir, efavirenz, didanosine, with or without hydroxyurea, in HIV-infected adults failing initial nucleoside/protease inhibitor-containing regimens. *BMC Infect Dis* 2005, 5:23. <http://amedeo.com/lit.php?id=15819974>
73. Tavel JA, Sereti I, Walker RE, A randomized, double-blinded, placebo-controlled trial of intermittent administration of interleukin-2 and prednisone in subjects infected with human immunodeficiency virus. *J Infect Dis* 2003;188:531-6. <http://amedeo.com/lit.php?id=12898439>
74. Valdez H, Mitsuyasu R, Landay A, et al. Interleukin-2 Increases CD4+ lymphocyte numbers but does not enhance responses to immunization: results of A5046s. *J Infect Dis* 2003; 187:320-5. <http://amedeo.com/lit.php?id=12552459>
75. Vento S, Cainelli F, Temesgen Z. Interleukin-2 therapy and CD4+ T cells in HIV-1 infection. *Lancet* 2006, 367:93-5.
76. Vogler MA, Tepler H, Gelman R, et al. Daily low-dose subcutaneous interleukin-2 added to single- or dual-nucleoside therapy in HIV infection does not protect against CD4+ T-cell decline or improve other indices of immune function: results of a randomized controlled clinical trial (ACTG 248). *J AIDS* 2004, 36:576-87. <http://amedeo.com/lit.php?id=15097300>
77. Wallis RS, Kalayjian R, Jacobson JM, et al. A Study of the immunology, virology, and safety of prednisone in hiv-1-infected subjects with CD4 cell counts of 200 to 700 mm<sup>3</sup>. *J AIDS* 2003; 32: 281-6. <http://amedeo.com/p2.php?id=12626887&s=hiv>
78. Weiss L, Aboulhab J, Babiker GA, et al. Preliminary results of ESPRIT (Evaluation of Subcutaneous Proleukin in a Randomised International Trial): baseline predictors of CD4 T-cell response to Interleukin-2. Abstract 13, 2nd IAS 2003, Paris.
79. Wood R, Montoya JG, Kundu SK, Schwartz DH, Merigan TC. Safety and efficacy of polyethylene glycol-modified interleukin-2 and zidovudine in HIV type 1 infection: a phase I/II study. *J Infect Dis* 1993, 167:519-25. <http://amedeo.com/lit.php?id=8095058>
80. Zala C, Salomon H, Ochoa C, et al. Higher rate of toxicity with no increased efficacy when hydroxyurea is added to a regimen of stavudine plus didanosine and nevirapine in primary HIV infection. *J Acquir Immune Defic Syndr* 2002, 29: 368-73. <http://amedeo.com/lit.php?id=11917241>

## 4. Goals and principles of therapy

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In the flood of monthly evaluations – including CD4+ T-cell count, viral load, routine laboratory, genotypic and phenotypic resistance testing, and drug plasma levels – the ultimate goal of antiretroviral therapy should always be borne in mind:

*To prolong the patient's life,  
while maintaining the best possible quality  
of health and life.*

This means, that it is equally important to not only prevent opportunistic infections and malignancies, but also to minimize the side effects of therapy. Ideally, antiretroviral treatment should have little or no influence on daily life. Even if a high CD4+ T-cell count and a low viral load are useful therapeutic goals, the patient's condition is at least as significant as the laboratory results! Patients, too, often lose focus on what really matters. The response to the doctor's query: "How are you?" is often accompanied by a glance toward the CD4 count result on the chart: "That's what I'd like you to tell me!" It may therefore be useful to reflect upon what one realistically aims to achieve. Treatment aimed only at improving laboratory values with little emphasis on the physical and mental well being of the patient cannot be successful.

### Success and failure of treatment

Both success and failure of treatment can be evaluated using different criteria – virological, immunological or clinical. Of these, the earliest indicator is **virological** success or failure (decrease or increase in viral load). This is followed, often a little later, by **immunological** treatment success or failure (rise or fall in CD4+ T-cell count). **Clinical** treatment failure, if it occurs, usually only becomes apparent much later – first the lab values deteriorate, then the patient! On the other hand, success of treatment may be seen much earlier; many patients suffering from constitutional symptoms rapidly improve on HAART. In the Swiss Cohort, the incidence of opportunistic infections after only three months on HAART was reduced from 15.1 to 7.7 per 100 patient years (Ledergerber 1999). For clinical treatment success, in particular for prevention of AIDS, immunological success is probably at least as important as virological success (Grabar 2000, Piketty 2001).

### Virological treatment success and failure

Virological treatment success is usually understood as being the reduction of viral load to below the level of detection of 50 copies/ml. This is based on the understanding that, the more rapid and greater the decrease in viral load, the longer the therapeutic effect (Kempf 1998, Powderly 1999, Raboud 1998).

In the INCAS Trial, the relative risk of treatment failure (defined here as an increase to above 5,000 copies/ml) in patients who had reached a viral load be-

low 20 copies/ml was 20 times lower than in those who had never reached a level under 400 copies/ml (Raboud 1998).

On HAART, viral load declines in two phases (see also the chapter “Monitoring”). An initial, very rapid decrease in the first few weeks is followed by a slower phase, in which plasma viremia declines only slowly. A decay to below the level of detection should be reached after 3–4 months; in cases of very high baseline viral load it may take even longer. However, a viral load above the level of detection after six months of treatment is almost always seen as failure. The same is true if a rebound in viral load is confirmed. If this occurs, and is quickly confirmed, consideration needs to be given to factors that will improve therapy (resorption, resistance, compliance?).

Virological treatment failure can be recognized quite early – therefore, initial monitoring even after only four weeks is useful not only to the patient for psychological reasons (“less viruses, more helper cells”). But it is also an important indication for the further success of treatment. If the viral load is not below 5,000 copies after four weeks of HAART, later treatment failure is likely (Maggiolo 2000).

The cut-off point of 50 copies/ml is arbitrary. It is based on the currently available assays for measurement of viral load. Whether 60 copies/ml are indeed worse than 30 copies/ml and indicate a lesser success of treatment has still not been proven. At these low levels, methodological inaccuracies must also be taken into account. A single viral load rebound (“blip”) to low levels (up to 1,000 copies/ml) is often irrelevant (see below).

A viral load “below the level of detection” of 50 copies/ml means just that – no more, no less. Numerous studies indicate that replication and therefore development of resistance can continue even with an undetectable virus load. 50 viral copies/ml indicate that 5 liters of blood contain 250,000 viruses; in addition, even more actively replicating viruses are present in the lymphatic organs. Thus, theoretically, a measurable viremia, even at very low levels, may possibly translate to a higher risk of resistance in the long-term. Perhaps there is indeed a relevant difference between 100 and 10 copies/ml with regard to the risk of developing resistance. But we just don’t know yet.

The good news is that morbidity and mortality may be lowered significantly even if the viral load is not decreased below the level of detection (Mezzaroma 1999, Deeks 2000, Grabar 2000). This should be borne in mind when treating patients who have a limited number of treatment options. In such cases, it may be more sensible to temporarily abandon viral load as a measure of success (see “Salvage Therapy” chapter). In patients with multiresistant viruses, virological success in the strict sense may not be possible; here, stabilizing the CD4+ T-cell count should be the top priority. Patients often remain immunologically stable for relatively long periods of time, even with insufficient viral suppression.

A large cohort study has shown that CD4+ T-cells do not drop as long as the viral load remains below 10,000 copies/ml or at least 1.5 logs below the individual set point (Lederberger 2004). The most important risk factors for virological treatment failure are extensive pre-treatment with antiretroviral drugs (pre-existing resistance mutations) and non-adherence (review: Deeks 2000). Whether viral load and CD4+ T-cell count at the time of treatment initiation really play a role, has not yet been conclusively proven; in several cohorts no influence was detected (Cozzi-Leprì

2001, Phillips 2001, Le Moing 2002; see also discussion in the chapter “When to Start HAART”).

### **How long does virological treatment success last?**

Little is known about how long treatments remain effective. The rumor that treatment success is limited to only a few years is still widespread. It originates from the early years of HAART. However, many patients at the time were still inadequately treated or had been pretreated with mono- or dual therapy, and had thus developed extensive resistance. In such patients, the effect of treatment was often limited, as even a single point mutation was often enough to topple a whole regimen. Today, especially in therapy-naïve patients without pre-existing mutations, the risk of treatment failure is much less.

After nearly ten years during which HAART has been employed, a surprisingly high number of patients still have viral loads below the level of detection, even after this considerable period of time. This is particularly true for patients who were adequately treated from the start, as judged by today’s standards (starting with triple therapy and/or rapid switching of several drugs). One of the few trials with a longer follow-up period studied 336 antiretroviral-naïve patients who had reached a viral load below 50 copies/ml within 24 weeks (Phillips 2001). After 3.3 years, the risk of viral rebound seemed at first glance to be relatively high at 25.3 %. More detailed analysis showed that a large proportion of the patients experiencing viral rebound had actually interrupted HAART. True virological failure was only seen in 14 patients, which corresponds to a risk of 5.2 % after 3.3 years. Most importantly, the risk of virological failure decreased significantly with time.

In the Phase II M97-720 Study, in which 100 patients were originally treated with d4T+3TC+lopinavir/r, 62 % still had less than 50 copies/ml after six years in the ITT analysis, compared to 98 % in the On-Treatment-Analysis (Gulick 2004). Real virological failure was very rare. In the Merck 035 subanalysis, patients on AZT+3TC+indinavir were also followed for six years. In the last ITT analysis, 58 % were still below the level of detection, despite the fact that these patients had been pre-treated with nucleoside analogs (Gulick 2003).

These studies clearly show that, providing treatment is not interrupted, viral load may remain below the level of detection for many years, perhaps even decades.

### **“Blips” – Do they mean virological failure?**

Blips are understood to be transient and, almost always, small increases in viral load, so long as the viral load before and after the blip was below the borderline value of 50 copies/ml. At least three measurements of viral load are therefore required to be able to identify a blip. Blips are a frequent phenomenon of HIV patients on HAART and are observed in 20-40 % (Sungkanuparph 2005). Blips often worry both patients and clinicians: does this signal treatment failure?

Although a few studies indicate that this is not the case in the medium-term (Havlir 2001, Moore 2002, Sklar 2002, Mira 2003, Sungkanuparph 2005), the causes of blips have, to a large extent, not been investigated. There has been no association found with compliance, which one might have initially presumed (Di Mascio 2003, Miller 2004). It is possible that blips are the result of immunological mechanisms. The earlier patients are treated in the course of infection, i.e., the higher the CD4+

T-cell count at the start of therapy, the more seldom blips seem to occur (Di Mascio 2003+2004, Sungkanuparph 2005). There does not appear to be any association with particular antiretroviral combinations – in a large cohort study (Sungkanuparph 2005), the frequency of blips on the NNRTI regimen was 34 versus 33 % on the PI regimen, and even the size of the blips were equivalent (median 140 and 144 copies/ml respectively). In both groups, the risk of virological failure at 2 years was approximately 8 %. One important observation of this trial was that the blips did not increase the risk of treatment failure, even under NNRTIs, which was originally feared because of the rapid development of resistance on NNRTIs. Another team has since confirmed these results (Martinez 2005).

But, what do blips actually mean? At the beginning of 2005, the study team led by Bob Siciliano set out to determine this. In a labor-intensive study (Nettles 2005), 10 stalwart patients who had had a viral load of less than 50 copies/ml for at least six months, had blood samples taken every 2-3 days (!) over a period of 3-4 months. The obvious result: the more you look, the more you will find. During the observation time, at least one transient increase in the viral load was measurable above 50 copies/ml, in nine of the ten patients. Each blip was moderate, with a median value of 79 copies/ml, ranging from 51 to 201 copies/ml. The blips could not be associated with either specific clinical data, low plasma levels, or resistances. This observation led the authors to believe, that blips (with low, measurable values) mainly represent biological or statistical exceptions, and are not involved with treatment failure. In an estimated steady state level of viral load at around 20 copies/ml, the values are distributed randomly. However, 96 % of the randomly distributed measurements were less than 200 copies/ml.

It should be noted that other factors may also be responsible for intermittent viremia. In one large, retrospective analysis, 26 % were caused by intercurrent infections (Easterbrook 2002). For example, syphilis can cause a significant increase in viral load and reduction of CD4+ T-cells (Buchacz 2004). Viral load can also increase temporarily after immunizations (Kolber 2002).

Summary: Based on available data, however, blips should not necessitate an immediate change of HAART. However, caution should be executed for higher blips (> 200-500 copies/ml). It should be stressed that blips need to be distinguished from low, repetitive, measurable plasma viremias, in which the risk of resistance has been shown to be much higher (Gunthard 1998, Nettlers 2004). Although there does not seem to be a relationship to compliance or drug levels, blips should nevertheless raise the opportunity to talk to the patient about the subject of adherence. Compliance cannot be discussed often enough. Does the patient take his or her drugs regularly, or are doses occasionally missed? Are the dosing directions (on an empty stomach or with a meal) followed correctly?

All these points should be considered before changing therapy prematurely. Each new therapy can cause new problems. Therefore, every suspected increase in the viral load should be controlled within a short interval, before the treatment is changed.

### **Immunological treatment failure and success**

Immunological treatment success is generally defined as an increase in the CD4+ T-cell count. A more precise definition for immunological treatment success does not

currently exist. Depending on the study, increases *by* 50, 100 or 200 CD4+ T-cells/ $\mu$ l or increases *to* above 200 or 500 CD4+ T-cells/ $\mu$ l are defined as success. Failure is usually described as the absence of an increase or as a decrease in the CD4+ T-cell count in patients receiving HAART.

It is difficult to individually predict the immunological success of therapy for patients on HAART, as it varies significantly from one person to another. As with the decrease in viral load, the increase in CD4+ T-cell count also occurs in two phases. After a first, usually rapid increase over the first three to four months, further increases are considerably less pronounced. In a prospective study involving some 1,000 patients, the CD4+ T-cell count increased during the first three months by a median of 21.2 CD4+ T-cells/ $\mu$ l per month; in the following months the increase was only 5.5 CD4+ T-cells/ $\mu$ l (Le Moing 2002). It is still under debate whether the immune system is restored continuously after a long period of viral load suppression or whether a plateau is possibly reached after three to four years, beyond which there is no further improvement (Smith 2004, Viard 2004).

The lower the CD4+ T-cell count at baseline, the less likely it is to normalize completely (Valdez 2002, Kaufmann 2003+2005). The immune system often does not recover completely. In the Swiss Cohort, only 39 % of 2,235 patients who had begun HAART in 1996-97 reached a CD4+ T-cell count above 500/ $\mu$ l (Kaufmann 2003) – see also the following chapter on “When To Start HAART”. However, it appears that the introduction of therapy within the first 3-6 months provides certain clues as to how well the immune system will be restored (Kaufmann 2005).

Immunological treatment success is not necessarily linked to maximal viral suppression; even partial suppression can result in improved CD4+ T-cell count (Kaufmann 1998, Mezzaroma 1999, Ledergerber 2004). The initial level of viral load is also not significant; what seems to be decisive is that the viral load remains lower than before treatment (Deeks 2002, Ledergerber 2004). In view of the numerous factors that occur independent of HAART, which are able to influence the success of therapy as well as the individual regeneration capacity (see below), it no longer makes sense to depend on the CD4+ T-cell count as the deciding criterion for the success of HAART. Virological success is more appropriate for judging the efficacy of specific regimens.

However, there is some evidence, that certain antiretroviral regimens have unfavorable effects on immune reconstitution. Significant drops in CD4+ T-cell count were observed in patients with a suppressed viremia who switched to a simplified regimen of ddI and tenofovir plus nevirapine (Negredo 2004). The reason for this is still not understood, but seems to be related to negative interactions between ddI and tenofovir. Where possible, this combination should no longer be used, especially not in primary therapy. In another study, the CD4 increase on abacavir+3TC was significantly better than on AZT+3TC (both combined with efavirenz), despite comparable virological success. This may be related to the myelotoxicity of AZT (DeJesus 2004).

Once CD4+ T-cells have normalized and plasma viremia remains undetectable, it is unlikely that they will reduce significantly (Phillips 2002). In such cases, immunological treatment success does not necessitate frequent continued monitoring. Many experts have subsequently switched to measuring the CD4+ T-cell count more seldomly.

### Discordant response

Failure to achieve every one of the therapeutic goals – clinical, immunological and virological – is referred to as a discordant response.

Some patients may have virological treatment success without immunological improvement, continuing to have a very low CD4+ T-cell count despite undetectable viral load (Piketty 1998, Renaud 1999, Gabrar 2000, Piketty 2001). In addition to age, the risk factors for a lack of immunological treatment response, despite good viral suppression, include low CD4+ T-cell counts at baseline, as well as having a low viral load at the start of treatment (Florence 2003, Kaufmann 2005). In older patients, immunological response is often only moderate in comparison to virological response. Various studies have demonstrated that the probability of not achieving a rise in CD4+ T-cell count increases with patient age and with progressive decrease in thymus size as detected by CT (Goetz 2001, Marimoutou 2001, Piketty 2001, Teixeira 2001, Viard 2001). Patients who are intravenous drug users also have relatively poor increases in CD4+ T-cells compared to other patients (Dragstedt 2004).

Other possible causes for a lack of immunological response despite good viral suppression may be immuno- or myelosuppressive concomitant therapies.

Conversely, HAART may be extremely effective immunologically and induce significant increases in the CD4+ T-cell count, while viral load remains detectable. This can sometimes be observed in children and adolescents (see “Pediatrics” chapter). The frequencies of such discordant responses in adults are outlined in the table below.

Table 4.1: Prospective cohort studies, treatment response\*

Response to HAART	Piketty 2001 n = 42	Grabar 2000 n = 2236
Virological and immunological response	60 %	48 %
Discordant: only immunological response	19 %	19 %
Discordant: only virological response	9 %	17 %
No treatment response	12 %	16 %

\* Immunological response: rise in CD4+ T-cells > 100/μl after 30 months (Piketty 2001) or > 50/μl after 6 months (Grabar 2000). Virological response: continually at least 1 log below baseline or < 500 copies/ml (Piketty 2001) or < 1,000 copies/ml (Grabar 2000).

### Practical considerations in dealing with viral load and CD4 T-cell count

- Viral load is the most important parameter in treatment monitoring.
- If possible, use only one type of assay (in the same lab) – bear in mind that there is considerable methodological variability (up to half a log)!
- Virological success should be monitored one month after initiation or modification of HAART.
- Viral load should be below 50 copies/ml after 3-4 months (with high initial viral load, after 6 months at the latest) – if it is not, look for a cause!
- The greater the decrease in viral load, the more durable the response to treatment.
- Transient, low-level increases in viral load (blips) are usually insignificant – but VL should be monitored at short intervals (e.g. 2-4 weeks after such blips).
- The older the patient, the likelier a discordant response (low viral load with no significant increase in CD4 count).
- In contrast to viral load, increase in CD4+ T-cells, i.e. immunological success, is difficult to influence. CD4+ T-cells are probably more predictive of the individual risk for AIDS.
- Once CD4 count is good, it requires less frequent monitoring. Remember that with higher CD4 counts, values may vary considerably from one measurement to the next (which may mislead the patient to either a false sense of euphoria or unnecessary concern).

### Clinical treatment success and failure

Clinical treatment success is dependent on virological and immunological therapeutic success (see Table 4.2). In individual patients, clinical response is not always easy to assess. After all, there is no way to show what might have occurred if treatment had not been started. As an asymptomatic patient cannot feel any better, it may be difficult to find good arguments to continue treatment in the presence of side effects, which, at least temporarily, may affect the quality of life.

Clinical success is almost always evaluated via clinical endpoints (AIDS-defining illnesses, death), although the improvement on HAART in a patient with considerable constitutional symptoms should also be seen as clinical success. With regard to risk of disease progression, the immunological response is at least as important as the virological response.

However, the extent of virological success is of great significance: in the Swiss Cohort, out of those with a constantly undetectable viral load, the proportion of patients developing AIDS or dying was 6.6 % after 30 months. In contrast, this proportion was 9.0 % in patients with viral rebound and even 20.1 % if the viral load was never suppressed to undetectable levels (Ledergerber 1999). The importance of complete and sustained virological treatment success for clinical benefit has also been reported from other cohorts (Salzberger 1999, Thiebaud 2000).



Table 4.2: Risk of progression, as defined by immunological and virological treatment response. See previous table caption for definitions. 95 % confidence interval in parentheses.

	<b>Grabar 2000</b>	<b>Piketty 2001</b>
CD4+ T-cells at baseline (median)	150	73
	Relative risk	Relative risk
Virological and immunological response	1	1
Immunological response only	1.6 (1.0-2.5)	6.5 (1.2-35.8)
Virological response only	2.0 (1.3-3.1)	9.7 (1.6-58.4)
No treatment response	3.4 (2.3-5.0)	51.0 (11.3-229.8)

Clinical failure is usually defined as the development of an AIDS-associated condition or even death. However, illness is not always indicative of clinical treatment failure. This is particularly true for the immune reconstitution inflammatory syndrome (IRIS), where a pre-existing, subclinical infection becomes apparent during the first weeks following initiation of antiretroviral therapy (see “AIDS” chapter). On the other hand, if a patient develops serious side effects or even dies, this should clearly be regarded as treatment failure. Luckily, this is rare. It should be noted that there might also be other causes. Many severe, life-threatening events that affect HIV infected patients on HAART today are associated neither with HAART nor AIDS (Reisler 2003).

### **What can be achieved today?**

Every HIV clinician sees the remarkable strides made possible by HAART reflected in his or her own patients (see example below). In many areas, the incidence of AIDS has been reduced to less than a tenth (Mocroft 2000). Some illnesses that occur only with severe immunodeficiencies are rarely seen today. CMV retinitis or MAC disease have become unusual. AIDS cases in Western countries occur mainly in patients who are not being treated with antiretroviral therapy – usually because they are unaware of their infection or do not want to acknowledge it. These so-called “late presenters” now make up a large proportion of AIDS cases. In patients who are continuously followed in specialized centers, AIDS has become a rare occurrence.

The mortality rate has continued to decline over time (Mocroft 2002). In the EuroSIDA Cohort, the risk of suffering or dying from AIDS in the years 1998-2002 was half that of 1996-1997 (Mocroft 2003). The Swiss cohort also showed that the effect of HAART increases over time – after more than two years on HAART, the risk of disease progression was only 4 % of the risk without HAART (Sterne 2005).

Data from prospective, controlled studies on this dramatic change is still limited, as there have been few randomized trials with clinical endpoints (Hammer 1997, Cameron 1998, Stellbrink 2000). The results seen in these studies, due to their design, led to licensing of the PIs. In a multi-center trial, 1,090 clinically advanced patients received ritonavir liquid formulation or placebo in addition to their ongoing treatment. The probability of AIDS and death with a follow-up of 29 weeks was 21.9 % in the ritonavir arm and nearly double (37.5 %) in the placebo arm (Cameron 1998). In the SV14604 Study, the largest study of its kind to date, involving 3,485 patients, the frequency of AIDS and death was reduced by about 50 % in the

group receiving AZT+ddC+saquinavir hard gel, compared to the groups on dual therapy (Stellbrink 2000).

Table 4.3: Patient case (female, 41 years) illustrating the success of HAART\*

		CD4 <sup>+</sup> T-cells	Viral load
Feb 95	AZT+ddC	23 (4 %)	NA
Nov 96	AIDS: Toxoplasmosis, MAC, Candida esophagitis	12 (1 %)	815,000
Feb 97	d4T+3TC+SQV	35 (8 %)	500
June 97	Stopped HAART due to polyneuropathy		
July 97	AZT+3TC+IDV	17 (4 %)	141,000
Mar 98		147 (22 %)	< 50
Mar 99	AZT+3TC+IDV/r+NVP	558 (24 %)	100
Mar 00		942 (31 %)	< 50
Apr 05	AZT+3TC+LPV/r+NVP	744 (30 %)	130
Jan 06		801 (29 %)	< 50

\* Excellent immune reconstitution despite initial severe immunodeficiency and several AIDS-defining illnesses. All prophylaxis (MAC, Toxoplasmosis, PCP) has now been discontinued.

Studies of mono- or dual therapy are no longer ethically justifiable and the number of clinical endpoints that occur is fortunately now extremely low. As a result, the duration of any contemporary study to prove clinical benefit of one combination over another would have to be extended over long periods. Unrealistically large study populations would also now be required given the extremely low probability of progression – only rarely will such investigations be undertaken in the future (Raffi 2001).

Table 4.4: Decline in morbidity and mortality in large cohorts

	Where? (n)	Patients (Period)	Mortality (/100 PY)	Morbidity (/100 PY)
Palella 1998	USA (1255)	< 100 CD4 <sup>+</sup> T-cells/ $\mu$ l (1/94-6/97)	29.4 → 8.8	21.9 → 3.7*
Ledergerber 1999	Switzerland (2410)	6 months <i>before</i> versus 3 months <i>after</i> HAART (9/95-12/97)	NA	15.1 → 7.7
Mocroft 2000	Europe (7331)	All (94-98)	NA	30.7 → 2.5
Mocroft 2002	Europe (8556)	All (94-01)	15.6 → 2.7	NA
D'Arminio 2005	Worldwide (12,574)	The first 3 months <i>after</i> versus 3 years <i>after</i> HAART	NA	12.9 → 1.3

\* MAC, PCP, CMV. Mortality/Morbidity each per 100 py = patient years

This is why data from large cohorts such as Euro-SIDA, the Swiss Cohort and American HOPS Cohort is usually used (see Table 4.4). According to a more recent investigation, the effect on the individual AIDS diseases appears to be different: the

most obvious is the decline in the incidence of viral OIs, although this is not so pronounced for fungal infections (D'Arminio 2005).

With regard to opportunistic infections and malignancies, the effect of HAART is equally as apparent on their clinical course as it is on their incidence. Illnesses such as cryptosporidiosis or PML can be cured, while Kaposi's sarcoma can resolve completely without specific therapy. Prophylaxis of pneumocystis pneumonia, toxoplasmic encephalitis, CMV, or MAC infection can usually be safely withdrawn. These effects are discussed in more detail in the corresponding chapters.

## References on therapy success and failure

1. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS* 2004, 18:2075-2079. <http://amedeo.com/p2.php?id=15577629&s=hiv>
2. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. The Advanced HIV Disease Ritonavir Study Group. *Lancet* 1998, 351:543-9. <http://amedeo.com/lit.php?id=9492772>
3. Cozzi Lepri A, Phillips AN, d'Arminio Monforte A, et al. When to start HAART in chronically HIV-infected patients: evidence from the ICONA study. *AIDS* 2001, 15:983-90. <http://amedeo.com/lit.php?id=11399980>
4. d'Arminio Monforte A, Sabin CA, Phillips A, et al. The changing incidence of AIDS events in patients receiving highly active antiretroviral therapy. *Arch Intern Med* 2005, 165:416-23. <http://amedeo.com/lit.php?id=15738371>
5. Deeks SG, Barbour JD, Grant RM, Martin JN. Duration and predictors of CD4 T-cell gains in patients who continue combination therapy despite detectable plasma viremia. *AIDS* 2002, 16: 201-7. <http://amedeo.com/lit.php?id=11807304>
6. Deeks SG. Determinants of virological response to antiretroviral therapy: implications for long-term strategies. *Clin Infect Dis* 2000, 30 Suppl 2: S177-84. <http://amedeo.com/lit.php?id=10860903>
7. DeJesus E, McCarty D, Farthing CF, et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naïve adults with HIV infection: a randomized equivalence trial. *Clin Infect Dis* 2004, 39:411-8. <http://amedeo.com/lit.php?id=15307010>
8. Di Mascio M, Markowitz M, Louie M, et al. Dynamics of intermittent viremia during highly active antiretroviral therapy in patients who initiate therapy during chronic versus acute and early HIV type 1 infection. *J Virol* 2004, 78:10566-73. <http://amedeo.com/lit.php?id=15367623>
9. Di Mascio M, Markowitz M, Louie M, et al. Viral blip dynamics during highly active antiretroviral therapy. *J Virol* 2003; 77:12165-72. <http://amedeo.com/lit.php?id=14581553>
10. Dragsted UB, Mocroft A, Vella S, et al. predictors of immunological failure after initial response to highly active antiretroviral therapy in HIV-1-infected adults: A EuroSIDA study. *J Infect Dis* 2004, 190:148-55. <http://amedeo.com/p2.php?id=15195254&s=hiv>
11. Easterbrook PJ, Ives N, Waters A, et al. The natural history and clinical significance of intermittent viraemia in patients with initial viral suppression to < 400 copies/ml. *AIDS* 2002; 16:1521-7. <http://amedeo.com/lit.php?id=12131190>
12. Florence E, Lundgren J, Dreezen C, et al. Factors associated with a reduced CD4 lymphocyte count response to HAART despite full viral suppression in the EuroSIDA study. *HIV Med* 2003;4:255-62. <http://amedeo.com/lit.php?id=12859325>
13. Goetz MB, Boscardin WJ, Wiley D, Alkasspooles S. Decreased recovery of CD4 lymphocytes in older HIV-infected patients beginning HAART. *AIDS* 2001, 15:1576-9. <http://amedeo.com/lit.php?id=11504992>
14. Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. *AIDS* 2004, 18:2029-2038. <http://amedeo.com/p2.php?id=15577624&s=hiv>
15. Grabar S, Le Moing V, Goujard C, et al. Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of HAART. *Ann Intern Med* 2000, 133: 401-10. <http://amedeo.com/lit.php?id=10975957>
16. Gulick RM, da Silva B, McMillan F, et al. Lopinavir/ritonavir (LPV/r)-based therapy in antiretroviral (ARV)-naïve, HIV-infected patients: 6-year follow-up of study 720. Abstract P28, 7th Int Congress Drug Ther HIV Inf 2004, Glasgow.

17. Gulick RM, Meibohm A, Havlir D, et al. Six-year follow-up of HIV-1-infected adults in a clinical trial of antiretroviral therapy with indinavir, zidovudine, and lamivudine. *AIDS* 2003; 17:2345-2349. <http://amedeo.com/lit.php?id=14571186>
18. Gunthard HF, Wong JK, Ignacio CC, et al. Human immunodeficiency virus replication and genotypic resistance in blood and lymph nodes after a year of potent antiretroviral therapy. *J Virol* 1998, 72:2422-8. <http://amedeo.com/lit.php?id=9499103>
19. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. ACTG 320 Study Team. *N Engl J Med* 1997, 337:725-33. <http://amedeo.com/lit.php?id=9287227>
20. Havlir DV, Bassett R, Levitan D, et al. Prevalence and predictive value of intermittent viremia with combination HIV therapy. *JAMA* 2001, 286:171-9. <http://amedeo.com/lit.php?id=11448280>
21. Kaufmann D, Pantaleo G, Sudre P, Telenti A. CD4-cell count in HIV-1-infected individuals remaining viraemic with HAART. Swiss HIV Cohort Study. *Lancet* 1998, 351:723-4.
22. Kaufmann GR, Perrin L, Pantaleo G, et al. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: the Swiss HIV Cohort Study. *Arch Intern Med* 2003; 163:2187-95. <http://amedeo.com/lit.php?id=14557216>
23. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/microL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *Clin Infect Dis* 2005;41:361-72. <http://amedeo.com/lit.php?id=16007534>
24. Kempf DJ, Rode RA, Xu Y, et al. The duration of viral suppression during protease inhibitor therapy for HIV-1 infection is predicted by plasma HIV-1 RNA at the nadir. *AIDS* 1998, 12: F9-14. <http://amedeo.com/lit.php?id=9543434>
25. Kolber MA, Gabr AH, De La Rosa A, et al. Genotypic analysis of plasma HIV-1 RNA after influenza vaccination of patients with previously undetectable viral loads. *AIDS* 2002, 16: 537-42. <http://amedeo.com/lit.php?id=11872996>
26. Le Moing V, Chene G, Carrieri MP, et al. Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. *AIDS* 2002, 16:21-9. <http://amedeo.com/lit.php?id=11741159>
27. Le Moing V, Thiebaut R, Chene G, et al. Predictors of long-term increase in CD4(+) cell counts in HIV-infected patients receiving a protease inhibitor-containing antiretroviral regimen. *J Infect Dis* 2002, 185: 471-80. <http://amedeo.com/lit.php?id=11865399>
28. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* 1999, 282: 2220-6. <http://amedeo.com/lit.php?id=1060597>
29. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on HAART in HIV-1 patients: a prospective cohort study. *Lancet* 1999, 353: 863- 868.
30. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet* 2004, 364:51-62. <http://amedeo.com/lit.php?id=15234856>
31. Lederman MM, McKinnis R, Kelleher D, et al. Cellular restoration in HIV infected persons treated with abacavir and a protease inhibitor: age inversely predicts naive CD4 cell count increase. *AIDS* 2000, 14: 2635-42. <http://amedeo.com/lit.php?id=11125881>
32. Maggiolo F, Migliorino M, Piralì A. Duration of viral suppression in patients on stable therapy for HIV-1 infection is predicted by plasma HIV RNA level after 1 month of treatment. *J AIDS* 2000, 25:36-43. <http://amedeo.com/lit.php?id=11064502>
33. Marimoutou C, Chene G, Mercie P, et al. Prognostic factors of combined viral load and CD4+ cell count responses under triple antiretroviral therapy, Aquitaine cohort, 1996-1998. *JAIDS* 2001, 27:161-7. <http://amedeo.com/lit.php?id=11404538>
34. Martinez V, Marcelin AG, Morini JP, et al. HIV-1 intermittent viraemia in patients treated by non-nucleoside reverse transcriptase inhibitor-based regimen. *AIDS* 2005;19:1065-1069. <http://amedeo.com/lit.php?id=15958838>
35. Mezzaroma I, Carlesimo M, Pinter E, et al. Clinical and immunologic response without decrease in virus load in patients with AIDS after 24 months of HAART. *Clin Infect Dis* 1999, 29:1423-30. <http://amedeo.com/lit.php?id=10585790>
36. Miller LG, Golin CE, Liu H, et al. No evidence of an association between transient HIV viremia ("Blips") and lower adherence to the antiretroviral medication regimen. *J Infect Dis* 2004, 189:1487-96. <http://amedeo.com/lit.php?id=15073687>
37. Mira JA, Macias J, Nogales C, et al. Transient rebounds of low-level viraemia among HIV-infected patients under HAART are not associated with virological or immunological failure. *Antivir Ther* 2002, 7:251-6. <http://amedeo.com/lit.php?id=12553479>

38. Mocroft A, Brettle R, Kirk O, et al. Changes in the cause of death among HIV positive subjects across Europe: results from the EuroSIDA study. *AIDS* 2002, 16:1663-71. <http://amedeo.com/lit.php?id=12172088>
39. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-98: the EuroSIDA study. *Lancet* 2000, 356:291-6. <http://amedeo.com/lit.php?id=11071184>
40. Mocroft A, Ledergerber B, Katlama C, et al. Decline in the AIDS and death rates in the EuroSIDA study: an observational study. *Lancet* 2003;362:22-9. <http://amedeo.com/lit.php?id=12853195>
41. Moore AL, Youle M, Lipman M, et al. Raised viral load in patients with viral suppression on HAART: transient increase or treatment failure? *AIDS* 2002, 16:615-8. <http://amedeo.com/lit.php?id=11873005>
42. Negredo E, Molto J, Munoz-Moreno JA, et al. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. *Antivir Ther* 2004, 9:335-42. <http://amedeo.com/lit.php?id=15259896>
43. Nettles RE, Kieffer TL, Kwon P, et al. Intermittent HIV-1 viremia (Blips) and drug resistance in patients receiving HAART. *JAMA* 2005, 293:817-29. <http://amedeo.com/lit.php?id=1571377>
44. Nettles RE, Kieffer TL, Simmons RP, et al. Genotypic resistance in HIV-1-infected patients with persistently detectable low-level viremia while receiving highly active antiretroviral therapy. *Clin Infect Dis* 2004, 39:1030-7. <http://amedeo.com/lit.php?id=15472857>
45. Palella FJ JR, Delaney KM, Moorman AC, et al. Declining morbidity and mortality among patients with advanced HIV infection. *N Engl J Med* 1998, 338:853-60. <http://amedeo.com/lit.php?id=9516219>
46. Phillips AN, Miller V, Sabin C, et al. Durability of HIV-1 viral suppression over 3.3 years with multi-drug antiretroviral therapy in previously drug-naive individuals. *AIDS* 2001, 15: 2379-84. <http://amedeo.com/lit.php?id=11740188>
47. Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to ART according to the baseline CD4 cell count and viral load. *JAMA* 2001, 286:2560-7. <http://amedeo.com/lit.php?id=11722270>
48. Phillips AN, Youle M, Lampe F, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/ml on antiretroviral therapy. *AIDS* 2002; 16: 1073-5.
49. Piketty C, Castiel P, Belec L, et al. Discrepant responses to triple combination antiretroviral therapy in advanced HIV disease. *AIDS* 1998, 12:745-50. <http://amedeo.com/lit.php?id=9619806>
50. Piketty C, Weiss L, Thomas F, et al. Long-term clinical outcome of HIV-infected patients with discordant immunologic and virologic responses to a protease inhibitor-containing regimen. *J Infect Dis* 2001, 183:1328-35. <http://amedeo.com/lit.php?id=11294663>
51. Powderly WG, Saag MS, Chapman S, et al. Predictors of optimal virological response to potent ART. *AIDS* 1999, 13:1873-80. <http://amedeo.com/lit.php?id=10513645>
52. Raboud JM, Montaner JS, Conway B, et al. Suppression of plasma viral load below 20 copies/ml is required to achieve a long-term response to therapy. *AIDS* 1998, 12: 1619-24. <http://amedeo.com/lit.php?id=9764780>
53. Raffi F, Chene G, Lassalle R, et al. Progression to AIDS or death as endpoints in HIV clinical trials. *HIV Clin Trials* 2001, 2:330-5. <http://amedeo.com/lit.php?id=11590536>
54. Reisler RB, Han C, Burman WJ, Tedaldi EM, Neaton JD. Grade 4 events are as important as AIDS events in the era of HAART. *J AIDS* 2003; 34: 379-86. <http://amedeo.com/lit.php?id=14615655>
55. Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. *AIDS* 1999, 13:669-76. <http://amedeo.com/lit.php?id=10397561>
56. Salzberger B, Rockstroh J, Wieland U, et al. Clinical efficacy of protease inhibitor based antiretroviral combination therapy—a prospective cohort study. *Eur J Med Res* 1999, 4:449-55. <http://amedeo.com/lit.php?id=10585299>
57. Sklar PA, Ward DJ, Baker RK, et al. Prevalence and clinical correlates of HIV viremia ('blips') in patients with previous suppression below the limits of quantification. *AIDS* 2002, 16:2035-41. <http://amedeo.com/lit.php?id=12370502>
58. Smith CJ, Sabin CA, Youle MS, et al. Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. *J Infect Dis* 2004, 190:1860-8. <http://amedeo.com/lit.php?id=15499544>
59. Smith K, Aga E, Bosch RJ, Valdez H, et al. Long-term changes in circulating CD4 T lymphocytes in virologically suppressed patients after 6 years of highly active antiretroviral therapy. *AIDS* 2004, 18:1953-6. <http://amedeo.com/lit.php?id=15353982>
60. Stellbrink HJ, Hawkin DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients. *Clin Drug Invest* 2000, 20:295-307.

61. Sterne JA, Hernan MA, Ledergerber B, et al. Long-term effectiveness of potent antiretroviral therapy in preventing AIDS and death: a prospective cohort study. *Lancet* 2005, 366:378-84. <http://amedeo.com/lit.php?id=16054937>
62. Sungkanuparph S, Overton ET, Seyfried W, et al. Intermittent episodes of detectable HIV viremia in patients receiving nonnucleoside reverse-transcriptase inhibitor-based or protease inhibitor-based highly active antiretroviral therapy regimens are equivalent in incidence and prognosis. *Clin Infect Dis*, 41:1326-32. <http://amedeo.com/lit.php?id=16206110>
63. Teixeira L, Valdez H, McCune JM, et al. Poor CD4 T cell restoration after suppression of HIV-1 replication may reflect lower thymic function. *AIDS* 2001, 15:1749-56. <http://amedeo.com/lit.php?id=11579235>
64. Thiebaut R, Morlat P, Jacqmin-Gadda H, et al. Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. Groupe d'Epidemiologie du SIDA en Aquitaine (GECSA). *AIDS* 2000, 14:971-8. <http://amedeo.com/lit.php?id=10853978>
65. Valdez H, Connick E, Smith KY, et al. Limited immune restoration after 3 years' suppression of HIV-1 replication in patients with moderately advanced disease. *AIDS* 2002, 16:1859-66. <http://amedeo.com/lit.php?id=12351945>
66. Viard JP, Burgard M, Hubert JB, et al. Impact of 5 years of maximally successful highly active antiretroviral therapy on CD4 cell count and HIV-1 DNA level. *AIDS* 2004, 18:45-9. <http://amedeo.com/lit.php?id=15090828>
67. Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in HIV-infected patients receiving highly active antiretroviral therapy: evidence from the EuroSIDA study. *J Infect Dis* 2001, 183: 1290-4. <http://amedeo.com/lit.php?id=11262215>

## Eradication – Is it feasible?

At this point in time, eradication of HIV in the sense of a cure is still unrealistic. Although as late as 1997, many still dreamt of eradication, leading researchers are now inclined to be pessimistic. The main problem lies in the pool of latently HIV-infected cells, which probably comprise a lifelong reservoir (review: Saksena 2003). Even after years of sufficient viral suppression to below 20-50 copies/ml, cellular viral transcription still takes place (Finzi 1999, Furtado 1999, Zhang 1999, Sharkey 2000). This is particularly true for blood cells, but also applies to lymph nodes and sperm (Lafeuillade 2001, Nunnari 2002).

In a more recent study, a half-life of 44.2 months was calculated for the latently infected reservoir in 62 patients, whose viral load had been successfully suppressed on HAART for seven years (Siciliano 2003). The calculated time to eradication of these reservoirs was 73.4 years. Even in a highly selected group of patients, without even a single viral blip measured during a minimum of three years of stable HAART, and with an overall trend for a slightly more rapid decrease in infected cells, the time to eradication was 51.2 years.

Latently infected reservoirs consist of very heterogeneous cell populations, the stability of which is probably even independent of residual viral replication. Therefore, even complete inhibition of viral replication would be insufficient to eradicate HIV (Strain 2004).

Different methods have been used in the last few years to attempt to flush out these latent reservoirs (IL-2, hydroxyurea, OKT), but all have failed (Kulkosky 2002, Pomerantz 2002). In summer 2005, a research team from Dallas (Lehrman 2005, Routy 2005) caused a stir with a novel approach using an old medication: they discovered that valproinic acid, an antiepileptic treatment used worldwide, is an inhibitor of histone deacetylase-1 (HDAC1). This enzyme mediates chromatin remod-

eling, the inhibition of viral gene expression and the production of virions. Exploratory work has shown that the blockade of HDAC1 results in HIV being washed out of dormant T cells. This small pilot study investigated four HIV-infected patients, in whom the virus had been suppressed using HAART for at least two years. The patients received valproinic acid for three months, in relatively low doses compared to standard anti-epileptic treatment. In order to intensify HAART and to catch the virus set free by valproinic acid, the entry inhibitor T-20 was added to the treatment regimen for three weeks prior to and during the administration of valproinic acid. The number of latently infected CD4+ T-cells was measured before and during treatment using a very complicated method. Result: although the level remained constant under conventional HAART, on valproinic acid it decreased significantly in three of the four patients, to the extent of 68 %, 72 % and more than 84 %. In addition, the half-life of the latent infected cells sank to 2-3 months, in comparison to other studies, which have reported 44.2 months under classical HAART (Siciliano 2004) and 10 months under intensive HAART (Ramratnam 2004).

So, what do these results tell us? First of all, the euphoria has to be restrained. As so often happens, more new questions are posed than answered. The most important questions are: Is the virological effect really due to valproinic acid? Is this effect, from just three patients, actually reproducible? Does it also apply to other cell compartments apart from blood? Why was the effect only measurable in three of the four patients? All these points can only be speculated on at the moment.

In other words: based on the currently available medication, eradication is still not possible. Latent infected cells differ from non-infected cells through a minute detail, which can hardly be detected using modern methods that are also unspecific. Washing out the reservoirs, or simply eliminating all infected memory cells is either unsuccessful, too toxic or much too dangerous. It remains to be seen whether valproinic acid or other immune therapies given in addition to HAART, will provide a perspective. Due to the complexity of the immune system, which is only gradually beginning to be understood, a solution seems to be a long way off.

## Other important aspects of HAART

Besides the goals described above – virological, immunological and clinical treatment success – several other aspects need to be considered. Although not the primary aim of HAART, they are nevertheless important. Cost reduction, prevention, and improving compliance remain a constant challenge for every HIV clinician.

### Reduction of costs

Antiretroviral treatment is expensive. It is important for clinicians to be informed about the price of drugs they prescribe, and to rationalize in any way that would be cost beneficial to patients and health services. For example, in Germany individual drugs cost between 270 Euro (Epivir™) and 2,000 Euro (Fuzeon™) per month. Even within drug classes, astonishing differences exist. In some countries, Crixivan™, at 325 Euro per month, is relatively cheap, while Aptivus™, at 1,100 Euro per month, is the most expensive PI. A combination regimen with Trizivir™ and Kaletra™ adds up to at least 1,700 Euro per month in some countries. As a

healthcare provider, it is therefore important to have an idea of costs. On the other hand, one should not be put under pressure by health insurances. Hopefully, their attempt to disqualify antiretroviral drugs as “me-too” preparations, through the modernization law to the legal insurance scheme, will not be successful.

The pricing policy of the pharmaceutical industry is, however, sometimes very questionable. For example, in some countries Combivir™ costs slightly less than the individual drugs AZT and 3TC, but Trizivir™ costs significantly more than AZT and 3TC or Combivir™ plus abacavir. The reason why directly concurrent preparations (nevirapine and efavirenz or 3TC and FTC) cost almost exactly the same, whilst other substances from the same drug class are over 300 % more expensive, cannot be explained through development costs alone.

Despite all criticism, the positive effect of HAART remains unquestioned and should not be forgotten despite the discussion of its cost. Reliable estimates assume an expenditure of between \$13,000 and \$23,000 per additional QUALY (quality-adjusted year of life; Freedberg 2001) – relatively cheap in comparison to many other therapies. HAART reduces the cost of expensive treatment of opportunistic infections, inpatient and outpatient care. In one German study, between 1997 and 2001, total annual outgoings per patient decreased from 35,865 Euro to 24,482 Euro (Stoll 2002). Many patients are able to work again, resulting in an overall economic gain for society (Sendi 1999).

Nevertheless, the fact remains, that HAART is expensive in Western countries. It is therefore reasonable to expect that patients use up remaining stores and packets of drugs, if the reason for changing medication is to reduce the pill burden or because of doubts about long-term toxicity. Patients should also be made aware of the cost of medication – not so that they feel guilty, or to blame the inaccessibility of the healthcare system on them, but to provide an awareness of the value of the therapy.

It is important that initially only one packet is prescribed, even if the standard dose of Retrovir™ 250 mg it is still just enough for 20 days – almost 20 years after its introduction! In this way, one avoids sitting on a mountain of drugs if intolerability occurs. Prescription of more than three months supply of medication should also be avoided. Since the reform of the health system in 2004 and the subsequent additional payment obligation, many patients refuse it anyway.

In any case, it is important to be informed about the costs of HAART. It is not only the patent on AZT that will be lifted, the patents on ddi (US patent until October 2006), 3TC, d4T and abacavir will also be removed within the next decade. It is interesting to see how the company policies will develop. However, it will take a little longer until the end of the patent on the first PI: saquinavir will be freed in 2010.

## Prevention

The lower the viral load, the less infectious the patient. A prospective study of 415 HIV-discordant couples in Uganda showed that of 90 new infections over a period of up to 30 months, none occurred from an infected partner with a viral load below 1,500 copies/ml. The risk of infection increased with every log of viral load by a factor of 2.45 (Quinn 2000). In a study from Thailand on 493 patients, this factor was 1.81 – no case of infection was recorded below 1,094 copies/ml (Tovanabutra 2002). In the San Francisco Cohort, infectiousness in the HAART era dropped by



60 %, based on the probability of transmission per couple (Porco 2004). HAART is thus an important component of prevention, which is often underestimated (Hosseinipur 2002).

Most patients are interested in knowing: “Do I still need to use a condom?” The answer is: “Yes!” Studies have shown that the decrease of viral load in plasma and seminal fluid is roughly parallel and that a decrease of several logs in plasma after several months may also be seen in semen (Liuzzi 1999). Although the same seems to be true for the vaginal and anorectal mucosa, individual risk remains difficult to estimate (Cu-Uvin 2000). Furthermore, viral load levels in blood and other body fluids do not always correlate with one another.

In addition, HIV-infected patients are not protected from superinfection with new viral strains. Dual infections with several subtypes are often associated with accelerated disease progression (Gottlieb 2004). Transmission of resistant strains is also possible (Yang 2005).

There has also been concern that the preventive effects of HAART lead to an increase in risk behavior. Calculations have shown that an increase in risk behavior of only 10 % would offset the effects of HAART (Blower 2001, Law 2001). However, one meta-analysis concluded that HAART does not increase risk behavior of patients, even if viral load is undetectable (Crepaz 2004). The gladly circulated scenario of the irresponsible HIV patient, who sets his desires loose again in the age of HAART, putting innocent people at risk, is just a rumor.

On the other hand, with the steadily decreasing interest in AIDS in the media and politics, a reduced awareness of the risks can also be observed. This is supported by the news that the sale of condoms in Germany in 2001 went down for the first time since 1998 (by 4.4 %). In the French PRIMO Cohort, so-called risk contacts of patients increased from 5 to 21 % between 1998 and 2001 (Desquilbet 2002). Small syphilis epidemics among HIV-infected individuals are now being reported in every major city in the US and Europe. Of equal concern is the increasing data on transmission of multiresistant viruses. A case, such as that of the New York patient, who became infected with a multidrug-resistant virus and underwent rapid progression within a few months (Markowitz 2005), as controversial as it was, at least showed how important protection still is. In Germany, the rate of new infections in homosexual men increased by 20 % in 2005 - an all time high.

### **Adherence as a goal of therapy**

Adherence is the Achilles heel of antiretroviral therapy. Non-adherence is a main, if not the most important factor in treatment failure (review: Turner 2002). Insufficient plasma drug levels and partial suppression of viral load are the conditions under which resistance can develop. There is no question that HAART has to be taken regularly. All or nothing: with regard to resistance, it is still better not to take any drugs at all. Taking more than 90 % or less than 69 % of drugs were both associated with a lower risk for resistance (Sethi 2003). Compliance is defined as consent and acceptance of a treatment regimen by the patient. In the mid-90s a newer, more politically correct term was adopted – “adherence”. This term describes both clinician and patient working together to achieve a treatment concept acceptable for both, and emphasizes, that not only the patient may be responsible for treatment failure.

Adherence includes all factors that influence staying on a regimen, in terms of “acceptability”. Whichever term is used, three facts remain:

1. If only 5 % of pills are not taken, treatment success is put at risk.
2. Clinicians usually overestimate the compliance of their patients.
3. The more complex the therapy, the worse the compliance.

“Risk patients” for noncompliance include individuals with substance or alcohol abuse or those experiencing side effects. Many studies have, however, also identified patients with depression, living alone, or of a younger age, as being particularly at risk (Murri 2001, Frank 2002, Glass 2006). Positive factors are physician experience, confidence of the patient in the positive effects of HAART, and social support. Race, sex or stage of disease does not seem to be relevant. The individual’s view of disease and health, acceptance of modern medicine and fear of side effects are further considerations. However, all of these factors vary greatly, and in the end, compliance is difficult to predict in individual cases (Lerner 1998).

The importance of taking drugs regularly has been demonstrated in numerous studies in recent years. In one study of 99 patients, in which compliance was evaluated by way of an electronic monitoring system, the rate of treatment failure was only 22 % in patients with a level of compliance of at least 95 % (95 % of doses taken). Failure rates in patients with 80-94 % or < 80 % compliance were 61 % and 80 %, respectively (Paterson 2000). However, it must be taken into consideration that this much cited study is now relatively old. Newer drugs with longer half-lives, higher resistance barriers and better overall pharmacokinetics may be more forgiving of noncompliance.

In the aforementioned study, with regard to compliance, 41 % of patients were misjudged by their treating clinicians. Nurses seemed to have a better understanding of their patients, judging incorrectly in only 30 % of cases (Paterson 2000). The importance of compliance is also demonstrated by the successes reported in patients with directly observed therapy (DOT). In Florida’s correctional facilities 100 % of participants in a DOT study had a viral load below 400 copies/ml at 48 weeks, compared with 81 % in an unmonitored control group in the general population (Fischl 2001).

Poor adherence not only leads to virological failure. It also has immunological consequences. In an analysis of two prospective studies, patients with a compliance of 100 %, 80-99 % and 0-79 % experienced reductions in viral load by 2.77, 2.33 and 0.67 logs after one year. At the same time, the CD4 cell count rose by 179, 159 and 53 cells/ $\mu$ l, respectively (Mannheimer 2002). Furthermore, noncompliance also has clinical effects beyond the surrogate markers. In a Spanish study, patients who did not take more than 10 % of their drugs had a four-fold increase in mortality risk (Garcia 2002). This data has been confirmed in other studies (Maher 1999, Hogg 2000, Wood 2004). Hospital stays are also less frequent in patients with high compliance (Paterson 2000). In addition, it should be considered that noncompliant patients increase the risk of transmission of resistant viruses.

The basic mechanisms for development of resistance should be explained to patients. One must emphasize that, in contrast with other chronic illnesses, resistance mutations do not disappear once they have developed. Diabetes and hypertension make effective examples: whereas these diseases may “tolerate” forgetting the oc-

casual tablet (blood glucose or blood pressure levels can easily be lowered again the next day), HIV is different. Even short-term lapses can have irreversible consequences. And every new occurrence of resistance makes therapy more complicated and more difficult. Patients have to be made aware of this unusual feature of HIV disease. These conversations should be repeated from time to time and become a standard component of routine care. Cooperation with special treatment discussion groups offered by various support organizations can be useful. The table below provides additional suggestions.

In addition, a number of very different strategies have been investigated in order to improve compliance. They range from the employment of additional nurses to telephoning patients regularly. A large recent ACTG study showed that at least the regular telephone reminders do not appear to have any influence on compliance (Collier 2005).

#### **Twelve steps to improve adherence**

1. Every patient should receive a written (legible!) treatment plan, which should be reviewed at the end of the visit. It should include a telephone number to call in case of problems or questions.
2. Patient and clinician should agree on the treatment plan. The patient's concerns or critical questions should be discussed.
3. The patient should have the impression that the treatment regimen was not randomly chosen, but tailored to his/her individual needs.
4. The explanation of a new or modified treatment plan takes time, and should not be rushed – all questions should be answered.
5. The reasons why adherence is so important should be explained. It makes sense to repeat such conversations – they should not only take place when initiating or modifying treatment, but should be part of routine care.
6. Possible side effects should be explained, as well as what can be done to alleviate them.
7. Support groups and other types of assistance should be utilized and offered.
8. It is important to tell the patient to come back if any problems are encountered with HAART – it is better to solve them together than have the patient try to deal with them alone at home.
9. The patient should know that the treatment regimen must be taken in its entirety (“Last month I left out the big tablets”).
10. Prescriptions should be documented, in order to get a rough idea of adherence. Irregularities should be addressed openly.
11. During the early phases of therapy, the patient should be informed of treatment success as seen by reduction of viral load and rise in CD4 count.
12. Ensure clinical vigilance to detect the early signs of depression and treat appropriately.

### **If compliance remains low**

Despite all efforts, some patients will not be able to improve their compliance. Physicians and other healthcare providers are advised not to take this personally or to feel offended should a patient not want to participate in the advances of medicine. Although it may be difficult to accept others' views on life, disease and treatment, tolerance and acceptance should remain fundamental to the interactions of all healthcare providers with their patients. Some providers, especially those who treat selective patient populations in university settings, sometimes forget the reality of routine medical practice. Rigidly upholding the principles of modern medicine usually doesn't help here, and putting patients under pressure achieves even less. It is important to clearly outline and explain one's own position.

The question of whether noncompliant patients should continue to be treated with antiretroviral therapy is not always easy to address. On the one hand, there are patients who benefit even from suboptimal therapy; on the other hand, drugs are expensive and should not be prescribed too readily. When resources are limited, available drugs should be used prudently. If poor compliance is suspected in the initial consultation, restraint should be applied.

One also needs to be aware of criminal intentions – there have repeatedly been reports of patients who have done deals with pharmacists (black sheep occur everywhere!) for other medication (methadone, etc.) or money. Therefore, written prescriptions should be endorsed where possible. If in doubt about the compliance or honesty of the patient, plasma levels can be measured (preferably without prior warning).

### **Duesbergians – a sect of HIV medicine**

The patients that refuse antiviral treatment on principal form a special case. These patients are frequently under treatment from (shockingly misdirected) doctors, who call themselves “Duesbergians” (after the US virologist and AIDS dissident Peter Duesberg, who denied any association between AIDS and illness). Here, it can be very difficult to watch patients go to their fate with open eyes. Informative consultations should be as detailed as possible and preferably documented in writing. Below is an actual example:

An approximately 40-year old patient with a long history of untreated HIV, 30 CD4+ T-cells/ $\mu$ l and cerebral toxoplasmosis, which improved significantly after 4 weeks of acute treatment (the last MRI still showed scattered lesions) presented at the HIV outpatients department. Clinically, he was relatively well and fully oriented, and due for discharge that day. In a conversation, the patient categorically refused to start the urgently recommended antiretroviral therapy (“one can die from AZT, and the other drugs are not much better”) as well as antibiotics. Therefore he could also not continue to take the toxoplasmosis maintenance therapy, which had caused him from the first day in hospital to suffer from diarrhea (NB, probably cryptosporidiosis), skin problems (seborrheic dermatitis, thrush), and an extreme loss of weight (MAC?). It was most important for him to have a break from everything.

In cases such as these, we make sure the patients sign the information sheets. Every patient is allowed to and should decide for himself (if fully oriented) – but he must know and be fully informed about what he is doing. It is important to give the pa-

tient control: if he changes his mind (and of course, being sarcastic about the above case: if the toxoplasmosis relapses), he can return! Arguing with medical Duesbergians does not achieve anything in our experience. The view of the world that this sect has is closed. A discussion about the prayer-wheel-like repeated old arguments just uses up time and wastes energy.

Fortunately, these cases have become more seldom. The initial widespread skepticism about HAART has decreased significantly, due to its overwhelming success in the last few years. And: where Peter Duesberg is concerned (thankfully), it has also become quieter, at least as far as his HIV activities goes. The sect is in decline.

## References

- Blower SM, Aschenbach AN, Gershengorn HB, Kahn JO. Predicting the unpredictable: transmission of drug-resistant HIV. *Nat Med* 2001, 7:1016-20. <http://amedeo.com/lit.php?id=11533704>
- Collier AC, Ribaudo H, Mukherjee AL, et al. A randomized study of serial telephone call support to increase adherence and thereby improve virologic outcome in persons initiating antiretroviral therapy. *J Infect Dis* 2005, 192:1398-406. <http://amedeo.com/p2.php?id=16170757>
- Crepaz N, Hart TA, Marks G. Highly active antiretroviral therapy and sexual risk behavior: a meta-analytic review. *JAMA* 2004, 292:224-36. <http://amedeo.com/p2.php?id=15249572>
- Cu-Uvin S, Callendo AM, Reinert S, et al. Effect of HAART on cervicovaginal HIV-1 RNA. *AIDS* 2000, 14: 415-21. <http://amedeo.com/lit.php?id=10770544>
- Desquillbet L, Deveau C, Goujard C, et al. Increase in at-risk sexual behaviour among HIV-1-infected patients followed in the French PRIMO cohort. *AIDS* 2002, 16:2329-33. <http://amedeo.com/lit.php?id=12441806>
- Finzi D, Blankson J, Siliciano JD, et al. Latent infection of CD4+ T cells provides a mechanism for lifelong persistence of HIV-1, even in patients on effective combination therapy. *Nat Med* 1999, 5: 512-7. <http://amedeo.com/lit.php?id=10229227>
- Fischl M, Castro J, Monroig R, et al. Impact of directly observed therapy on long-term outcomes in HIV clinical trials. Abstract 528, 8th CROI 2001, Chicago, USA. <http://hiv.net/link.php?id=203>
- Frank I. Once-daily HAART: toward a new treatment paradigm. *J AIDS* 2002, 31 Suppl 1:S10-5, discussion S24-5. Review.
- Freedberg KA, Losina E, Weinstein MC, et al. The cost effectiveness of combination antiretroviral therapy for HIV disease. *N Engl J Med* 2001;344:824-31. <http://amedeo.com/lit.php?id=11248160>
- Friedland GH, Williams A. Attaining higher goals in HIV treatment: the central importance of adherence. *AIDS* 1999, 13 Suppl 1: S61-72. <http://amedeo.com/lit.php?id=10546786>
- Furtado MR, Callaway DS, Phair JP, et al. Persistence of HIV-1 transcription in peripheral-blood mononuclear cells in patients receiving potent antiretroviral therapy. *N Engl J Med* 1999, 340:1614-22. <http://amedeo.com/lit.php?id=10341273>
- Garcia de Olalla P, Knobel H, Carmona A, et al. Impact of adherence and HAART on survival in HIV-infected patients. *J Acquir Imm Defic Syndr* 2002, 30:105-10. <http://amedeo.com/lit.php?id=12048370>
- Glass TR, De Geest S, Weber R, et al. Correlates of Self-Reported Nonadherence to Antiretroviral Therapy in HIV-Infected Patients: The Swiss HIV Cohort Study. *J AIDS* 2006, 41:385-392. <http://amedeo.com/lit.php?id=16540942>
- Gottlieb GS, Nickle DC, Jensen MA, et al. Dual HIV-1 infection associated with rapid disease progression. *Lancet* 2004, 363:619-22. <http://amedeo.com/lit.php?id=14987889>
- Hogg R, Yip B, Chan K. Non-adherence to triple combination therapy is predictive of AIDS progression and death in HIV-positive men and women. Abstract TuOrB419, 13th International AIDS Conference 2000, Durban, South Africa.
- Hosseinipour M, Cohen MS, Vernazza PL, Kashuba AD. Can antiretroviral therapy be used to prevent sexual transmission of HIV type 1? *Clin Infect Dis* 2002, 34:1391-5. <http://amedeo.com/lit.php?id=11981736>
- Kulkosky J, Nunnari G, Otero M, et al. Intensification and stimulation therapy for HIV type 1 reservoirs in infected persons receiving virally suppressive HAART. *J Infect Dis* 2002, 186:1403-11. <http://amedeo.com/lit.php?id=12404155>

18. Lafeuillade A, Khiri H, Chadapaud S, Hittinger G, Halfon P. Persistence of HIV-1 resistance in lymph node mononuclear cell RNA despite effective HAART. *AIDS* 2001, 15:1965-9. <http://amedeo.com/lit.php?id=11600824>
19. Law MG, Prestage G, Grulich A, Van de Ven P, Kippax S. Modelling the effect of combination antiretroviral treatment on HIV incidence. *AIDS* 2001, 15:1287-94. <http://amedeo.com/lit.php?id=11426074>
20. Lehrman G, Hogue IB, Palmer S, et al. Depletion of latent HIV-1 infection in vivo: a proof-of-concept study. *Lancet* 2005, 366: 549-55. <http://amedeo.com/lit.php?id=16099290>
21. Lerner BH, Gulick RM, Dubler NN. Rethinking nonadherence: historical perspectives on triple-drug therapy for HIV disease. *Ann Intern Med* 1998, 129:573-8. <http://amedeo.com/lit.php?id=9758579>
22. Liuzzi G, Chirianni A, Bagnarelli P, Clementi M, Piazza M. A combination of nucleoside analogues and a protease inhibitor reduces HIV-1 RNA levels in semen: implications for sexual transmission of HIV infection. *Antivir Ther* 1999, 4:95-9. <http://amedeo.com/lit.php?id=10682154>
23. Maher K, Klimas N, Fletcher MA. Disease progression, adherence, and response to protease inhibitor therapy for HIV infection in an Urban Veterans Affairs Medical Center. *J Acquir Immune Defic Syndr* 1999, 22:358-63. <http://amedeo.com/lit.php?id=10634197>
24. Mannheimer S, Friedland G, Matts J, et al. The consistency of adherence to antiretroviral therapy predicts biologic outcomes for HIV-infected persons in clinical trials. *Clin Infect Dis* 2002, 34: 1115-21. <http://amedeo.com/lit.php?id=11915001>
25. Markowitz M, Boden D. Multidrug-resistant, dual-tropic HIV-1 and rapid progression. *Lancet* 2005, 365:1924. <http://amedeo.com/lit.php?id=15936415>
26. Murri R, Ammassari A, De Luca A, et al. Self-reported nonadherence with antiretroviral drugs predicts persistent condition. *HIV Clin Trials* 2001, 2:323-9. <http://amedeo.com/lit.php?id=11590535>
27. Nunnari G, Otero M, Dornadula G, et al. Residual HIV-1 disease in seminal cells of HIV-1-infected men on suppressive HAART: latency without on-going cellular infections. *AIDS* 2002, 16:39-45. <http://amedeo.com/lit.php?id=11741161>
28. Paterson DL, Swindells S, Mohr J. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med* 2000, 133:21-30. <http://amedeo.com/lit.php?id=10877736>
29. Pomerantz RJ. Reservoirs of HIV type 1: the main obstacles to viral eradication. *Clin Infect Dis* 2002, 34: 91-7. <http://amedeo.com/lit.php?id=11731950>
30. Porco TC, Martin JN, Page-Shafer KA, et al. Decline in HIV infectivity following the introduction of highly active antiretroviral therapy. *AIDS* 2004, 18:81-8. <http://amedeo.com/p2.php?id=15090833&s=hiv>
31. Quinn TC, Wawer MJ, Sewankambo N, et al. Viral load and heterosexual transmission of HIV type 1. *N Engl J Med* 2000, 342:9219. <http://amedeo.com/lit.php?id=10738050>
32. Ramratnam B, Ribeiro R, He T, et al. Intensification of antiretroviral therapy accelerates the decay of the HIV-1 latent reservoir and decreases, but does not eliminate, ongoing virus replication. *J AIDS* 2004, 35:33-7. <http://amedeo.com/lit.php?id=14707789>
33. Routy JP. Valproic acid: a potential role in treating latent HIV infection. *Lancet* 2005, 366: 523-524.
34. Saksena NK, Potter SJ. Reservoirs of HIV-1 in vivo: implications for antiretroviral therapy. *AIDS Rev* 2003; 5:3-18. <http://amedeo.com/lit.php?id=12875103>
35. Schwarze S. Getretener Quark wird breit, nicht stark: Was man von den "AIDS-Skeptikern" wirklich lernen kann. <http://hiv.net/2010/news2001/n1219.htm>
36. Sendi PP, Bucher HC, Harr T, et al. Cost effectiveness of HAART in HIV-infected patients. *Swiss HIV Cohort Study*. *AIDS* 1999, 13:1115-22. <http://amedeo.com/lit.php?id=10397543>
37. Sethi AK, Celentano DD, Gange SJ, Moore RD, Gallant JE. Association between adherence to antiretroviral therapy and HIV drug resistance. *Clin Infect Dis* 2003;37:1112-8. <http://amedeo.com/lit.php?id=14523777>
38. Sharkey ME, Teo I, Greenough T, et al. Persistence of episomal HIV-1 infection intermediates in patients on HAART. *Nat Med* 2000, 6: 76-81. <http://amedeo.com/lit.php?id=10613828>
39. Siliciano JD, Kajdas J, Finzi D, et al. Long-term follow-up studies confirm the stability of the latent reservoir for HIV-1 in resting CD4+ T cells. *Nature Med* 2003;9:727-728. <http://amedeo.com/lit.php?id=12754504>
40. Stoll M, Claes C, Schulte E, et al. Direct costs for the treatment of HIV-infection in a German cohort after the introduction of HAART. *Eur J Med Res* 2002, 7:463-471
41. Strain MC, Gunthard HF, Havlir DV, et al. Heterogeneous clearance rates of long-lived lymphocytes infected with HIV: intrinsic stability predicts lifelong persistence. *Proc Natl Acad Sci U S A* 2003, 100:4819-24. <http://amedeo.com/lit.php?id=12684537>
42. Tovanabutra S, Robison V, Wongtrakul J, et al. Male viral load and heterosexual transmission of HIV-1 subtype E in northern Thailand. *J Acquir Immune Defic Syndr*. 2002. 29:275-83. <http://amedeo.com/lit.php?id=11873077>

43. Turner BJ. Adherence to antiretroviral therapy by HIV-infected patients. *J Infect Dis* 2002; 185 Suppl 2: S143-51. Abstract: <http://amedeo.com/lit.php?id=12001036>
44. Wood E, Hogg RS, Yip B, et al. The impact of adherence on CD4 cell count responses among HIV-infected patients. *J Acquir Immune Defic Syndr* 2004, 35:261-8. <http://amedeo.com/lit.php?id=15076240>
45. Yang O, Daar E, Jamieson B, et al. HIV-1 Clade B superinfection: evidence for differential immune containment of distinct clade b strains. *J Virol* 2005; 79:860-868. <http://amedeo.com/lit.php?id=15613314>
46. Zhang L, Ramratnam B, Tenner-Racz K, et al. Quantifying residual HIV-1 replication in patients receiving combination antiretroviral therapy. *N Engl J Med* 1999, 340: 1605-13. <http://amedeo.com/lit.php?id=10341272>

## 5. When to start HAART

Christian Hoffmann, Fiona Mulcahy

*"It's the most important question in HIV therapy" (A. Fauci)*

The indication for antiretroviral therapy is based on the clinical assessment, CD4+ T-cell count, and viral load. These three important factors determine whether therapy should be started or if it can still be deferred. At first glance, it appears straightforward: the lower the CD4+ T-cell count and the higher the viral load, the higher the risk of AIDS (Mellors 1997, Lyles 2000), and the more urgent the indication for treatment.

But, how high is the individual risk really? The following table lists the (selected) risks of developing AIDS within six months, as identified in 3,326 patients from the pre-HAART era (Phillips 2004). The range of individual risk of progression varies widely – from 0 to almost 50 %. For a 55 year-old patient with a CD4+ T-cell count of 50/μl and a viral load of 300,000 copies/ml, the risk of progressing to AIDS within the next 6 months was 44.8 %. In a 25 year-old patient with 500 CD4+ T-cells/μl and a viral load of 3,000 copies/ml, the risk was only 0.3 %. This demonstrates the importance of these parameters for estimating the individual risk and indication for treatment (some other examples of possible constellations and their respective risks are shown in Table 5.1). Surprisingly, the age of the patients, which according to these data significantly increases the risk of progression, has so far not been included in any of the guidelines.

Table 5.1: Predicted six-month percentage risk of developing AIDS, according to age, viral load and CD4+ T-cell count (data from the pre-HAART era)

	100 CD4/μl	200 CD4/μl	350 CD4/μl
35 years			
VL 10,000	5.3	2.0	1.1
VL 100,000	10.6	4.1	2.3
55 years			
VL 10,000	10.7	4.6	1.8
VL 100,000	20.5	9.2	3.6

VL = Viral load. (From: Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4+ T-cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. AIDS 2004, 18:51-8. <http://amedeo.com/lit.php?id=15090829>)

Nevertheless, the best time for initiation of therapy remains the subject of controversial debate. The risk of AIDS must be weighed against the risks of long-term toxicity and viral resistance. These risks and the realization that eradication cannot be achieved at present have led to less rigid guidelines in many countries in recent years. The initial “hit hard and early” dogma of 1996, which recommended therapy from the earliest stages of infection, has since been discarded. Similarly, it is now



no longer common practice to treat every patient with a viral load above 10,000 copies/ml, independent of the CD4+ T-cell count, as was still generally recommended in the 1997 US guidelines (Carpenter 1997).

Table 5.2: Recommendations from various guidelines on when to initiate therapy

Clinical	CD4 cells/ $\mu$ l	Initiation of HAART is...
CDC B+C	All values	“recommended” (DHHS, GA, GB)
CDC A	< 200	“recommended” (DHHS, GA, GB)
CDC A	200-350	“should be offered” (DHSS) “generally advisable, independent of viral load” (GA) “recommended for most patients, but should depend on individual factors”* (GB)
CDC A	350-500	“most experts recommend deferring with VL > 100,000, some clinicians will treat; defer with VL < 100,000” (DHHS) “recommended by some experts with VL 50,000–100,000; most were hesitant to treat with VL of 50,000” (GA) “to be deferred” (GB)
CDC A	> 500	“deferral recommended by most experienced clinicians and treatment recommended only by some for VL > 100,000; defer with VL < 100,000”*** (DHHS) “to be deferred”** (GB) “most experts hesitant to treat” (GA)

VL = viral load. \*The individual factors include symptoms, patient wishes, expected adherence, potential toxicity, decline in CD4+ T-cells, level of viral load and age \*\*No distinction is made between 350-500 and > 500 CD4+ T-cells

DHHS: Guidelines for the Use of Antiretroviral Agents in HIV-1 Infected Adults and Adolescents, Department of Health and Human Services (DHHS), 06 October 2005.

<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>

GA: German-Austrian Guidelines on Antiretroviral Therapy of HIV Infection (May 2004).

[http://www.rki.de/INFEKT/AIDS\\_STD/BR\\_LINIE/BR\\_LINIE.HTM](http://www.rki.de/INFEKT/AIDS_STD/BR_LINIE/BR_LINIE.HTM)

GB: British HIV Association (BHIVA) guidelines for the treatment of HIV-infected adults with antiretroviral therapy, 2005. <http://www.bhiva.org/guidelines/2005/BHIVA-guidelines/index.html>

The question now is how to practically apply the new, more appealing motto of “hit hard but only when necessary” (Harrington 2000). At least all international guidelines agree that all symptomatic patients as well as patients with less than 200 CD4+ T-cells/ $\mu$ l should be treated. However, for patients with more than 200 CD4+ T-cells/ $\mu$ l, the situation becomes more confusing. Lack of randomized studies forces all guidelines to rely on cohort studies, meta-analyses and evaluation of larger databases. Such data is problematic, however, as important aspects such as compliance or prior treatment regimens are not captured, and very heterogeneous patient populations are included. As a result, a range of interpretations is possible. In Table 5.2, the current guidelines from the USA, Europe, Britain and Germany on starting therapy are summarized.

Guidelines merely provide points of reference and are not set in stone. Decisions must be made on a case-by-case basis, even if some health insurance providers tend

to ignore this and use such guidelines to their advantage. In some situations, therapy may be started earlier than recommended in the guidelines; in other cases, therapy might (or even should) be deferred. The following chapter discusses relevant studies on initiation of therapy in chronic HIV infection (the special case of acute HIV infection is discussed in a separate chapter).

## Experiences from practice

Even if the indication for HAART seems obvious, it should be clarified whether the patient is indeed prepared to start treatment. The problem is not the initiation of HAART, but the continuity. The decision to initiate treatment is often made prematurely. It is usually unwise to prescribe antiretroviral medication to a patient in the first consultation. One should first attain an overall picture of the patient, and try to get to know something about his lifestyle and motives – why he has come to see a doctor, and what he expects.

In some cases, patients put themselves under pressure unnecessarily, or let others do so. A single lower CD4 count, a prolonged case of flu seeming to indicate a weakened immune system (“I never had anything like that before”), springtime lethargy, new study results, a promising new drug in the newspaper (“I’ve heard a lot about T-20”), a partner who has started therapy – none of these are therapeutic indications. It is often particularly difficult to inform people from other cultures that not every person with an HIV infection needs immediate therapy.

As a rule, as much time as is needed should be taken for the decision to start therapy. This is usually possible. A well-informed patient complies better with treatment! We recommend that patients come for several consultations to prepare them emotionally for treatment. There are two exceptions: acute HIV infection, and severe immunodeficiency. However, even in the presence of most AIDS-defining conditions, the acute disease should often be treated first before initiating ART, as the potential for complications with PCP, toxoplasmosis or CMV therapies unnecessarily jeopardize treatment options. Not a single study to date has shown a benefit of commencing HAART simultaneously with OI therapy.

If a long vacation is planned, it is better to delay therapy so that treatment response and side effects can be adequately monitored. On the other hand, patients may sometimes find one reason after another (stress at work, exams, change of job, etc.) to delay initiation of treatment. Many patients are afraid of AIDS, but often just as afraid of HAART (“the pills are the beginning of the end!”). They may have irrational or simply false expectations of HAART and its consequences – starting therapy does not mean that one will be subjected to daily infusions and no longer able to work!

Therapy should be explained to every patient from the outset. It is also useful to define individual threshold values for the commencement of therapy with patients early on, so that therapy is started only when these levels are reached. In our experience, patients are more motivated by this approach.

We also tend to start HAART earlier in older patients (above 50 years). Although the regenerative capacity of the immune system in older patients is significantly reduced (Ledermann 2002, Grabar 2004), this has not been acknowledged in any guidelines to date. More importantly, the risk of developing opportunistic infections

also depends on age (Phillips 2004). Another example from the CASCADE Study (Table 5.1) exemplifies this: a 25 year-old patient with 100 CD4+ T-cells/ $\mu$ l and a viral load of 100,000 copies/ml has a risk of approximately 10 % for developing AIDS within six months – for a 55 year-old, this level of risk is reached at 150 CD4+ T-cells/ $\mu$ l and a viral load of 30,000 copies/ml!

It is also important that not only the absolute CD4+ T-cell count is considered, but the percentage value too. In particular, when the CD4 count is high and the immune status appears good, the CD4 percentage is the most important parameter for predicting the risk of developing AIDS. In one study, the risk of progression for patients with more than 350 CD4+ T-cells/ $\mu$ l was increased approximately four fold, if the percentage of CD4+ T-cells was below 17 % (Hulgan 2005).

Finally, it should not be forgotten, that the whole discussion is based on bare figures, as the CD4+ T-cells are actually surrogate markers. As a “surrogate”, they are conceived as a replacement for clinical endpoints. Therefore, they are only a rough expression of the clinical reality. Although they usually do this supremely, and even though the CD4+ T-cell count is one of the best surrogate markers in medicine, it is not everything. The patient also has to be examined!

## Symptomatic patients

There is currently consensus that every symptomatic patient should receive antiretroviral therapy. This is, of course, mainly true for patients in WHO Stage C (with AIDS), but also for all patients in Stage B. Although this should be correct in most cases, it may be advisable to consider the situation more closely in individual cases. To avoid misunderstanding: all opportunistic infections indicative of severe immunodeficiency, such as CMV, MAC, toxoplasmosis or PCP, and also AIDS malignancies (including the non-AIDS-defining Hodgkin’s Disease), should therefore prompt rapid initiation of therapy, especially if there is no specific treatment available, as in the case of PML. In such cases, rapid initiation of maximally suppressive HAART is the only treatment option available.

However: Herpes zoster (Stage B) may occur even with a slight immune defect and does not necessarily indicate immunological deterioration. Thrombocytopenia or constitutional symptoms may also have other causes. A further example: tuberculosis, which is an AIDS-defining illness and therefore an “urgent” indication for therapy, is a facultative opportunistic infection. It may occur without or with only moderate immunodeficiency. In our experience, one is justified in waiting with HAART in a TB patient with good CD4+ T-cells (see example in Table 5.3). The British guidelines (<http://www.bhiva.org>) specifically mention pulmonary tuberculosis as being a possible exception in which treatment may be deferred.

On the other hand, typical illnesses that may be relatively harmless in comparison, such as oral candida or oral hairy leukoplakia, are also unerring indications of an impaired immune system. They may often precede far more serious illnesses. In such cases, it is advisable to offer the patient therapy, even if the CD4+ T-cell count is relatively stable. The same applies to constitutional or cognitive disturbances. A patient who develops concentration deficits within a short period of time, or who complains of forgetfulness, could – if other causes have been ruled out – have developed the first cognitive deficiency associated with HIV. Neuropsychological changes are seen early in the course of infection and sometimes are observed in

otherwise asymptomatic patients (Review: McArthur 2005) – initiation of therapy should be seriously considered in such situations.

Table 5.3: Case study, in which HIV treatment, if it had been given in accordance to the guidelines, could have led to almost ten years of over-treatment. NA = not available

		CD4 (%)	Viral load
May 95	Pulmonary tuberculosis (= AIDS)	330 (27)	NA
Feb 96	End of tuberculosis treatment	437 (29)	NA
	Patient refuses (urgently recommended) HAART		
Oct 97	Patient refuses (urgently recommended) HAART	402 (33)	29,500
Oct 99	Patient refuses (urgently recommended) HAART	393 (29)	13,500
Oct 00	Patient refuses (recommended) HAART	520 (30)	12,500
Jun 02	Doctor does not want to start HAART	521 (29)	7,440
Oct 04	HAART is rarely discussed...	391 (26)	15,300
Mar 06	Nothing new. Will it change again?	408 (25)	8,500

On the other hand, if after a detailed discussion, a patient wants to begin treatment, even though the results justify waiting, HAART should not be withheld. For many patients, treatment can be a psychological support. Not everybody can sleep peacefully at night knowing that inside his/her body a hundred million new viruses are being produced every day and a huge number of helper cells are being destroyed.

### Asymptomatic patients – below 200 CD4+ T-cells/ $\mu$ l

It is agreed, that there is a clear indication for initiation of therapy in asymptomatic patients with less than 200 CD4+ T-cells/ $\mu$ l. 200 CD4+ T-cells/ $\mu$ l is the cut-off, and one should not wait for values to drop below this level, as the risk for severe complications increases significantly with increasing duration (Mellors 1997, Egger 2002). For patients with CD4+ T-cells of 200/ $\mu$ l and a high viral load, the six-month risk for AIDS is sometimes greater than 10 % (Phillips 2004). It is therefore advisable not to let this happen: the first manifestation of AIDS may not be an easily treatable infection such as PCP or esophageal thrush. If PML, CMV, or toxoplasmic encephalitis occurs instead, the result is often permanently damaging.

However, such considerations are redundant for many of the patients presenting for the first time in outpatient clinics and private practices today. At least one third have a CD4+ T-cell count below 200/ $\mu$ l. Nevertheless, even here the point is not to start therapy within a matter of days, but rather to prepare patients for initiation of HAART. Is the patient going to return at all? We have now made it our practice to start PCP prophylaxis in such patients. The first two weeks are used for diagnostic procedures (fundoscopy! thoracic x-ray, ultrasound) to provide informative counseling – as well as explaining whether the patient is eligible to enter a study - and to identify patients with psychosocial issues. Requirements with respect to pill burden and dosing schedules need to be raised. HAART is started only when these issues have been addressed.

The risk of AIDS remains elevated in these patients even after initiation of HAART. This is logical – severe immunodeficiency requires a longer time to re-

constitute, and patients therefore remain at risk during the initial months. A completely destroyed immune system cannot recover so quickly. However, this risk is relatively low: in an analysis of treatment-naïve patients with less than 200 CD4+ T-cells/ $\mu$ l at the beginning of therapy, 8.3 new AIDS-defining illnesses per 100 patient years were observed - in patients with at least 350 CD4+ T-cells/ $\mu$ l this value was 1.8/100 patient years. Similarly, mortality was slightly elevated at 2.9 versus 0.7/100 patient years (Phillips 2001).

### **Asymptomatic patients – 200-350 CD4+ T-cells/ $\mu$ l**

Even in these patients, most guidelines more or less urgently recommend starting treatment, although the risk of developing AIDS is still low. In the MACS Cohort, frozen blood samples obtained in the years 1985-1988 were analyzed and correlated with the clinical course of disease in these patients (Phair 2002). Results showed that not a single patient with more than 200 CD4+ T-cells/ $\mu$ l and a viral load below 20,000 copies/ml had developed AIDS within the following year. The authors concluded that it is possible to wait in cases of low viral load in such patients. It is nevertheless advisable to consider individual factors in this CD4+ T-cell category. Is the patient willing and able to take therapy? If there are doubts, it is better to wait. How rapid is the CD4+ T-cell decline? What are the percentage values? If there is no clear trend, it may also be appropriate to wait. See below for results of cohort studies.

### **Asymptomatic patients – above 350 CD4+ T-cells/ $\mu$ l**

The cut-off level of 350 CD4+ T-cells/ $\mu$ l is important in many guidelines. Above 350 CD4+ T-cells/ $\mu$ l, it is usually recommended to defer therapy. In the MACS Cohort, not a single patient with more than 350 CD4+ T-cells/ $\mu$ l and a viral load below 60,000 copies/ml developed an AIDS illness within a year (Phair 2002). For patients with more than 350 CD4+ T-cells/ $\mu$ l, the 2004 recommendations from the US and Germany have been slightly revised. At a viral load below 50,000 copies/ml, both guidelines recommend deferring treatment – but it should be considered with a high viral load, although it is no longer strongly recommended. Only the British guidelines, even in the latest edition, recommend deferring initiation of treatment.

It is now more widely recognized that only a few studies have so far been able to show the advantage of beginning with HAART at these CD4+ T-cell counts; all others have not found any such advantage for the patient. Proponents of early initiation of therapy often cite a matched-pair analysis from Switzerland, which indicated a small, though statistically significant clinical benefit if HAART was started with CD4+ T-cells above this level (Opravil 2002). 283 patients, who were started on HAART with a count above 350 CD4+ T-cells/ $\mu$ l, were matched by age, sex, CD4+ T-cell count, viral load and risk group for HIV infection with control patients who had been untreated for at least 12 months. At follow up around three years later, the AIDS risk was more than twice as high in the untreated group. However, besides considerable methodological problems due to the design of this study, the small print also has to be looked at more closely. The 52 illnesses (10 AIDS cases), which occurred additionally in the untreated group, have to be compared to the side effects of HAART. Certain are: OHL (8 cases), oral thrush (10), herpes zoster (9),

thrombocytopenia (9), and a few cases of tuberculosis, pneumonia and *Candida* esophagitis worse than the side effects of antiretroviral therapy? Over one third (35 %) of treated patients discontinued HAART, 51 due to gastrointestinal complaints, 25 due to CNS, renal problems, or lipodystrophy. Is there really clinical benefit in starting treatment early? If one takes into account the toxicity of the drugs and the associated reduction in the quality of life, this benefit seems to come at quite a high price.

Another study came to the conclusion, that there is a survival benefit if antiretroviral therapy is started in patients with more than 350 CD4+ T-cells/ $\mu$ l (Palella 2003). In this highly complicated analysis based on data from the American HOPS Cohort, patients were assigned to groups based on the first (baseline) CD4+ T-cell count. Patients of the same group, who had either started ART immediately or waited until they had “dropped” into a lower group, were compared. This design eliminated a problem encountered in most cohort studies, in that a patient’s risk is usually only determined at the time when therapy is started. In the HOPS Study, the clock was theoretically started at the same time point for all patients. However, even this study raises many questions when analyzed more closely. For example, the overall analysis also included patients that had started treatment with ART (i.e. mono or dual therapy). The first patients included in the analysis were from 1994. Therefore it is possible to argue that no difference would have been seen with the highly effective combinations available today. Adherence was not considered in this analysis. Patients who started therapy later were more frequently black substance abusers with no health insurance. Nevertheless, the risk of mortality was low in the end. In the group of patients that actually started HAART at levels above 350 CD4 cells/ $\mu$ l, the mortality risk was 6.9/1,000 patient years, compared to 10.0/1,000 patient years in patients with 200-350 CD4+ T-cells/ $\mu$ l at the beginning of treatment.

According to expert commentaries, this data cannot be used to swing the pendulum back in favor of starting treatment early (Mocroft 2004).

Why has no randomized study been performed to address this question? An editorial on the cohort described above provided some calculations (Lane 2003): in order to design a randomized study with 80 % power on starting treatment above or below 250 CD4+ T-cells/ $\mu$ l, about 650 events would be required to detect a 20 % difference in mortality. With an estimated probability for progression of 1 % per patient year, around 65,000 patients would have to be followed for one year, or 6,500 patients for 10 years – an impossible venture.

In summary: as many different cohorts have not shown any difference between groups of patients with 200-350 and above 350 CD4+ T-cells/ $\mu$ l (see also Table 5.5), the available data is unconvincing.

## **Consequences for the further course of disease**

In addition to the risk of death and disease progression, the controversy over the optimal time for starting therapy also raises other questions. Large cohorts repeatedly attempt to prove that the starting time point influences virological or immunological treatment success. But, do the so-called late presenters, the patients that present late in the course of their illness, really have a worse prognosis? The following is a summary of the data based on this discussion.

### **Is virological response less durable with a low CD4+ T-cell count and a high viral load?**

At first glance, many cohort studies have clearly demonstrated that virological response is poorer if the CD4+ T-cell count at initiation of treatment was low and the viral load high (Casado 1998, Mocroft 1998 and 2000, Miller 1999, Wit 1999, Deeks 1999, Chaisson 2000, Grabar 2000, Le Moing 2002, Yamashita 2001, Palella 2003, Wood 2005). In a meta-analysis of 30 prospective studies, baseline CD4+ T-cell count was important for viral load decline on treatment (Skowron 2001). It might appear straightforward: the higher the viral load and the lower the CD4+ T-cell count, the less the virological success of HAART. Defenders of an early initiation of HAART, who often cite this data, forget three important points:

First, this is not true for the two large cohorts in which only treatment-naïve patients were studied (Cozzi-Lepri 2001, Phillips 2001). These confirm our observations that even a treatment-naïve patient with a high viral load and a low CD4+ T-cell count has good chances of sufficient and long-term suppression of viral load. Under these circumstances, the initial values are less important – if the patient is compliant! Even in the French APROCO Cohort, in which greater differentiation existed between treatment-naïve and treatment-experienced patients (Le Moing 2002), treatment-naïve patients with a high viral load at baseline showed at most an insignificant negative trend. That viral load and CD4+ T-cell count have predictive values in all cohort studies in which most (up to 91 %) patients included were usually pre-treated with NRTIs, indicates one thing above all: virological success of HAART may be compromised in patients with prolonged mono or dual therapy. Previous nucleoside analog therapy has been a risk factor for virological treatment failure in many cohorts (Casado 1998, Deeks 1999, Chaisson 2000, Grabar 2000, Le Moing 2002). In the HOPS Cohort, lack of prior therapy was decisive particularly for long-term treatment success (Holmberg 2003). As there are fortunately hardly any patients on mono or dual therapy nowadays, it is justified to concentrate on treatment-naïve patients.

Secondly, the relative risk of virological failure was often only increased in patients with substantial immunosuppression (below 50 CD4+ T-cells/ $\mu$ l) or very high viral load (above 100,000 copies/ml). At levels above 200 CD4+ T-cells/ $\mu$ l or a viral load of less than 100,000 copies/ml, differences could generally not be detected (see below).

Thirdly, only a few of these studies considered compliance. A patient who starts HAART under emergency conditions at 30 CD4+ T-cells/ $\mu$ l (and who went to the physician only shortly before or even after clinical manifestation of AIDS) may have a different view on sickness and health, and may be less adherent than someone who seeks medical advice with a good CD4+ T-cell count and begins HAART after thorough reflection. It seems clear that the benefit of HAART differs for such patients. Adherence was an important and even decisive predictor in the few studies in which it has been investigated (Le Moing 2002, Wood 2003+2004).

If these aspects are considered, the issue of whether virological response is really poorer with less favorable baseline values becomes less clear-cut. Even a patient with high viral load and a very low CD4+ T-cell count can potentially control infection quite successfully! The prerequisite for this is that the drugs are taken regularly – and the regimen administered must be a potent one: data from prospective

studies such as SOLO or M98-863, in which nelfinavir (a relatively weak PI) was tested against lopinavir or fosamprenavir showed poorer responses in highly viremic patients on nelfinavir.

### **Is immunological response less with unfavorable initial values?**

Multiple factors influence the increase in CD4+ T-cells: duration of immunosuppression, age, thymus size or extent of thymus degeneration (see chapter “Goals and Principles of Therapy”). Do these include values at initiation of therapy? Astonishingly, several cohorts found no association (Yamashita 2001, Pezzotto 2001, Cozzi-Lepri 2001). However, these studies all showed that the rise in CD4+ T-cells is similar, although levels remained lower if the CD4 count was initially low. Furthermore, in our experience immune reconstitution is rarely complete if values were low initially; the more damaged the immune system, the less likely a complete recovery in the long run (Garcia 2004). In the Swiss Cohort, having a low CD4+ T-cell count at baseline was a clear risk factor for not attaining 500 CD4+ T-cells/ $\mu$ l after four years (Kaufmann 2002+2005). There is also concern over the 10-15 % of patients with a discordant response where HAART is virologically extremely successful, but CD4+ T-cell count remains low (Piketty 1998, Renaud 1999).

Another consequence of starting therapy later can be that antigen-specific immune reconstitution remains impaired, both against HIV and other pathogens. Numerous studies suggest that qualitative immune reconstitution does not initially occur at the same pace as quantitative reconstitution (Gochorov 1998, Tortatjada 2000, Lederman 2001, Lange 2002). One can make the analogy with a patch of desert where weeds will grow before flowers. So, what are the clinical consequences of these lab data? Why does the risk of AIDS decrease so impressively and rapidly with a rising CD4+ T-cell count? The weed does not appear to be so bad after all. Why can even severely immunodeficient patients discontinue their prophylaxis quite safely, once their CD4+ T-cell count has risen to above 200/ $\mu$ l? These clinical observations – at least in the short term – seem to contradict our knowledge of the currently observed immune reconstitution.

### **Does the risk of clinical progression remain high even after starting HAART with a low CD4+ T-cell count and a high viral load?**

Most studies have found a clear correlation between CD4+ T-cell count at initiation of HAART and rates of both AIDS and death (Hogg 2000, Grabar 2000, Cozzi-Lepri 2001, Kaplan 2001, Phillips 2001, Egger 2002, Kaplan 2003, Palella 2003, Sterling 2003). Above all, if the CD4+ T-cell count is below 50/ $\mu$ l when starting therapy, the risk for developing AIDS remains permanently high (Hogg 2003). In other cohorts, the risk remained elevated even below a CD4+ T-cell count of 200/ $\mu$ l (Phillips 2001, Sterling 2001, Kaplan 2003).

The largest study to date was published in 2002 by the ART Cohort Collaboration (Egger 2002), in which almost 13,000 patients on HAART were analyzed. The data seems clear-cut. The CD4+ T-cell count at the start of treatment correlated highly with the probability later in the course of the illness of AIDS or death. In comparison to the patients who started HAART with less than 50 CD4+ T-cells/ $\mu$ l, the risks with higher levels of helper cells were significantly less (see Table 5.4).



Table 5.4: Risk of progression in the ART Cohort Collaboration (Egger 2002)

Baseline CD4+ T-cells/ $\mu$ l	Relative risk
50-99 versus < 50	0.74 (0.62-0.89)
100-199 versus < 50	0.52 (0.44-0.63)
200-349 versus < 50	0.24 (0.20-0.30)
> 350 versus < 50	0.18 (0.14-0.22)

One should note the moderate difference between the groups above 200 CD4+ T-cells/ $\mu$ l. Viral load at baseline was only relevant if it was at a very high level, i.e. above 100,000 copies/ml.

#### Are there any differences between 200-350 and >350 CD4+ T-cells/ $\mu$ l?

In the above-mentioned meta-analysis, the difference was minimal (Egger 2002). The AIDS rate was 2.3 versus 1.8; the mortality rate 1.0 versus 0.7 per 100 patient years. This means one more case of AIDS in 200 patient years! Vast randomized studies would probably be necessary to detect a difference between the two patient groups. Other cohort studies have also posed the question of whether there is a difference if patients first start at a CD4+ T-cell count of 200-350 cells or earlier. So far, most have not been able to detect an advantage for starting treatment early (Table 5.5). However, the observation periods were usually relatively short. It is possible that differences will be found in the long term.

Table 5.5: The influence of CD4+ T-cell count on treatment success. Comparison between 200-350 CD4+ T-cells/ $\mu$ l and > 350 CD4+ T-cells/ $\mu$ l at initiation of HAART.

Study	Less AIDS, fewer deaths?	More pronounced increase in CD4+ T-cells?	Improved virological response?
Canadian Cohort (Chaisson 2000, n=553)	**	**	No (trend)
Italian Cohort (Cozzi-Lepri 2001, n=1.421)	No	No	No
CDC database, USA (Kaplan 2001, n=10.885)	No	**	**
Baltimore Cohort (Sterling 2003, n=333)	No	**	No
Swiss, Frankfurt, EuroSIDA Cohorts (Phillips 2001, n=3226)	No	**	No
Swiss Cohort (matched pair) (Opraval 2002, n=2x283)	Yes	**	**
MACS Cohort (Ahdieh-Grant 2003, n=349)	No	**	**
HOPS Cohort (Palella 2003, n=1464)	Yes	**	Yes
Barcelona Cohort, single-center (Garcia 2004, n = 861)	No	No (trend)	**

\*\* not specified

A problem of many cohort studies is that they do not consider the success of HAART on the individual level. A very complex analysis on almost 10,000 patients, which considered the baseline values as well as the values after six months (Chene 2003), produced a very clear result: the success of HAART is key for the further risk of suffering AIDS and/or dying. Baseline values were irrelevant. In other words – if HAART is successful, the initial status does not matter.

All in all, the available results, despite their limitations, do support the current trend of deferring initiation of therapy at levels above 200 CD4+ T-cells/ $\mu$ l.

This risk assessment will probably change again as soon as treatment regimens with better long-term tolerability become available. The less worries there are about long-term side effects, the more likely they are to be used. The current criteria therefore have a preliminary character and have to be continuously re-evaluated. Some experts are already propagating an earlier start for anti-retroviral therapy (Holmberg 2004, Schechter 2004). However, better treatment options could also mean that it would actually be possible to start later.

#### **Practical tips for starting therapy in asymptomatic patients**

- Below 200 CD4+ T-cells/ $\mu$ l treatment should be started as soon as possible.
- “As soon as possible” does not mean “immediately”: one should still take the time to get acquainted with the patient, give proper counseling, start prophylaxis in advance, and undergo diagnostic procedures (fundoscopy!) – it’s not usually a question of having to start within a few days!
- Above 200 CD4+ T-cells/ $\mu$ l, there is even more time – the individual course of the CD4+ T-cell count is important. Beware the percentage values!
- A decrease of more than 80-100 CD4+ T-cells/ $\mu$ l per year is too much! Don’t delay too long in such patients!
- Because of considerable variability a single CD4+ T-cell count (especially when in the range of 200-350/ $\mu$ l) should be repeated before starting therapy.
- Above 350 CD4+ T-cells/ $\mu$ l: wait, but continue to monitor at least every three months.
- The higher the viral load, the more frequent checks of CD4+ T-cell counts are necessary: > 100,000 copies/ml, testing should be performed at least every two months.
- Initiation of treatment may be justified at levels above 350 CD4+ T-cells/ $\mu$ l – if viral load is very high, CD4+ T-cell count is decreasing rapidly or the patient requests it (after careful counseling).
- Check ahead of time whether a patient may be suitable for enrolment in a clinical trial!

Finding the optimal time to start treatment is one of the most difficult decisions of HIV therapy. To conclude, here are a few typical arguments about the pros and cons of starting therapy.

**Arguments for and against an EARLY start**

Statement	Counter
"The lower the CD4 count, the longer the patient will remain at risk later."	"This statement applies mainly to patients with substantial immunosuppression in whom initiation of therapy should not be debated. The earlier one starts, the more long-term toxicities will occur!"
"A lower CD4 count often implies that only moderate immunological-virological treatment success is possible – at some stage, the destruction of the immune system is irreversible."	"This is mainly true for patients with substantial immunosuppression. However, the virological response does not seem to be reduced in treatment-naïve patients."
"The longer one waits, the fitter the virus becomes via generation of quasispecies and immune escape variants, and the more difficult it is to treat."	"Interesting laboratory hypothesis. But, where's the relevant clinical data?"
"The worse the condition of the patient, the worse the tolerability of HAART."	"Ancient, proven medical wisdom. But, does it apply here, where we are referring to asymptomatic patients."
"HIV should be treated as early as possible, as should any other infectious disease."	"HIV is not akin to any other infectious disease. HIV cannot be cured like many bacterial infections. Herpes viruses, for which there is no cure, are also treated only as needed."
"It has been proven that patients are less infectious on treatment."	"And may be more prone to risk behavior. In addition, the risk of transmission of primary resistance mutations increases."

**Arguments for and against a LATE start**

Statement	Counter
"The earlier one starts, the sooner and more certain the side effects."	"This may be true. The question is: does one more year without therapy, but with an increasing risk of AIDS, really make a difference?"
"The earlier one starts, the higher the risk for resistance in the long term."	"OK, but... compliant patients, who have sufficient suppression of viral load, have good chances of not developing resistance, even over many years."
"Even a bad immune system can regenerate; after all, prophylaxis can be safely stopped after a rise in CD4 count."	"This may be true for some patients, but not for all. There are indications that the qualitative response remains impaired."
"It is never too late to start therapy at 200 CD4 cells."	"Who can be so sure? Some AIDS diseases may rarely occur even in this scenario; there is no certainty that PML or lymphoma might not develop – and if should they, good advice is hard to find."

**References on starting therapy**

- Ahdieh-Grant L, Yamashita TE, Phair JP, et al. When to initiate highly active antiretroviral therapy: a cohort approach. *Am J Epidemiol* 2003, 157:738-46.
- Carpenter CC, Fischl MA, Hammer SM, et al. Antiretroviral therapy for HIV infection in 1997. Updated recommendations of the International AIDS Society-USA panel. *JAMA*. 1997;277:1962-9.
- Casado JL, Perez-Elias MJ, Antela A, et al. Predictors of long-term responses to protease inhibitor therapy in a cohort of HIV-infected patients. *AIDS* 1998; 12:F131-F135. <http://amedeo.com/lit.php?id=9708403>
- Chaisson RE, Keruly JC, Moore RD. Association of initial CD4 cell count and viral load with response to HAART. *JAMA* 2000; 284:3128–29. Originalarbeit: <http://hiv.net/link.php?id=204>

5. Chene G, Sterne JA, May M, et al. Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies. *Lancet* 2003; 362: 679-686. <http://hiv.net/link.php?id=12957089>
6. Cozzi-Lepri A, Phillips AN, d'Arminio Monforte A, et al. When to start HAART in chronically HIV-infected patients: evidence from the ICONA study. *AIDS* 2001; 15:983-90. <http://amedeo.com/lit.php?id=11399980>
7. Deeks SG, Hecht FM, Swanson M, et al. HIV RNA and CD4 cell count response to protease inhibitor therapy in an urban AIDS clinic: response to both initial and salvage therapy. *AIDS* 1999, 13:F35-43. <http://amedeo.com/lit.php?id=10397555>
8. Egger M, May M, Chene G, et al. Prognosis of HIV-1-infected patients starting HAART: a collaborative analysis of prospective studies. *Lancet* 2002; 360:119-29. <http://amedeo.com/lit.php?id=12126821>
9. Garcia F, De Lazzari E, Plana M, et al. Long-Term CD4+ T-Cell Response to Highly Active Antiretroviral Therapy According to Baseline CD4+ T-Cell Count. *J AIDS* 2004, 36:702-713. <http://amedeo.com/lit.php?id=15167289>
10. Goicoechea M, Haubrich R. CD4 lymphocyte percentage versus absolute CD4 lymphocyte count in predicting HIV disease progression: an old debate revisited. *J Infect Dis* 2005, 192:945-7.
11. Gorochov G, Neumann AU, Kereveur A, et al. Perturbation of CD4+ and CD8+ T-cell repertoires during progression to AIDS and regulation of the CD4+ repertoire during antiviral therapy. *Nat Med* 1998; 4: 215-21. <http://amedeo.com/lit.php?id=9461196>
12. Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. *AIDS* 2004, 18:2029-2038. <http://amedeo.com/lit.php?id=15577624>
13. Grabar S, Pradier C, Le Corfec E, et al. Factors associated with clinical and virological failure in patients receiving a triple therapy including a protease inhibitor. *AIDS* 2000, 14:141-9. <http://amedeo.com/lit.php?id=10708284>
14. Harrington M, Carpenter CC. Hit HIV-1 hard, but only when necessary. *Lancet* 2000, 355:2147-52. <http://amedeo.com/lit.php?id=10902643>
15. Hogg RS, Yip B, Chan KJ, et al. Rates of disease progression by baseline CD4 cell count and viral load after initiating triple-drug therapy. *JAMA* 2001; 286:2568-77. <http://amedeo.com/lit.php?id=11722271>
16. Holmberg SD, Hamburger ME, Moorman AC, Wood KC, Palella FJ Jr. Factors associated with maintenance of long-term plasma HIV virus RNA suppression. *Clin Infect Dis* 2003; 37: 702-7. <http://amedeo.com/lit.php?id=12942404>
17. Holmberg SD, Palella FJ Jr, Lichtenstein KA, Havlir DV. The case for earlier treatment of HIV infection. *Clin Infect Dis* 2004, 39:1699-704. <http://amedeo.com/lit.php?id=15578373>
18. Hulgian T, Raffanti S, Kheshti A, et al. CD4 lymphocyte percentage predicts disease progression in HIV-infected patients initiating HAART with CD4 lymphocyte counts >350 lymphocytes/mm<sup>3</sup>. *J Infect Dis* 2005, 192:950-7. <http://amedeo.com/lit.php?id=16107946>
19. Kaplan JE, Hanson DL, Cohn DL, et al. When to begin HAART? Evidence supporting initiation of therapy at CD4+ lymphocyte counts <350 cells/uL. *Clin Infect Dis* 2003; 37:951-8. <http://amedeo.com/p2.php?id=13130408&s=hiv>
20. Kaplan JE, Hanson DL, Jones JL, Dworkin MS. Viral load as an independent risk factor for opportunistic infections in HIV-infected adults and adolescents. *AIDS* 2001; 15:1831-6. <http://amedeo.com/lit.php?id=11579245>
21. Kaufmann G, Perrin L, Pantaleo G. CD4 T-lymphocyte recovery in individuals with advanced HIV-1 infection receiving potent antiretroviral therapy for 4 years: The Swiss HIV Cohort Study. Abstract LB4, 9<sup>th</sup> CROI 2002, Seattle, USA. <http://www.retroconference.org//2002/Abstract/14064.htm>
22. Kaufmann GR, Furrer H, Ledergerber B, et al. Characteristics, determinants, and clinical relevance of CD4 T cell recovery to <500 cells/uL in HIV type 1-infected individuals receiving potent antiretroviral therapy. *CID* 2005, 41:361-72. <http://amedeo.com/lit.php?id=16007534>
23. Lane HC, Neaton JD. When to start therapy for HIV infection: a swinging pendulum in search of data. *Ann Intern Med* 2003;138:680-1.
24. Lange CG, Valdez H, Medvik K, Asaad R, Lederman MM. CD4+ T-lymphocyte nadir and the effect of highly active antiretroviral therapy on phenotypic and functional immune restoration in HIV-1 infection. *Clin Immunol* 2002, 102:154-61. <http://amedeo.com/lit.php?id=11846457>
25. Le Moing V, Chene G, Carrieri MP, et al. Predictors of virological rebound in HIV-1-infected patients initiating a protease inhibitor-containing regimen. *AIDS* 2002, 16:21-9. <http://amedeo.com/lit.php?id=11741159>
26. Ledergerber B, Egger M, Opravil M, et al. Clinical progression and virological failure on highly active antiretroviral therapy in HIV-1 patients: a prospective cohort study. Swiss HIV Cohort Study. *Lancet* 1999, 353:863-8. <http://amedeo.com/lit.php?id=10093977>

27. Lederman MM, McKinnis R, Kelleher D, et al. Cellular restoration in HIV infected persons treated with abacavir and a protease inhibitor: age inversely predicts naive CD4 cell count increase. *AIDS* 2000, 14: 2635-42. <http://amedeo.com/lit.php?id=11125881>
28. Lederman MM. Immune restoration and CD4+ T-cell function with antiretroviral therapies. *AIDS* 2001, Suppl 2:S11-5. <http://amedeo.com/lit.php?id=11424971>
29. Lyles RH, Munoz A, Yamashita TE, et al. Natural history of HIV type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. *J Infect Dis* 2000, 181:872-880. <http://amedeo.com/lit.php?id=10720507>
30. McArthur JC, Brew BJ, Nath A. Neurological complications of HIV infection. *Lancet Neurol* 2005, 4:543-55.
31. Mellors JW, Munoz AM, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med*. 1997, 126:946-954. <http://amedeo.com/lit.php?id=9182471>
32. Miller V, Staszewski S, Sabin C, et al. CD4 lymphocyte count as a predictor of the duration of HAART-induced suppression of HIV load. *J Infect Dis* 1999, 180:530-3. <http://amedeo.com/lit.php?id=10395876>
33. Mocroft A, Devereux H, Kinloch-de-Loes S, et al. Immunological, virological and clinical response to highly active antiretroviral therapy treatment regimens in a complete clinic population. *AIDS* 2000, 14:1545-1552
34. Mocroft A, Gill MJ, Davidson W, Phillips AN. Predictors of a viral response and subsequent virological treatment failure in patients with HIV starting a protease inhibitor. *AIDS* 1998, 12:2161-2167.
35. Mocroft A, Phillips AN, Lundgren JD. HIV survival benefit associated with earlier antiretroviral therapy. *Ann Intern Med* 2004, 140:578-9. <http://amedeo.com/lit.php?id=15068990>
36. Opravil M, Ledergerber B, Furrer H, et al. Clinical efficacy of early initiation of HAART in patients with asymptomatic HIV infection and CD4 cell count > 350 x 10(6)/l. *AIDS* 2002, 16:1371-81. <http://amedeo.com/lit.php?id=12131214>
37. Palella FJ Jr, Deloria-Knoll M, Chmiel JS, et al. Survival benefit of initiating antiretroviral therapy in HIV-infected persons in different CD4+ cell strata. *Ann Intern Med* 2003; 138:620-6. <http://amedeo.com/lit.php?id=12693883>
38. Pezzotti P, Pappagallo M, Phillips AN, et al. Response to HAART according to duration of HIV infection. *J Acquir Immune Defic Syndr* 2001, 26:473-9. <http://amedeo.com/lit.php?id=11391168>
39. Phair JP, Mellors JW, Detels R, et al. Virologic and immunologic values allowing safe deferral of antiretroviral therapy. *AIDS* 2002; 16:2455-9. <http://amedeo.com/lit.php?id=12461420>
40. Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naive individuals and those treated in the monotherapy era. *AIDS* 2004, 18:51-8. <http://amedeo.com/lit.php?id=15090829>
41. Phillips AN, Staszewski S, Weber R, et al. HIV viral load response to ART according to the baseline CD4 cell count and viral load. *JAMA* 2001, 286:2560-7. <http://amedeo.com/lit.php?id=11722270>
42. Piketty C, Castiel P, Belec L, et al. Discrepant responses to triple combination antiretroviral therapy in advanced HIV disease. *AIDS* 1998, 12:745-50. <http://amedeo.com/lit.php?id=9619806>
43. Powderly WG, Saag MS, Chapman S, Yu G, Quart B, Clendeninn NJ. Predictors of optimal virological response to potent antiretroviral therapy. *AIDS* 1999, 13:1873-1880. <http://amedeo.com/lit.php?id=10513645>
44. Powderly WG. Long-term exposure to lifelong therapies. *J Acquir Immune Defic Syndr* 2002, 29 Suppl 1: S28-40. <http://amedeo.com/lit.php?id=11832699>
45. Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. *AIDS* 1999, 13:669-76. <http://amedeo.com/lit.php?id=10397561>
46. Schechter M. Therapy for early HIV infection: how far back should the pendulum swing? *J Infect Dis* 2004, 190:1043-5.
47. Skowron G, Street JC, Obree EM. Baseline CD4+ cell count, not viral load, correlates with virologic suppression induced by potent antiretroviral therapy. *J Acquir Immune Defic Syndr* 2001, 28: 313-9. <http://amedeo.com/lit.php?id=11707666>
48. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. *N Engl J Med* 1999, 341:1865-1873. <http://amedeo.com/lit.php?id=10601505>
49. Sterling TR, Chaisson RE, Moore RD. HIV-1 RNA, CD4 T-lymphocytes, and clinical response to HAART. *AIDS* 2001, 15:2251-7. <http://amedeo.com/p2.php?id=12627368&s=hiv>
50. Chaisson RE, Moore RD. Initiation of HAART at CD4+ T lymphocyte counts of > 350 cells/mm3: disease progression, treatment durability, and drug toxicity. *Clin Infect Dis* 2003; 36: 812-5. <http://amedeo.com/lit.php?id=11698698>

51. Tortajada C, Garcia F, Plana M, Gallart T, Maleno MJ, Miro JM et al. Comparison of T-cell subsets' reconstitution after 12 months of highly active antiretroviral therapy initiated during early versus advanced states of HIV disease. *J Acquir Immune Defic Syndr* 2000, 25: 296-305. <http://amedeo.com/lit.php?id=11114829>
52. Wit FW, van Leeuwen R, Weverling GJ. et al. Outcome and predictors of failure of HAART: One-year follow-up of a cohort of HIV type 1-infected persons. *J Inf Dis* 1999, 179: 790-798. <http://amedeo.com/lit.php?id=10068573>
53. Wood E, Hogg RS, Yip B, et al. Effect of medication adherence on survival of HIV-infected adults who start highly active antiretroviral therapy when the CD4+ cell count is 0.200 to 0.350 x 10<sup>9</sup> cells/L. *Ann Int Med* 2003; 139:810-816. <http://amedeo.com/lit.php?id=14623618>
54. Wood E, Hogg RS, Yip B, et al. The impact of adherence on CD4 cell count responses among HIV-infected patients. *J Acquir Immune Defic Syndr* 2004, 35:261-8. <http://amedeo.com/lit.php?id=15076240>
55. Wood E, Hogg RS, Yip B, et al. Why are baseline HIV RNA levels 100,000 copies/mL or greater associated with mortality after the initiation of antiretroviral therapy? *JAIDS* 2005;38:289-295.
56. Yamashita TE, Phair JP, Munoz A, et al. Immunologic and virologic response to HAART in the Multicenter AIDS Cohort Study. *AIDS* 2001, 15:735-46. <http://amedeo.com/lit.php?id=11371688>

## 6. Which HAART to start with?

Christian Hoffmann

Once the decision has been made that HAART is necessary, the next question is: what to start with? More than two dozen drugs are now available, and the number of theoretically possible combinations seems to be almost infinite. Thus, it is preferable that every treatment-naïve patient participates in a clinical study. This is the only way that the quality of antiretroviral therapy can be improved further. In the last few years, several combinations have turned out to be suboptimal, which would never have emerged without the conduction of controlled studies, for example ddI+tenofovir. However, in practice it is not always possible to treat patients in clinical trials. For information regarding the treatment of these patients, the following summarizes the data available to date.

### Recommended initial regimens at a glance

Combinations that we currently recommend for first-line therapy (as of January 2006) are shown in Table 6.1. Of note, there is no order of preference. Moreover, many other combinations are possible. These combinations may be acceptable in individual cases or in investigational studies, but general recommendations for their use cannot be given. Problematic drugs or combinations, that are not advisable for use, are listed at the end of this chapter.

Table 6.1: Combinations suitable for initial HIV therapy (not in order of preference!)

NRTIs		plus either	NNRTI/PI
AZT + 3TC			Lopinavir/ritonavir
*TDF + 3TC			Efavirenz
*TDF + FTC			Nevirapine**
Alternatives			Alternatives
AZT + FTC			Fosamprenavir/ritonavir
***ABC + 3TC			Saquinavir/ritonavir
****AZT + 3TC + ABC			

NRTI combinations recommended for initial regimens (left upper column) may also be combined with alternative NNRTIs/Pis (right lower column) and vice versa.

\* Convincing data only on combination with efavirenz.

\*\* Beware hepatotoxicity when CD4+ T-cells are high (women > 250, men > 400/μl)

\*\*\* May be problematic with nevirapine due to possible allergies, therefore use only with Pis if possible.

\*\*\*\* In some special circumstances, when NNRTIs or Pis are not suitable.

## Practical approach to the first regimen – important rules

All current initial regimens consist of two nucleoside analogs, combined with either a boosted PI, an NNRTI or – with distinct restrictions - a third nucleoside analog. No single combination has clearly been shown to be superior to another (Olsen 2005). There is no gold standard.

### Practical tips for first-line therapy:

- The first regimen offers the patient the best chance. This means that the viral load must decrease to below detection levels within 3-6 months!
- Don't rush – the patient must be ready for HAART, no half-hearted start! If in doubt, wait and continue to monitor the levels.
- If possible, don't prescribe medication in the first consultation with a new patient who brings along his results. Do you know the patient well enough? Is he really motivated? Will he ever come back again?
- For every patient, only prescribe the ART he is able to take! Don't insist on theoretically superior combinations.
- The pros and cons (side effects) of different combinations should be discussed – there is usually enough time for this.
- The initial regimen should be taken no more than twice daily. Once-daily treatment should be considered if it is important for the patient.
- The toxicity profiles should not overlap, if possible – never use several allergenic drugs simultaneously.
- Ask about other medication (and drug consumption) – are relevant interactions to be expected?
- Concomitant illnesses should also be checked – what about the liver (hepatitis), kidneys?
- All drugs are started on the same day – no lead-in mono- or dual therapy!
- Be sure to check whether the patient would be eligible for a clinical study! All patients, especially if treatment-naïve, should be encouraged to participate in clinical trials!

When choosing primary therapy, many factors are involved, besides the antiviral potency and tolerability. Individual situations, such as compliance, concurrent illnesses and concomitant medications, and the needs of the patient should be included in the decision. One should be aware that primary therapy is of great significance and needs to be well prepared. It is at this time that the chance of viral suppression is greatest.

## What should be clarified beforehand?

### Dosing issues

Can the patient really take drugs several times a day? Is this realistic with regard to his individual, professional or social situation? If in doubt, a simpler regimen is preferable to one that is presumed to be more effective. For example, it is often not



realistic to expect intravenous drug users to take ten or more tablets a day according to a strict protocol. However, junkies also need treatment, and there have been successful attempts at once-daily regimens for drug addicts (Staszewski 2001), which are also suitable for DOT (Directly Observed Therapy) together with the substitution.

For many patients, the numbers of pills or requirements for food intake are important. The range of licensed and recommended initial regimens varies from 2 to 13 pills per day. Some find it unacceptable to have to take pills at certain times during the day with fatty foods. Patients today are more demanding than earlier – justifiably so. There are now alternatives. Even the size or consistency of tablets can be a problem. Such issues must be discussed *before* initiating therapy.

### **Concurrent illnesses**

Before starting treatment, possible concurrent illnesses must be identified (thoroughly questioning and examination). The knowledge of their presence is important to proceed further (see Table 6.2). For example, a patient with diarrhea should not be given nelfinavir or lopinavir. ddI is contraindicated in patients with a history of pancreatitis! Caution with tenofovir or indinavir in renal disease! Polyneuropathy requires that any d-drugs (ddI, ddC, d4T) be avoided; they are only used as exceptions in primary therapy. Non-insulin-dependent diabetes can become insulin-dependent for the first time on PI treatment.

Liver disease and chronic hepatitis must also be taken into account, because then the risk of developing severe hepatotoxicity on nevirapine or ritonavir is highest (Den Brinker 2000, Martinez 2001, Sulkowski 2000+2002). Caution is also required with boosted PIs. However, one study conducted in over 1,000 patients found no difference between lopinavir/ritonavir and an unboosted PI such as nelfinavir in patients co-infected with hepatitis C (Sulkowski 2004). In co-infections with HBV, the good HBV-efficacy of 3TC or FTC (not simultaneously!) and preferably also tenofovir should be utilized.

Table 6.2: Concurrent illnesses requiring caution with specific drugs. There are no absolute contraindications.

Illness	Caution with
Active hepatitis B	Nevirapine, boosted PIs (In contrast: 3TC, FTC, tenofovir are beneficial!)
Active hepatitis C	Nevirapine, boosted PIs
Active substance abuse, substitution	NNRTIs, ritonavir
Anemia	AZT, possibly also 3TC
Arterial hypertension	Indinavir
Chronic diarrhea, intestinal diseases	Nelfinavir, lopinavir, other PIs
Diabetes mellitus	PIs (especially if a NIDDM is at risk of becoming an IDDM!)
Kidney disease	Indinavir, tenofovir
Myocardial infarction	PIs (potentially beneficial: nevirapine)
Pancreatitis	ddl
Polyneuropathy	d4T, ddl
Psychoses, other CNS illnesses	Efavirenz

## Interactions with medications and drugs

Interactions are important in the choice of combination regimens. Whereas interactions between antiretroviral drugs are well known, interactions with other concomitant medications are often less well characterized. The urgent need for more research was demonstrated in a study investigating the interactions between HAART and statins. In healthy volunteers, the measurement of plasma levels showed that levels of simvastatin were elevated by 3.059 % after concurrent dosing with ritonavir or saquinavir (Fichtenbaum 2002). One case of fatal rhabdomyolysis on simvastatin and nelfinavir has been described (Hare 2002).

Many drugs should be avoided in combination with particular antiretroviral drugs, as incalculable interactions may occur. These include certain contraceptives. Even drugs that seem unproblematic at first glance can have unfavorable effects: for example, the plasma levels of saquinavir can be reduced by half due to concurrent administration of garlic capsules (Piscitelli 2002). Even a seemingly harmless substance such as vitamin C can influence plasma levels. A small study in healthy volunteers showed that 1 g of vitamin C can significantly lower (14 %) unboosted indinavir levels (Slain 2005).

Coumarin-derivative anticoagulants such as warfarin can also be a problem; ritonavir can significantly lower plasma levels (Llibre 2002). Further typical “problem drugs” include migraine remedies, prokinetic drugs and sedatives/hypnotics. One fatal case has been described with ergotamine and ritonavir (Pardo 2003). The simultaneous administration of HAART and PDE-5 inhibitors (sildenafil, vardenafil, tadalafil) can also be problematic, see section on “Sexual Dysfunction”.

Drugs or alcohol can also interact with HAART. For those in substitution programs, the methadone requirement may be significantly increased by certain antiretroviral drugs such as nevirapine and efavirenz (Clarke 2001). To a lesser extent, this is also true for ritonavir and nelfinavir. There is inconsistent data on lopinavir, but it may

also require dose adjustments (McCance-Katz 2003, Stevens 2003). Tenofovir does not seem to have significant interactions with methadone (Smith 2004).

Other interactions have even more dangerous consequences. Several deaths have been reported after simultaneous dosing with ritonavir and amphetamines or MDMA/ecstasy, or the popular narcotic gamma hydroxybutyric acid (GHB, Samsonit™ or “liquid ecstasy”; Henry 1998, Harrington 1999, Hales 2000). Ritonavir in particular inhibits the metabolism of amphetamines (speed or MDMA/ecstasy), ketamines or LSD (review in: Antoniou 2002). Clinician and patient are well advised to have an open conversation about drug use before starting therapy. Marijuana and THC appear to have a low potential for interactions (Kosel 2002). Amphetamines seem to be particularly dangerous and neurotoxic in HIV patients (Langford 2003).

Not every substance can be discussed here. Many are described in the respective drug chapters. It is always recommended to check the package insert. Initiation of HAART provides a good opportunity to re-evaluate existing prescribed medications.

### **Additive toxicities**

Several potential additive toxicities should be considered in the choice of therapy.

If other myelotoxic drugs (valganciclovir!) are necessary, caution is required with AZT. The same is true for hydroxyurea or dapsone. When treating hepatitis C with interferon and ribavirin, AZT must be avoided. Ribavirine should also never be combined with ddi.

Patients taking acyclovir have significantly more frequent renal problems on indinavir (Herman 2001). Tenofovir should also be avoided with renal problems or potentially nephrotoxic drugs.

Lastly, it is not advisable during the primary therapy to start with potential allergy-inducing substances if anti-infectious prophylaxis with co-trimoxazole or other sulphonamides is necessary. Included in this are nevirapine, efavirenz, and abacavir (and possibly fosamprenavir). In order not to disturb the prophylaxis, it is better to avoid these drugs. Otherwise, it can be difficult to clearly identify the causative agent for a drug-induced exanthema.

### **Which drug classes are to be used?**

All combinations currently used as initial regimens consist of two nucleoside analogs plus either a PI, an NNRTI, or - with limitations - a third nucleoside analog. These three strategies reduce the risk of AIDS approximately equally (Olsen 2005). In contrast, all other combinations are experimental or not justified for use outside the framework of clinical studies. Advantages and problems of these three strategies are outlined in the Table 6.3.

There are only a few studies comparing all three strategies. The interest of the pharmaceutical industry in such large projects is limited. Indeed, why determine, with huge financial commitments, that one's own drug may be weaker? Such studies are therefore usually performed independently of the industry, but also take longer.

Table 6.3: Combining drug classes: Advantages (↑) and disadvantages (↓)

2 Nukes + PI	2 Nukes + NNRTI	2 Nukes + 3rd Nuke
↑ a lot of data, including clinical endpoints and severely immuno-compromised patients	↑ equivalent, perhaps even better suppression of viral load than with PIs	↑ low pill burden, easy dosing
↑ long-term data available	↑ low pill burden! once-daily may be possible	↑ leaves many options
↑ high genetic resistance barrier	↑ leaves PI options	↑ few interactions
↓ high pill burden (for the older PIs), partly strict dosing requirements, most once-daily regimens not licensed	↓ clinical effect not proven (only surrogate marker studies)	↓ less potent, with higher viral load, and in particular tenofovir-containing triple nuke therapy
↓ frequent drug interactions	↓ less data in severely immunocompromised patients	↓ once-daily with AZT not possible
↓ some PIs with crossresistance, leaving limited options	↓ rapidly occurring complete cross-resistance	↓ No clinical endpoints, no long-term data
↓ long-term toxicity, lipodystrophy, dyslipidemia with most PIs	↓ strict monitoring required initially (esp. nevirapine), allergies frequent	↓ Possible raised mitochondrial toxicity

In the Atlantic Study, 298 patients were openly randomized to receive d4T+ddI+3TC versus d4T+ddI+nevirapine versus d4T+ddI+indinavir (Van Leeuwen 2003). After 48 weeks, 49 %, 49 % and 40 % of patients, respectively, attained a viral load of less than 50 copies/ml in the intent-to-treat analysis (ITT). These differences were not significant. However, several subanalyses (96 weeks, patients with high viral load) did show differences: although indinavir and nevirapine were both quite comparable, they were significantly better than 3TC. This study provided the first arguments against triple-nuke therapy. However, the combinations tested in the Atlantic Study are now fairly outdated.

In the CLASS Trial, the following three classes were tested with an ABC+3TC backbone: amprenavir/ritonavir as a boosted PI regimen, efavirenz as an NNRTI option and d4T as a third nucleoside analog (Bartlett 2004). As in the Atlantic Study, the differences in the various arms after 48 weeks were not significant, based on the normal viral load assay with a detection limit of 400 copies/ml. Differences only became apparent with the ultrasensitive assay, where only the NNRTI arm had an advantage. This was also true for a subgroup of patients with a high viral load of above 100,000 copies/ml. Interestingly, there was no difference between the other two arms (boosted PI regimen versus triple nuke!), although it did seem like the virological failure rate in the triple nuke arm was relatively high. However, some of the CLASS regimens are also no longer current.

The different strategies are discussed here in more detail. Options that will probably play a more important role in the future will also be considered, such as once-daily, nuke sparing, and so-called induction therapies. These are effective and

promising according to current data, but cannot, at least in part, be generally recommended yet. Combinations that are problematic and better avoided will also be mentioned.

In the following, various strategies or primary therapies are discussed. These include:

1. Two nucleoside analogs plus a protease inhibitor
2. Two nucleoside analogs plus a NNRTI
3. Three nucleoside analogs (“triple nuke”)
4. Once-daily combination
5. Experimental combinations (“nuke sparing”, intensive approaches)
6. Problematic primary therapies

When nucleoside analogs are mentioned below, the nucleotide analog tenofovir is also included, but for simplicity it is not presented separately each time.

### **1. Two Nucleoside Analogs Plus a PI**

The combination of two nukes plus one protease inhibitor is the only HAART that is supported by efficacy data from randomized studies with clinical endpoints (Hammer 1997, Cameron 1998, Stellbrink 2000). Most importantly, data is available over longer periods than for other combinations. Some studies have been ongoing for over five or six years (Gulick 2003, Hicks 2003). Many experts still like to use these combinations today, particularly in patients with AIDS or high viral load, as another advantage is the robustness of boosted PIs with respect to viral resistance. However, it has not yet been proven whether this does actually have an advantage in primary therapy. Disadvantages of the PI-containing primary therapy are the, sometimes considerable, pill burden and relatively frequent side effects, which makes compliance difficult. The following briefly describes the most common combinations:

#### **Two nukes plus lopinavir/r**

These are categorized in many guidelines as a combination that should be used in preference to other regimens. Long-term efficacy seems to be good (Hicks 2003). No resistance has been described for such primary therapy to date. The combination of d4T+3TC+lopinavir/r seemed to show better efficacy than d4T+3TC+nelfinavir in the only comparative study described to date. After week 48, 67 versus 52 % of patients had a viral load below 50 copies/ml (Walmsley 2002). Whether lopinavir/r is really more effective for initial therapy than other boosted PIs remains uncertain at the moment. Many large studies are currently underway to compare other boosted PIs with lopinavir (saquinavir, atazanavir, TMC-114). It is also not clear what treatment would be effective if lopinavir/r fails. The nuke backbone used in most studies is currently TDF+FTC (Molina 2004).

#### **Two nukes plus saquinavir/r**

The combination of AZT+ddC+saquinavir-HGC was the first PI-combination for which survival benefit was shown in a randomized study. This was the largest randomized HIV study ever (Stellbrink 2000). Nevertheless, saquinavir is still given

with other nukes, rather than with AZT+ddC, and more importantly still, in its boosted form alone (saquinavir/r). Without the booster effect of ritonavir, the bioavailability is too low. Tolerability is probably better than for indinavir/r, which is no longer recommended for first-line therapy (Dragstedt 2003). The boosted combination of 1,000 mg saquinavir with 100 mg ritonavir, both twice daily, has been licensed. More data is available for the AZT-containing nuke backbones than for those containing tenofovir.

### **ABC+3TC plus fosamprenavir**

With the end of the patent protection of the long-lasting phenomenon AZT looming ahead, GSK has set up a number of studies in recent years testing its other two nukes ABC+3TC as a backbone. The fixed combination tablet Kivexa™ (US: Epzicom™) has been available since 2005 and provides an additional once-daily option. In the NEAT and SOLO studies, ABC+3TC showed good efficacy in combination with fosamprenavir (Gathe 2004, Rodriguez-French 2004). As there is little data available for other PI combinations, we would therefore recommend fosamprenavir as the best option for combination with the ABC+3TC backbone. Despite some encouraging data on efavirenz (DeJesus 2004), we do not recommend the combination of ABC+3TC plus an NNRTI for first-line therapy, due to the difficult differential diagnosis of an allergy (abacavir? NNRTI?) that can unnecessarily jeopardize future treatment options.

### **Two nukes plus nelfinavir**

Nelfinavir combinations were previously among the most frequently used ART regimens. The licensing studies tested nelfinavir mainly with AZT+3TC (Saag 2001, Gartland 2001). In the Combine Study, nelfinavir seemed slightly weaker than nevirapine (Podczamzer 2002); in INITIO it was significantly weaker than efavirenz (Cooper 2005). In direct comparison to boosted PIs such as lopinavir/r or fosamprenavir/r, nelfinavir is also less potent (Walmsley 2002, Gathe 2004, Rodriguez-French 2004). Nelfinavir-containing combinations have a high pill burden and are associated with unpleasant diarrhea, so that we generally no longer recommend it for first-line therapy. Unfortunately, Roche has not managed to overcome the production problems of the new formulation (625 mg, less pills, better tolerability) for the European market. This is in contrast to Pfizer, who distribute nelfinavir internationally.

## **2. Two Nucleoside Analogs Plus an NNRTI**

NNRTIs have an equal, if not presumably even superior effect on surrogate markers as PI combinations. NNRTIs have done well in numerous randomized studies: efavirenz-based regimens in studies such as 006, ACTG 384, ACTG 5095 or CLASS were superior to indinavir, nelfinavir, amprenavir/r or triple nuke (Staszewski 1999, Robbins 2003, Gulick 2004, Bartlett 2004). The nevirapine-containing regimens in Combine or Atlantic were at least equivalent to nelfinavir and indinavir, and better than triple nuke (Podzamczar 2002, van Leeuwen 2003). A direct comparison in the 2NN Study showed no major differences between efavirenz and nevirapine (van Leth 2004).

Advantages of NNRTI-regimens include the low pill burden and good tolerability. In contrast to PIs, however, data with clinical endpoints is unavailable. Neither is there any long-term data or studies on severely immunocompromised patients. A disadvantage of NNRTI combinations is the rapid development of cross-resistance. This could, at least theoretically, result in a problem, especially for highly viremic patients, although this has not yet been confirmed in a study.

### **TDF+3TC/FTC plus efavirenz (or nevirapine)**

In our opinion, this seems to be one of the preferable combination at present. In the double blind, randomized Gilead 903 Study, virological efficacy was equivalent to d4T+3TC (plus efavirenz), although tolerability was significantly better (Gallant 2004). Toxicity was reduced, and polyneuropathy, lipodystrophy and even dyslipidemia were significantly less frequent in the tenofovir arm. In the Gilead 934 Study, TDF+FTC plus efavirenz was more effective than AZT+3TC plus efavirenz after 48 weeks, because of tolerability (Gallant 2006). There is no reliable data on nevirapine in combination with TDF+3TC/FTC yet. However, it is not expected to be significantly different. For all TDF-containing combinations, care must be taken to monitor renal function on a monthly basis.

### **AZT+3TC plus efavirenz or nevirapine**

These regimens were among those most frequently used (006, Combine, ACTG 384, 5095, 934). Side effects may occur during the first weeks. In the 934 Study, anemia and gastrointestinal problems occurred frequently in some cases, which significantly compromised the efficacy of AZT+3TC in contrast to TDF+FTC (Gallant 2006). Allergies to NNRTIs are not rare. Dose escalation of nevirapine after 2 weeks is essential due to auto-induction of its own metabolism, as is monitoring for the possible CNS side effects of efavirenz. Once the first weeks have passed without complications, a combination such as AZT+3TC plus nevirapine or efavirenz can often be continued for many years without major problems.

Some clinicians occasionally use ddI instead of 3TC. We do not recommend this, since ddI needs to be taken on an empty stomach and AZT is tolerated better when taken with a meal. Still: AZT+ddI+nevirapine is probably the oldest HAART combination and should therefore at least be mentioned. It was already tested between 1993 and 1996, in the ACTG 193A Study. Here it proved superior to dual therapies in immunologically advanced patients with regard to both survival and disease progression, although not significantly for the latter (Henry 1998). AZT+ddI+nevirapine was also well investigated in the INCAS Trial and ACTG 241 (Raboud 1999, D'Aquila 1996).

### **d4T+3TC plus efavirenz or nevirapine**

Since the 903 Study (see above) and the ABCDE Study (Podzamczar 2004) the usefulness of d4T+3TC has become limited. This combination is only useful if problems of hematopoiesis (anemia or thrombocytopenia) exist at the start of therapy. This applies, for example, to patients receiving chemotherapy or ganciclovir.

The advantages over TDF+3TC are the amount of data in existence and the fact that d4T was subjectively well tolerated initially.

d4T+3TC plus NNRTI combinations have been thoroughly investigated. In the 2NN Study, d4T+3TC+efavirenz and d4T+3TC+nevirapine were about comparable (Van Leth 2004); in the Australian OzCombo2 Study, d4T+3TC in combination with nevirapine was as effective as d4T+ddI or AZT+3TC (French 2002).

### 3. Three Nucleos(t)ide Analogs – Triple Nuke

Triple nuke therapies, i.e. combinations of three nucleoside or nucleotide analogs, have several advantages: few pills, few interactions, no side effects typical of PIs or NNRTIs, and the fact that all other drug classes can be spared for later. A big disadvantage of triple nuke therapies is that they are virologically less potent than other combinations.

#### AZT+3TC+ABC

The combination of AZT+3TC+ABC in a single tablet (Trizivir™) is the classic triple nuke combination and a very simple HAART regimen: two pills a day provide a triple combination. However, a disadvantage of Trizivir™ is that it has to be given twice daily. Apart from that, Trizivir™ is not as potent as “divergent” combinations from other drug classes. Initially, the combination with two NRTIs plus either nelfinavir (Matheron 2003, Kumar 2006) or indinavir (Staszewski 2001, Vibhagool 2004) was accepted, but since ACTG 5095, Trizivir™ is no longer valid as a primary therapy in many countries.

ACTG 5095 tested AZT+3TC+ABC against NNRTI-containing regimens for the first time (Gulick 2004). In this double blind, randomized study, 1,147 treatment-naïve patients received either AZT+3TC+ABC, AZT+3TC plus efavirenz, or AZT+3TC+ABC plus efavirenz. The endpoint was virological failure, defined as a viral load above 200 copies/ml after 16 weeks or later. After an average 32 study weeks, 21 % of patients in the Trizivir™ arm had a viral load above 200 copies/ml – in a combined evaluation of the efavirenz arms this proportion was only 11 %. This difference was significant, and the triple nuke arm with AZT+3TC+ABC was discontinued as a result. However, ACTG 5095 was not able to answer one question: if approximately 10-15 % therapy failure is risked in the first year of triple nuke therapy, is this not compensated by the better follow-up options? A patient, who develops resistance under triple nuke therapy, usually develops the mutation M184V, and if left too long, TAMS too. But, rapid changeover should keep the viral load under control despite these mutations, often without a PI. In contrast, a patient on a failing NNRTI regimen has usually lost the benefit of the whole class of NNRTI drugs – and in addition often has nuke resistances. PIs are essential for this patient.

Nevertheless: today, only patients taking co-medications with a high potential for drug interactions (tuberculosis and MAC therapy, warfarin), and low viral load are well suited to Trizivir™. The combination is usually well tolerated, although careful counseling on the hypersensitivity reaction to abacavir is necessary. With respect to the AZT dose, the same applies for Trizivir™ as for Combivir™: it may be too high for some patients.



### **TDF-containing triple nuke therapy (and quadruple nuke)**

Several studies have shown that the combination of tenofovir plus two nucleoside analogs is unfavorable. After an initial pilot study in 19 patients reported poor responses on ABC+3TC+tenofovir (Khanlou 2005), the ESS3009 Study finally heralded the end of TDF-triple nuke therapies (Gallant 2005). The study investigated a fixed once-daily combination of ABC+3TC plus tenofovir against ABC+3TC plus efavirenz. After evaluation of the first 194 of a total of 345 treatment-naïve patients, the study was discontinued – 49 % of patients in the tenofovir arm experienced virological treatment failure, compared to only around 5 % in the efavirenz arm. Resistance analyses showed that when treatment failure occurred in the tenofovir arm, the M184V mutation was present combined, in the majority of cases, with the TDF-resistance mutation K65R. The low genetic resistance barrier is probably the reason for this poor result (Landman 2005), which was also observed in treatment-experienced patients who wanted to simplify HAART (Hoogewerf 2003, Perez-Elias 2005).

The combination of ddI+3TC+tenofovir also seems to be poor (Jemsek 2004). However, we have had fairly good experience with AZT+3TC+tenofovir in a retrospective study. The thymidine analog seems to be protective against tenofovir-associated mutations (Mauss 2005). At least two prospective studies have reported good responses on quadruple nuke therapy with AZT+3TC+abacavir plus tenofovir (DeJesus 2004, Moyle 2005). The long-term toxicity and efficacy of these combinations is still unknown. Most experts agree that in general, on the basis of the poor experiences made with the above-mentioned tenofovir combinations, no thymidine analog sparing combinations (i.e., without AZT) should be used for triple nuke therapy.

### **Other triple nuke therapies**

Besides those involving Trizivir™ and tenofovir, a number of other studies have investigated triple nuke. In the open-label, randomized CLASS Study, ABC+3TC+d4T were just as effective as ABC+3TC plus amprenavir/r, but less effective than ABC+3TC plus efavirenz. (Bartlett 2004). Poorer results came from Denmark on the d4T+ddI+ABC combination (Gerstoft 2003). In this study, only 43 % of patients had a viral load below 20 copies/ml after 48 weeks (versus 69 % under AZT+3TC plus nelfinavir+nevirapine, 62 % under AZT+3TC plus saquinavir/r). In Atlantic, d4T+ddI+3TC were significantly weaker than d4T+ddI plus indinavir or nevirapine (Van Leeuwen 2003).

Summary on triple nuke as primary therapy: It is difficult for this strategy to continue to carry the flag. Even when disregarding the dismal results from tenofovir-containing therapies, it is poorer in comparison to divergent regimens. On the other hand, it would be wrong to dismiss triple nuke therapy completely. The strategy is not entirely bad and is still particularly useful for patients with compliance problems or co-medications with the potential for interactions. One may also wonder whether triple nuke are perhaps not just as good in the long term as divergent strategies, since subsequent regimens work better. Triple nuke therapy also remains under consideration for maintenance therapy (see following chapter).

#### 4. Once-daily combinations

In recent years, many drugs have been licensed for administration once a day (“once-daily”). As a result, multiple new once-daily options for primary therapy have emerged. It should be noted, however, that there are still no large studies on these regimens, with the exception of TDF(ddI)+FTC(3TC)+EFV (Saag 2004, Gallant 2006), ABC+3TC+EFV (Moyle 2005), and TDF+FTC+LPV/r (Molina 2004).

This is the reason why some experts still fear that once-daily dosing is unfavorable with respect to the theoretical development of resistance. If one dose is forgotten, a whole day of treatment is lost at once. These regimens may therefore be “less forgiving”, particularly if there are problems with compliance (and this is exactly the patient group in which these therapies are being used).

The higher peak levels may also reduce the tolerability, as suggested by several studies. In the 418 Study, for example, once-daily lopinavir led to significantly more diarrhea than twice-daily doses (Molina 2004). But, once-daily regimens do not only affect the peak levels – the lengthened interval between doses also causes the trough levels to sink, especially with boosted PIs (Gibbons 2005). In the CONTEXT Study, this became relevant, as trough levels for fosamprenavir in treatment-experienced patients were too low (Elston 2004). For this reason, fosamprenavir is not recommended for once-daily use in treatment-experienced patients. Trough levels for once-daily lopinavir are also sometimes too low, and often cannot be increased to sufficient levels even with additional pills (la Porte 2005).

It has still not been confirmed that once-daily regimens really improve compliance. In our experience, it is a bigger step to go from three to two doses than from two to one. One meta-analysis showed that compliance is better for once-daily than three or four times daily dosing. However, the difference to twice-daily dosing (bid) was not significant (Claxton 2001). Another study also showed that once-daily and bid dosing were no different, if the bid regimens were simple and well tolerated (Stone 2004). Patients often request once-daily treatment, but only if there are no restrictions regarding food intake and the number of pills is low (Moyle 2003). The higher number of pills associated with once-daily PI combinations such as saquinavir/r, indinavir/r and lopinavir/r therefore limit the popularity of such regimens despite the fairly good data available (Hugen 2000, Eron 2004, Molina 2004, Ananworanich 2005).

Table 6.4: Antiretroviral drugs and their usage in once-daily regimens (OD)

Trade name	Abbr. drugs	OD?	Comment
<b>Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)</b>			
Combivir™	AZT+3TC	No	OD not possible due to AZT
Emtriva™	FTC	Yes	
Epivir™	3TC	Yes	
Kivexa/Epzicom™	3TC+ABC	Yes	
Retrovir™	AZT	No	OD not possible
Trizivir™	AZT+3TC+ABC	No	OD not possible due to AZT
Truvada™	FTC+TDF	Yes	
Videx™	ddI	Yes	Must be taken on an empty stomach
Viread™	TDF	Yes	
Zerit™	d4T	No	d4T-XP is no longer coming
Ziagen™	ABC	Yes	
<b>Non-nucleoside reverse transcriptase inhibitors (NNRTIs)</b>			
Rescriptor™	DLV	No	OD not possible
Sustiva/Stocrin™	EFV	Yes	
Viramune™	NVP	Possibly	A lot of data, OD-license planned
<b>Protease inhibitors</b>			
Aptivus™	TPV/r	No	OD not possible
Crixivan™	IDV/r	No	Little data available
Invirase 500™	SQV/r	Possibly	OD studies are underway
Kaletra™	LPV/r	Possibly	OD licensed in the USA since 10/05
Reyataz™	ATV/r	Yes	OD also unboosted in the USA
Telzir/Lexiva™	FPV/r	Possibly	OD licensed in the USA
Viracept™	NFV	No	Hardly any data available
<b>Fusion inhibitors</b>			
Fuzeon™	T-20	No	OD not possible

Unboosted ritonavir, amprenavir and ddC are no longer mentioned.

It is advisable to discuss the pros and cons of once-daily therapy with the patient. It is certainly not required that all patients are treated with these regimens, even if the drug companies like to claim otherwise. On the other hand, the wish of the patient should also be considered. In particular, it may be difficult for individuals in employment with shift work, or with irregular lifestyles to take medication twice a day at set times. However, even these patients must be advised that it is just as important in once-daily regimens to take the medication on time.

## 5. Experimental Combinations

Future combinations need to be more effective, simple and tolerable. However, there is not always time to wait for new drugs to be developed! As a result, two approaches are currently being closely investigated: combinations without any nucleoside analogs (nuke sparing), and so-called induction therapies, comprised of

intensive combinations using more than three active drugs or drugs from three different classes.

### Nuke sparing

All classical HAART regimens have to date included a “backbone” consisting of two nucleoside or nucleotide analogs. This mainly has historical reasons: nucleoside analogs were the first drugs on the market, and by the time NNRTIs and PIs were under development, treatment with two nucleoside analogs was standard. With growing knowledge of the mitochondrial toxicity of nucleoside analogs, more people are questioning this concept. Nuke sparing, i.e. complete omission of nucleoside analogs, is being discussed more and more (see Table 6.5). A few studies on pre-treated patients have already tested nuke sparing successfully (see “When to change HAART”), and salvage therapy with double PI combinations is also being investigated.

Table 6.5: Prospective studies on nuke sparing in treatment-naïve patients and patients with little prior treatment experience (intent-to-treat analyses)

	n (naïve)	Combination (Study name)	Proportion viral load < 50 copies/ml
Staszewski 1999	148 (126)*	EFV+IDV (006 Study)	47 % at 48 weeks 35 % at 144 weeks
Gisolf 2000	104 (104)	SQV+RTV (Prometheus)	63 % at 48 weeks (< 400)
Lopez-Cortez 2003	42 (0)**	EFV+SQV/r	71 % at 52 weeks
Boyd 2005	61 (0)*	EFV+IDV/r (HIVNAT 009)	69 % at 96 weeks
Stek 2003	47 (na)*	EFV+IDV/r (EASIER)	53 % at 48 weeks
Hellinger 2005	20 (4)*	SQV+LPV/r (PIN)	70 % at 48 weeks
Cameron 2005	16 (16)	SQV+LPV/r (ACTG 384)	63 % at 48 weeks
Allavena 2005	86 (65)*	EFV+LPV/r (BIKS)	73 % at 48 weeks (< 400)
Harris 2005	14 (14)	NVP+LPV/r (CTN 177)	78 % at 48 weeks

\*Patients all PI-naïve. \*\*22/42 with less than 50 copies/ml at the time of switch. Number of treatment-naïve patients in parentheses. na = not available.

But for primary therapy? Since an NRTI-free combination of indinavir+efavirenz fared quite badly in the 006 Study (Staszewski 1999), nuke sparing initially seemed to be a thing of the past. But the pressure on nucleoside analogs is increasing. In a long-term study, in which 65 PI-naïve patients intensified their saquinavir/r combination with nucleoside analogs or not (Cohen 2002), lipodystrophy was significantly less frequent after five years in the 28 patients, who had not received additional nucleoside analogs. In the Prometheus Study, patients (all treated with ritonavir plus saquinavir) also had more lipodystrophy with d4T than without (Gisolf 2000).

There are only a few randomized studies to date. The EASIER Study treated patients with indinavir/r and efavirenz with or without addition of d4T. The 48-week analysis showed comparable effects with respect to the surrogate markers – and d4T did not have any additional effect. However, this study was compromised by the relatively high dropout rate, reflected in the poor results of the ITT analysis (Stek

2003). Two other small, randomized studies found no significant difference between nuke sparing and standard regimens (Harris 2005, Cameron 2005).

It is still unclear whether mitochondrial toxicity and side effects really improve with nuke sparing or whether less are to be found. A substudy of HIVNAT009 reported that lipoatrophy resolved, and that visceral fat and subcutaneous limb fat increased (Boyd 2003b). In CTN 177, nuke sparing had a favorable effect on lactate (Harris 2005).

Despite this data, it is still premature to be able to recommend nuke sparing as an equal alternative in its own right. Innovative concepts such as the randomized LORAN Study should prove interesting, testing the double-PI combo atazanavir+lopinavir/r against AZT+3TC+lopinavir/r in treatment-naïve patients. Currently running in the US is ACTG 5142, a similarly exciting study, with a nuke-sparing arm of efavirenz-lopinavir/r. Results are expected in 2006.

### **Other experimental strategies: PI monotherapy, alternating therapy**

Does it get any easier? Several studies introduced a very avant-garde concept in the summer of 2003: monotherapy with boosted PIs. Although the negative experience with mono or dual therapies during the first years of antiretroviral therapy seems to prohibit such approaches, the high resistance barrier and good efficacy profile of lopinavir/r have prompted a few clinicians to dare to explore the proof-of-principle. The data is astonishing: in a study from Texas on 30 treatment-naïve patients, lopinavir/r monotherapy showed sustained good efficacy lasting beyond 48 weeks – 18 of 20 patients had a viral load below 50 copies/ml at this time point (Gathe 2004). Monotherapies are now also being tested in so-called maintenance therapies (see Chapter 8, “How to Change HAART?”).

Another new approach is alternating therapy, which involves changing treatment every few weeks. In the SWATCH Study (Martinez-Picado 2003), a total of 161 patients were randomized to a regimen of d4T+ddI+efavirenz or AZT+3TC+nelfinavir. A third arm changed between the two regimens every three months, as soon as the viral load was below the level of detection. After 48 weeks, virological failure in the alternating arm was significantly reduced. There was no difference for all other parameters (CD4+ T-cells, side effects, adherence, quality of life). It is interesting to see whether this experimental approach will hold up to further investigation.

### **Induction with 4 or 5 drugs**

There is widespread consensus for the use of triple combinations in first-line therapy. A meta-analysis (Jordan 2002) of 58 randomized clinical studies found that the relative risk of disease progression with triple therapy was approximately 0.6 compared to dual therapy.

However, some clinicians are speculating whether more intensive approaches are necessary in some patients. Rapid development of resistance, which is theoretically more likely in patients with a high viral load, is a growing concern. A number of physicians have already started to give initial treatment with four or even five

drugs, and then to simplify the regimen to a triple combination after several months, once the viral load has dropped below the level of detection.

This mainly theoretical concept has not yet been validated, and is only based on theoretical hypotheses or smaller proof-of-concept studies (Louie 2003, Ramratnam 2004), in which it has been shown that the viral load falls faster under intensive combinations than under standard therapies with three active drugs.

Approaches in which multiple individual drugs (usually nucleoside analogs) are given have to be distinguished from approaches in which three instead of two classes of drugs are used.

### ***Multiple individual drugs***

Current data indicates that there is no advantage to using this strategy. Giving two PIs (or two NNRTIs) instead of one sometimes produced even negative results in studies such as SPICE, Danish PI or 2NN (Moyle 2000, Katzenstein 2000, van Leth 2004). There is also little evidence at the moment in favor of giving three instead of two nucleoside analogs (Staszewski 2003, Orkin 2004). In ACTG 5095, there was clearly no difference between Combivir<sup>TM</sup>+efavirenz and Trizivir<sup>TM</sup>+efavirenz, not even when the starting viral load was higher, or with regard to resistances (Gulick 2005). The subgroup analysis did not reveal any difference. As a result of this study, the concept of using additional individual substances can be laid to rest.

### ***More drug classes***

The data on whether to use three or two drug classes is not so clear.

**ACTG 388:** in this open-label study, 517 treatment- or PI-naïve patients with relatively advanced HIV infection (less than 200 CD4<sup>+</sup> T-cells/μl or a high viral load above 80,000 copies/ml, with an AZT+3TC backbone) were randomized to three different regimens: indinavir versus indinavir+efavirenz versus the double PI combination indinavir+nelfinavir (Fischl 2003). After two years, virological failure on indinavir+efavirenz was significantly lower than in the other two arms. The poorest results came from the indinavir+nelfinavir arm, which showed a trend towards more serious adverse events. Thus, ACTG 388 showed an advantage of triple-class therapy over two-class therapy with the (old) PI indinavir. However, a few patients in the study were treatment-experienced and around 10 % already had resistance mutations at baseline.

**ACTG 384:** In this trial, 980 patients were randomized to six treatment arms (Robbins 2003, Shafer 2003): either AZT+3TC or d4T+ddI combined with efavirenz, nelfinavir or efavirenz+nelfinavir. The NRTI combinations were blinded; the other drugs were given open-label. Preliminary data after an average follow-up of 28 months (with a relatively high number of dropouts) is confusing: AZT+3TC was more effective than d4T+ddI, but only in combination with efavirenz, not with nelfinavir. Conversely, efavirenz was superior to nelfinavir, but only with AZT+3TC as a backbone. The quadruple arm was better than all triple regimen arms combined, but not in comparison to the single most effective arm of AZT+3TC+efavirenz. The latter, however, had a relatively high number of patients dropping out. The toxicity of d4T+ddI was higher than that of AZT+3TC.

**INITIO** is a multinational trial with approximately 900 patients, which compared efavirenz, nelfinavir or efavirenz+nelfinavir, each with a backbone of d4T+ddI, in an open-label randomized design. No significance was seen between the triple and quadruple arms (Cooper 2005). The main disadvantage of this long-term study was that the treatment regimens being studied became somewhat outdated, and dropout rates were correspondingly high as a result.

**ANRS 081** tested a triple-class regimen consisting of d4T+nevirapine+indinavir compared to a conventional d4T+3TC+indinavir regimen in 145 patients who were either treatment-naïve or had only little prior treatment experience. The triple-class arm fared significantly worse. At week 72, 52 versus 79 % had a viral load below 20 copies/ml. 43 % discontinued their nevirapine therapy (Launay 2002).

**FORTE** tested triple-class therapy containing two nucleoside analogs, one PI and one NNRTI against the standard therapy with two nucleoside analogs plus a NNRTI. Different individual drugs were used (Williams 2004). Triple-class therapy was administered for 24-36 weeks, and then switched to a simpler regimen. In the ITT analysis, more patients in the standard therapy arm had developed virological failure after 32 weeks (43 versus 18 %,  $p = 0.002$ ), and there was a 0.86 log higher decrease in viral load in the triple-class arm. At 48 weeks, 81 versus 65 % of patients had less than 50 copies/ml. There were no significant differences in toxicity.

In summary: the studies cited above currently indicate that any supposed improved efficacy of these regimens is counterbalanced by more side effects. Indeed, there is the risk of scaring patients away with the higher number of pills and side effects. Conspicuously little data is available on patients who first start with HAART at an advanced stage of their disease (“late presenters”). It is still unclear whether and in which patients such intensification of therapy is useful, and which drugs should be chosen.

## 6. Unfavorable Primary Therapies

Combinations generally considered to be suboptimal include all forms of mono- and dual therapy, especially two nucleoside analogs. Even one nucleoside analog plus one NNRTI is not good, as shown by the INCAS Trial (Montaner 1998). When using nucleoside analogs, it is important to make sure that they are not competing for the same bases. Therefore, combinations of thymidine analogs (AZT and d4T) or cytidine analogs (FTC, 3TC) make no sense. The thymidine analogs AZT and d4T are even antagonistic (Havlir 2000, Pollard 2002). Also to be avoided are ddC (HIVID™), saquinavir-SGC (Fortovase™) and amprenavir (Agenerase™), which have partially been taken off the market. T-20 and tipranavir as well as delavirdine and atazanavir (in some countries) are not licensed for use in primary therapy. Ritonavir in full dose can be rejected as an active substance, as the tolerability is so poor. This is also the case for the earlier much-used combination d4T+ddI, due to mitochondrial toxicity.

### **Problem: Starting abacavir plus NNRTIs simultaneously**

A new abacavir-containing combination should not include a new NNRTI. Both can cause allergies, which are hardly distinguishable from one another. In the case of abacavir, even a suspected allergy rules out re-exposure, and this important drug

may be “lost” unnecessarily for all future combinations. In the CNA30024 Study, a notable 9% of patients developed a hypersensitivity reaction on ABC+3TC+efavirenz (DeJesus 2004). Thus, if abacavir and NNRTIs are to be taken together in a new combination, initiation of treatment with each of the two drugs should be spaced at least 4-6 weeks apart.

### **Problem: Combination of NNRTIs**

NNRTIs act non-competitively at the same site, and furthermore all can cause a rash, making differential diagnosis difficult. Efavirenz levels seem to be lowered considerably in combination with nevirapine (Veldkamp 2001). This is probably also true for delavirdine (Harris 2000). In the wake of the 2NN Study, it finally seems clear that the combination of efavirenz and nevirapine should be avoided. The study arm with this combination fared worse than the other arms, mainly due to toxicity (Van Leth 2004).

### **Problem: TDF+ddI and TDF-containing triple nuke**

Tenofovir should not be administered as part of a triple nuke regimen. Too many studies have reported poor response rates, particularly in combination with ABC+3TC (Hoogewerf 2003, Jemsek 2004, Khanlou 2005, Gallant 2005). See section: “Triple Nuke”.

Another combination that is not advised is TDF+ddI with an NNRTI or PI, although until 2004 it was considered to be a very promising combination for potential once-daily regimens. It is rare that a combination is discarded so quickly within only a few months of data collection: at least five trials which tested tenofovir+ddI plus a NNRTI, resulted in a high failure rate of therapy, and some were stopped prematurely (Leon 2005, Podzamczar 2005, Maitland 2005, van Lunzen 2005, Torti 2005). The worst efficacy was observed in patients with a significant immune defect and high viral load. The company BMS even sent a warning letter concerning TDF+ddI. Meanwhile, there have been other reports that CD4+ T-cells have decreased under this combination, even when a good virological effect has been obtained (Kakuda 2004, Barrios 2005). The reasons for this are still being controversially discussed, but may be due to the unfavorable interactions between tenofovir and ddI. Reports on the higher toxicity and in particular pancreatitis (Martinez 2004, Masia 2005), have shown that the combination of TDF+ddI no longer has a place in antiretroviral therapy.

### **Problem: Starting gradually**

All drugs should be started simultaneously. A number of studies have investigated whether the number of drugs should be slowly increased. At least since 1996 – the end of the era of mono- and dual therapy – such strategies should be obsolete. In the Merck 035 Study, highly significant differences were shown between patients who had received three drugs immediately and those who were started on only two drugs (Gulick 1998). The CNA3003 Study (Ait-Khaled 2002) provides a further example: 173 treatment-naïve patients were randomized in a double blind design to a combination of AZT+3TC+ABC versus AZT+3TC. At week 16, patients from the dual therapy arm could switch open-label to AZT+3TC+ABC or add further antiretroviral drugs if the viral load was above 400 copies/ml. At week 16, the viral load was above 400 copies/ml in 10% in the triple therapy arm versus 62% in the dual ther-



apy arm. More importantly, 37 (versus 3) patients in the dual therapy arm had developed the M184V mutation. Although abacavir remained effective in most cases where it was added and TAMs were the exception, this example shows how quickly resistance can develop. This is significant in the long-term: a large cohort study showed that the risk of virological treatment failure was doubled even after years if dual therapy had been given for as short as a few weeks (Phillips 2002).

Thus, initiating triple therapy only gradually, as is sometimes practiced due to concern over too many side effects, is wrong and dangerous.

### Avoidable mistakes in primary therapy

- Mono- or dual therapy (except in controlled trials), as well as a “slow” introduction of therapy – always start with a complete HAART regimen!
- Lowering the doses at the beginning (with the exception of nevirapine!)
- T-20, delavirdine, tipranavir (not licensed for primary therapy)
- ddC (HIVID™), SQV-SGC (Fortovase™), amprenavir (Agenerase™) – distribution has been partially stopped
- Ritonavir (not tolerated – only for use as booster)
- AZT+d4T and 3TC+FTC (antagonistic effects)
- TDF+ddI (diverse reasons), d4T+ddI (too toxic)
- TDF in triple nuke therapy (especially without thymidine analogs)
- Simultaneous introduction of ABC and NNRTIs (allergy potential)
- Efavirenz+nevirapine (too toxic)

### References

1. Ait-Khaled M, Rakik A, Griffin P, et al. Mutations in HIV-1 reverse transcriptase during therapy with abacavir, lamivudine and zidovudine in HIV-1-infected adults with no prior antiretroviral therapy. *Antivir Ther* 2002, 7:43-51. <http://amedeo.com/lit.php?id=12008787>
2. Allavena C, Ferre V, Brunet-Francois C, et al. Efficacy and tolerability of a nucleoside reverse transcriptase inhibitor-sparing combination of lopinavir/ritonavir and efavirenz in HIV-1-infected patients. *J AIDS* 2005, 39:300-6. 15980689
3. Ananworanich J, Hill A, Siangphoe U, Ruxrungtham K, et al. A prospective study of efficacy and safety of once-daily saquinavir/ritonavir plus two nucleoside reverse transcriptase inhibitors in treatment-naïve Thai patients. *Antivir Ther* 2005, 10:761-7.
4. Antoniou T, Tseng AL. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002, 36:1598-613. <http://amedeo.com/lit.php?id=12243611>
5. Barrios A, Rendon A, Negredo E, et al. Paradoxical CD4+ T-cell decline in HIV-infected patients with complete virus suppression taking tenofovir and didanosine. *AIDS* 2005;19:569-575. <http://amedeo.com/lit.php?id=15802975>
6. Bartlett JA, Johnson J, G Herrera G, et al. Initial therapy with abacavir+lamivudine combined with efavirenz, amprenavir/ritonavir or stavudine: ESS40001(CLASS). Abstract TuPeB4544, XV World AIDS Conference 2004, Bangkok
7. Boyd M, Bien D, van Warmerdam P, et al. Lipodystrophy in patients switched to indinavir/ritonavir 800/100 mg BID and efavirenz 600 mg QD after failing nucleoside combination therapy. Abstract 738, 10th CROI 2003, Boston.
8. Boyd MA, Siangphoe U, Ruxrungtham K, et al. Indinavir/ritonavir 800/100 mg bid and efavirenz 600 mg qd in patients failing treatment with combination nucleoside reverse transcriptase inhibitors: 96-week outcomes of HIV-NAT 009. *HIV Med* 2005, 6:410-20.

9. Boyd MA, Aarnoutse RE, Ruxrungtham K, et al. Pharmacokinetics of indinavir/ritonavir (800/100 mg) in combination with efavirenz (600 mg) in HIV-1-infected subjects. *J AIDS* 2003; 34:134-9. <http://amedeo.com/lit.php?id=14526202>
10. Cameron DW, Becker S, Eron J, et al. Comparative safety and anti-HIV activity of a dual protease inhibitor (PI) regimen (lopinavir/ritonavir (LPV/r) + saquinavir (SQV)) versus a nucleoside-containing regimen. Abstract H-523, 45th ICAAC 2005, Washington.
11. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998, 351:543-9. <http://amedeo.com/lit.php?id=9492772>
12. Claxton AJ, Cramer J, Pierce C. A systematic review of the associations between dose regimens and medication compliance. *Clin Ther* 2001, 23:1296-310. <http://amedeo.com/lit.php?id=11558866>
13. Cohen C, Shen Y, Rode R, et al. Effect of Nucleoside (NRTI) intensification on prevalence of morphologic abnormalities (moas) at year 5 of ritonavir plus saquinavir therapy in an HIV-infected cohort. Abstract 683, 9th CROI 2002, Seattle, USA.
14. Cooper D, Yeni P. Virological and immunological outcomes at 3 years following initiation of ART with regimens containing a NNRTI or PI or both: The INITIO Trial. Abstract 165B, 12th CROI 2005, Boston.
15. D'Aquila RT, Hughes MD, Johnson VA, et al. Nevirapine, zidovudine, and didanosine compared with zidovudine and didanosine in patients with HIV-1 infection. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996, 124:1019-30. <http://amedeo.com/lit.php?id=8633815>
16. DeJesus E, Elion R, Cohen C, et al. Week 24 analysis of one-daily (QD) Trizivir (TZV) and Tenofovir DF (TDF) in antiretroviral naive subjects (COL40263). Abstract H-564, 44th ICAAC 2004, Washington.
17. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis* 2004, 39:1038-46. <http://amedeo.com/lit.php?id=15472858>
18. Den Brinker M, Wit FW, Wertheim-van Dillen PM, et al. Hepatitis B and C virus co-infection and the risk for hepatotoxicity of HAART in HIV-1 infection. *AIDS* 2000, 14: 2895-902. <http://amedeo.com/lit.php?id=11153671>
19. Dragstedt UB, Gerstoft J, Pedersen C, et al. Randomised trial to evaluate indinavir/ritonavir versus saquinavir/ritonavir in human HIV type-1 infected patients: the MaxCmin1 trial. *J Inf Dis* 2003, 188:635-42. <http://amedeo.com/lit.php?id=12934178>
20. Elston RC, Yates P, Tisdale M, et al. GW433908 (908)/ritonavir (r): 48-week results in PI-experienced subjects: A retrospective analysis of virological response based on baseline genotype and phenotype. Abstract MoOrB1055, XV Int AIDS Conf 2004; Bangkok.
21. Eron JJ, Feinberg J, Kessler HA, et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naive HIV-positive patients: a 48-week randomized clinical trial. *J Inf Dis* 2004, 189:265-72. <http://amedeo.com/lit.php?id=14722892>
22. Fichtenbaum CJ, Gerber JG, Rosenkranz SL, et al. Pharmacokinetic interactions between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002, 16:569-77. <http://amedeo.com/lit.php?id=11873000>
23. Fischl MA, Ribaldo HJ, Collier AC, et al. A randomized trial of 2 different 4-drug antiretroviral regimens versus a 3-drug regimen, in advanced human immunodeficiency virus disease. *J Infect Dis* 2003; 188:625-34. <http://amedeo.com/lit.php?id=12934177>
24. French M, Amin J, Roth N, et al. Randomized, open-label, comparative trial to evaluate the efficacy and safety of three antiretroviral drug combinations including two nucleoside analogues and nevirapine for previously untreated HIV-1 infection: the OzCombo 2 study. *HIV Clin Trials* 2002, 3:177-85. <http://amedeo.com/lit.php?id=12032876>
25. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006, 354:251-60. <http://amedeo.com/lit.php?id=16421366>
26. Gallant JE, Rodriguez AE, Weinberg WG, et al. Early virologic nonresponse to tenofovir, abacavir, and lamivudine in HIV-infected antiretroviral-naive subjects. *J Infect Dis* 2005, 192:1921-30. <http://amedeo.com/lit.php?id=16267763>
27. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA*. 2004, 292: 191-201. <http://amedeo.com/lit.php?id=15249568>
28. Gartland M. AVANTI 3: a randomized, double-blind trial to compare the efficacy and safety of lamivudine plus zidovudine versus lamivudine plus zidovudine plus nelfinavir in HIV-1-infected antiretroviral-naive patients. *Antivir Ther* 2001, 6:127-34. <http://amedeo.com/lit.php?id=11491417>
29. Gathe JC Jr, Ive P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naive HIV-1-infected patients. *AIDS* 2004, 18:1529-37. <http://amedeo.com/lit.php?id=15238771>

30. Gathe JC Jr, Washington MY, Mayberry C, et al. IMANI-1 TC3WP Single drug HAART- proof of concept study. Pilot study of the safety and efficacy of Kaletra (LPV/r) as single drug HAART in HIV + ARV-naive patients-interim analysis of subjects completing final 48 week data. Abstract MoOrB1057, XV Int AIDS Conf 2004, Bangkok.
31. Gerstoft J, Kirk O, Obel N, et al. Low efficacy and high frequency of adverse events in a randomized trial of the triple nucleoside regimen abacavir, stavudine and didanosine. AIDS 2003, 17:2045-2052. <http://amedeo.com/lit.php?id=14502007>
32. Gibbon S, Dickinson L, Boffito M. Is once-daily dosing of protease inhibitors associated with decreased tolerance for missed or late doses? Abstract PE4.1/8, 10th EACS 2005, Dublin
33. Gisolf EH, Jurriaans S, Pelgrom J, et al. The effect of treatment intensification in HIV-infection: a study comparing treatment with ritonavir/saquinavir and ritonavir/saquinavir/stavudine. Prometheus Study Group. AIDS 2000, 14:405-13. 10770543
34. Gulick R, Ribaudo H, Shikuma C, et al. ACTG 5095: Zidovudine/lamivudine/abacavir vs zidovudine/lamivudine + efavirenz vs zidovudine/lamivudine/abacavir + efavirenz for initial HIV therapy. Abstract H416a, 45th ICAAC 2005, Washington.
35. Gulick RM, Meibohm A, Havlir D, et al. Six-year follow-up of HIV-1-infected adults in a clinical trial of antiretroviral therapy with indinavir, zidovudine, and lamivudine. AIDS 2003; 17:2345-2349. <http://amedeo.com/lit.php?id=14571186>
36. Gulick RM, Mellors JW, Havlir D, et al. Simultaneous vs sequential initiation of therapy with indinavir, zidovudine, and lamivudine for HIV-1 infection: 100-week follow-up. JAMA 1998, 280:35-41. <http://amedeo.com/lit.php?id=9660361>
37. Gulick RM, Mellors JW, Havlir D, et al. Treatment with indinavir, zidovudine, and lamivudine in adults with HIV infection and prior antiretroviral therapy. N Engl J Med 1997, 337: 734-9. <http://amedeo.com/lit.php?id=9287228>
38. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. N Engl J Med. 2004, 350:1850-1861. <http://amedeo.com/lit.php?id=15115831>
39. Hales G, Roth N, Smith D. Possible fatal interaction between protease inhibitors and methamphetamine. Antivir Ther 2000, 5:19.
40. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. N Engl J Med 1997, 337: 725-33. <http://amedeo.com/lit.php?id=9287227>
41. Hare CB, Vu MP, Grunfeld C, Lampiris HW. Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. Clin Infect Dis 2002; 35: e111-2. <http://amedeo.com/lit.php?id=12410494>
42. Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. Arch Intern Med 1999, 159:2221-4. <http://amedeo.com/lit.php?id=10527300>
43. Harris M, Ochoa C, Allavena C, et al. NRTI sparing trial (CTN 177): antiviral and metabolic effects of nevirapine (NVP) + lopinavir/ritonavir (LPV/r) vs. zidovudine/lamivudine (AZT/3TC) + NVP vs. AZT/3TC + LPV/r. Abstract WePe6.3C14, 3rd IAS 2005, Rio de Janeiro.
44. Harris M. Evaluation of the pharmacokinetics of the concurrent administration of two NNRTIs, nevirapine/delavirdine and nevirapine/efavirenz, in patients receiving multi-drug rescue therapy. Abstract 14, 3rd Int Workshop Salvage Ther HIV Inf 2000, Chicago, USA.
45. Havlir DV, Tierney C, Friedland GH, et al. In vivo antagonism with zidovudine plus stavudine combination therapy. J Infect Dis 2000, 182:321-5. <http://amedeo.com/lit.php?id=10882616>
46. Hellinger J, Cohen C, Morris A, et al. Pilot study of saquinavir and lopinavir/ritonavir twice daily in protease inhibitor-naive HIV-positive patients. HIV Clin Trials 2005, 6:107-17. 15983895
47. Henry JA, Hill IR. Fatal interaction between ritonavir and MDMA. Lancet 1998, 352:1751-2.
48. Henry K, Erice A, Tierney C, et al. A randomized, controlled, double-blind study comparing the survival benefit of four different reverse transcriptase inhibitor therapies (three-drug, two-drug, and alternating drug) for the treatment of advanced AIDS. ACTG 193A Study Team. J AIDS Hum Retroviral 1998, 19:339-49. <http://amedeo.com/lit.php?id=9833742>
49. Hicks C, Da Silva B, King KR, et al. 5-Year results of lopinavir/ritonavir (LPV/r)-based therapy in antiretroviral-naïve HIV-Infected Patients. Abstract 7.3/16, 9th EACS 2003, Warsaw, Poland.
50. Hoogewerf M, Regez RM, Schouten WE, Weigel HM, Frissen PH, Brinkman K. Change to abacavir-lamivudine-tenofovir combination treatment in patients with HIV-1 who had complete virological suppression. Lancet 2003; 362:1979-80. <http://amedeo.com/lit.php?id=14683659>
51. Hugen PW, Burger DM, ter Hofstede HJ, et al. Dose-finding study of a once-daily indinavir/ritonavir regimen. J Acquir Immune Defic Syndr 2000, 25: 236-45. <http://amedeo.com/lit.php?id=11115954>

52. Jemsek J, Hutcherson P, Harper E. Poor virologic responses and early emergence of resistance in treatment naive, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir DF. Abstract 51, 11th CROI 2004, San Francisco.
53. Jordan R, Gold L, Cummins C, Hyde C. Systematic review and meta-analysis of evidence for increasing numbers of drugs in antiretroviral combination therapy. *BMJ* 2002, 324:757. <http://amedeo.com/lit.php?id=11923157>
54. Kakuda TN, Anderson PL, Becker SL. CD4 cell decline with didanosine and tenofovir and failure of triple nucleoside/nucleotide regimens may be related. *AIDS* 2004;18:2442-4. <http://amedeo.com/lit.php?id=15622326>
55. Katzenstein TL, Kirk O, Pedersen C, et al. The danish protease inhibitor study: a randomized study comparing the virological efficacy of 3 protease inhibitor-containing regimens for the treatment of HIV type 1 infection. *JID* 2000, 182:744-50. <http://amedeo.com/lit.php?id=10950767>
56. Khanlou H, Yeh V, Guyer B, Farthing C. Early virologic failure in a pilot study evaluating the efficacy of once-daily abacavir, lamivudine, and tenofovir in treatment-naive HIV-infected patients. *AIDS Pat Care STD* 2005, 19:135-40. <http://amedeo.com/lit.php?id=15798380>
57. Kosel BW, Aweeka FT, Benowitz NL, et al. The effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir. *AIDS* 2002, 16:543-50. <http://amedeo.com/lit.php?id=11872997>
58. Kumar PN, Rodriguez-French A, Thompson MA, et al. A prospective, 96-week study of the impact of Trizivir, Combivir/nelfinavir, and lamivudine/stavudine/nelfinavir on lipids, metabolic parameters and efficacy in antiretroviral-naive patients: effect of sex and ethnicity. *HIV Med* 2006, 7:85-98. <http://amedeo.com/lit.php?id=16420253>
59. la Porte CJ, Schippers EF, van der Ende ME, et al. Pharmacokinetics of once-daily lopinavir/ritonavir and the influence of dose modifications. *AIDS* 2005, 19:1105-7.
60. Lacombe K, Pacanowski J, Meynard JL, et al. Risk factors for CD4 lymphopenia in patients treated with a tenofovir/didanosine high dose-containing highly active antiretroviral therapy regimen. *AIDS* 2005, 19:1107-8.
61. Landman R, Descamps D, Peytavin G, et al. early virologic failure and rescue therapy of tenofovir, abacavir, and lamivudine for initial treatment of HIV-1 Infection: TONUS Study. *HIV Clin Trials* 2005, 6:291-301. <http://amedeo.com/lit.php?id=16452063>
62. Langford D, Adame A, Grigorian A, et al. Patterns of selective neuronal damage in methamphetamine-user AIDS patients. *J AIDS* 2003, 34:467-74. <http://amedeo.com/lit.php?id=14657756>
63. Launay O, Gerard L, Morand-Joubert L, et al. Nevirapine or lamivudine plus stavudine and indinavir: examples of 2-class versus 3-class regimens for the treatment of HIV type 1. *Clin Infect Dis* 2002; 35: 1096-105. <http://amedeo.com/lit.php?id=12384844>
64. Leon A, Martinez E, Mallolas J, et al. Early virological failure in treatment-naive HIV-infected adults receiving didanosine and tenofovir plus efavirenz or nevirapine. *AIDS* 2005, 19:213-5. <http://amedeo.com/lit.php?id=15668550>
65. Llibre JM, Romeu J, Lopez E, Sirera G. Severe interaction between ritonavir and acenocoumarol. *Ann Pharmacother* 2002, 36:621-3. <http://amedeo.com/lit.php?id=11918509>
66. Lopez-Cortes LF, Ruiz-Valderas R, Viciano P, et al. Once-daily saquinavir-sgc plus low-dose ritonavir (1200/100 mg) in combination with efavirenz: pharmacokinetics and efficacy in HIV-infected patients with prior antiretroviral therapy. *J AIDS* 2003, 32:240-2.
67. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS* 2005, 19:1183-8. <http://amedeo.com/lit.php?id=15990571>
68. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001, 15:1261-8. <http://amedeo.com/lit.php?id=11426070>
69. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet* 2004, 364:65-7. <http://amedeo.com/lit.php?id=15234858>
70. Martinez-Picado J, Negro E, Ruiz L, et al. Alternation of antiretroviral drug regimens for HIV infection. A randomized, controlled trial. *Ann Intern Med* 2003; 139: 81-9. <http://amedeo.com/lit.php?id=12859157>
71. Masia M, Gutierrez F, Padilla S, et al. Severe toxicity associated with the combination of tenofovir and didanosine: case report and review. *Int J STD AIDS* 2005, 16:646-8. <http://amedeo.com/lit.php?id=16176639>
72. Matheron S, Descamps D, Boue F, et al. Triple nucleoside combination zidovudine/lamivudine/abacavir versus zidovudine/lamivudine/nelfinavir as first-line therapy in HIV-1-infected adults: a randomized trial. *Antivir Ther* 2003, 8:163-71. <http://amedeo.com/lit.php?id=12741629>

73. Mauss S, Milinkovic A, Hoffmann C, et al. Low rate of treatment failure on antiretroviral therapy with tenofovir, lamivudine and zidovudine. *AIDS* 2005 (in press)
74. McCance-Katz EF, Rainey PM, Friedland G, Jatlow P. The protease inhibitor lopinavir-ritonavir may produce opiate withdrawal in methadone-maintained patients. *Clin Infect Dis* 2003; 37: 476-82. <http://amedeo.com/lit.php?id=12905130>
75. Molina JM, Gathe J, Lim JL, et al. Comprehensive resistance testing in antiretroviral naive patients treated with once-daily lopinavir/ritonavir plus tenofovir and emtricitabine: 48-week results from study 418. Abstract WePeB5701, XV Int AIDS Conf 2004, Bangkok.
76. Montaner JS, Reiss P, Cooper D, et al. A randomized, double-blind trial comparing combinations of nevirapine, didanosine, and zidovudine for HIV-infected patients: the INCAS Trial. *JAMA* 1998, 279: 930-7. <http://amedeo.com/lit.php?id=9544767>
77. Moyle G, Higgs C, Teague A, et al. An open-label, randomized comparative pilot study of a single-class quadruple therapy regimen versus a 2-class triple therapy regimen for individuals initiating antiretroviral therapy. *Antivir Ther* 2006, 11:73-8
78. Moyle G, Pozniak A, Opravil M, et al. The SPICE study: 48-week activity of combinations of saquinavir soft gelatin and nelfinavir with and without nucleoside analogues. *J Acquir Immune Defic Syndr* 2000, 23: 128-37. <http://amedeo.com/lit.php?id=10737427>
79. Moyle G. The Assessing Patients' Preferred Treatments (APPT-1) study. *Int J STD AIDS*. 2003, 1:34-6. <http://amedeo.com/lit.php?id=14617402>
80. Moyle GJ, Dejesus E, Cahn P, et al. Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naive HIV-infected adults: results of the ziagen once daily in antiretroviral combination study. *J AIDS* 2005, 38:417-425. <http://amedeo.com/lit.php?id=15764958>
81. Olsen CH, Gatell J, Ledergerber B, et al. Risk of AIDS and death at given HIV-RNA and CD4 cell count, in relation to specific antiretroviral drugs in the regimen. *AIDS* 2005, 19:319-330. <http://amedeo.com/lit.php?id=15718843>
82. Orkin C, Stebbing J, Nelson M, et al. A randomized study comparing a three- and four-drug HAART regimen in first-line therapy (QUAD study). *J Antimicrob Chemother* 2005, 55:246-51 <http://amedeo.com/lit.php?id=15608053>
83. Pardo REY C, Yebra M, Borralló M, et al. Irreversible coma, ergotamine, and ritonavir. *Clin Infect Dis* 2003; 37: e72-3. <http://amedeo.com/lit.php?id=12942422>
84. Perez-Elias MJ, Moreno S, Gutierrez C, et al. High virological failure rate in HIV patients after switching to a regimen with two nucleoside reverse transcriptase inhibitors plus tenofovir. *AIDS* 2005, 19:695-8. <http://amedeo.com/lit.php?id=15821395>
85. Phillips AN, Staszewski S, Lampe F, et al. HIV rebound after suppression to <400 copies/mL during initial HAART regimens, according to prior nucleoside experience and duration of suppression. *J Infect Dis* 2002; 186:1086-91. <http://amedeo.com/lit.php?id=12355358>
86. Piscitelli SC, Burstein AH, Welden N, Gallicano KD, Falloon J. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis* 2002; 34:234-8. <http://amedeo.com/lit.php?id=11740713>
87. Podzamczar D, Ferrer E, Consiglio E, et al. A randomized clinical trial comparing nelfinavir or nevirapine associated to zidovudine/lamivudine in HIV-infected naive patients (the Combine Study). *Antivir Ther* 2002, 7:81-90. <http://amedeo.com/lit.php?id=12212928>
88. Podzamczar D, Ferrer E, Gatell JM, et al. Early virologic failure with a combination of tenofovir, didanosine and efavirenz. *Antiviral Therapy* 2004. [http://www.informedhorizons.com/resistance2004/Posters/POSTERS/Podzamczar\\_POSTER\\_Resist%20ININ%202004.pdf](http://www.informedhorizons.com/resistance2004/Posters/POSTERS/Podzamczar_POSTER_Resist%20ININ%202004.pdf)
89. Podzamczar D, Ferrer E, Gatell JM, et al. Early virological failure with a combination of tenofovir, didanosine and efavirenz. *Antivir Ther* 2005, 10:171-7. <http://amedeo.com/lit.php?id=>
90. Podzamczar D, Ferrer E, Sanchez P, et al. Toxicity and Efficacy of 3TC/EFV Associated with Stavudine or Abacavir in Antiretroviral-naive Patients: 48-week Results of a Randomized Open and Multicenter Trial (ABCDE Study). Abstract 716, 11th CROI 2004, San Francisco.
91. Pollard RB, Tierney C, Havlir D, et al. A phase II randomized study of the virologic and immunologic effect of zidovudine + stavudine versus stavudine alone and zidovudine + lamivudine in patients with >300 CD4 cells who were antiretroviral naive (ACTG 298). *AIDS Res Hum Retroviruses* 2002, 18:699-704. <http://amedeo.com/lit.php?id=12167276>
92. Raboud JM, Rae S, Vella S, et al. Meta-analysis of two randomized controlled trials comparing combined zidovudine and didanosine therapy with combined zidovudine, didanosine, and nevirapine therapy in patients with HIV. *J AIDS* 1999, 22:260-6. <http://amedeo.com/lit.php?id=10770346>
93. Ramratnam B, Ribeiro R, He T, et al. Intensification of antiretroviral therapy accelerates the decay of the HIV-1 latent reservoir and decreases, but does not eliminate, ongoing virus replication. *J AIDS* 2004, 35:33-7. <http://amedeo.com/lit.php?id=14707789>

94. Robbins GK, De Gruttola V, Shafer RW, et al. Comparison of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349: 2293-303. <http://amedeo.com/lit.php?id=14668455>
95. Rodriguez-French A, Boghossian J, Gray GE, et al. The NEAT study: a 48-week open-label study to compare the antiviral efficacy and safety of GW433908 versus nelfinavir in antiretroviral therapy-naive HIV-1-infected patients. *J AIDS* 2004, 35:22-32. <http://amedeo.com/lit.php?id=14707788>
96. Shafer RW, Smeaton LM, Robbins GK, et al. Comparison of four-drug regimens and pairs of sequential three-drug regimens as initial therapy for HIV-1 infection. *N Engl J Med* 2003; 349: 2304-15. <http://amedeo.com/lit.php?id=14668456>
97. Slain D, Amsden JR, Khakoo RA, Effect of high-dose vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. *Pharmacotherapy* 2005, 25:165-70. <http://amedeo.com/lit.php?id=15767232>
98. Smith PF, Kearney BP, Liaw S, et al. Effect of tenofovir disoproxil fumarate on the pharmacokinetics and pharmacodynamics of total, R-, and S-methadone. *Pharmacotherapy* 2004, 24:970-7. <http://amedeo.com/lit.php?id=15338845>
99. Staszewski I S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA* 2001, 285: 1155-63. <http://amedeo.com/lit.php?id=11231744>
100. Staszewski S, Haberl A, Carlebach A, et al. A simple, once-daily dosing regimen for treating HIV-1 infection in intravenous drug users. *HIV Med* 2000, 1:162-3. <http://amedeo.com/lit.php?id=11737345t>
101. Staszewski S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral naive HIV-infected adults: a randomized equivalence trial. *JAMA* 2001, 285: 1155-1163. <http://amedeo.com/lit.php?id=11231744>
102. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 1999, 341:1865-73. <http://amedeo.com/lit.php?id=10601505>
103. Staszewski S, Stark T, Knecht G, et al. The Quad study: A pilot-study to assess the efficacy and safety of trizivir + RTV-boosted saquinavir compared to combivir + RTV-boosted saquinavir in ART-naive patients with high viral load and low CD4 count. Abstract 1/1, 9th EACS 2003, Warsaw, Poland.
104. Stek M Jr, Hirschel B, Benetucci J, et al. Comparison of PI-boosted indinavir with efavirenz plus stavudine regimens in easier (European and South American study of indinavir, efavirenz, and ritonavir). Abstract 39, 2nd IAS 2003, Paris.
105. Stellbrink HJ, Hawkins DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients. *Clin Drug Invest* 2000, 20:295-307.
106. Stevens RC, Rapaport S, Maroldo-Connolly L, Patterson JB, Bertz R. Lack of methadone dose alterations or withdrawal symptoms during therapy with lopinavir/ritonavir. *J AIDS* 2003; 33: 650-1.
107. Stone VE, Jordan J, Tolson J, Miller R, Pilon T. Perspectives on adherence and simplicity for HIV-infected patients on antiretroviral therapy: self-report of the relative importance of multiple attributes of HAART regimens in predicting adherence. *J AIDS* 2004, 36:808-816. <http://amedeo.com/lit.php?id=15213564>
108. Sulkowski MS, Mehta SH, Chaisson RE, Thomas DL, Moore RD. Hepatotoxicity associated with protease inhibitor-based antiretroviral regimens with or without concurrent ritonavir. *AIDS* 2004, 18:2277-84.
109. Sulkowski MS, Thomas DL, Chaisson RE, Moore RD. Hepatotoxicity associated with antiretroviral therapy in adults infected with HIV and the role of hepatitis C or B virus infection. *JAMA* 2000, 283: 74-80. <http://amedeo.com/lit.php?id=10632283>
110. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated with nevirapine or efavirenz-containing antiretroviral therapy: role of hepatitis C and B infections. *Hepatology* 2002, 35:182-9. <http://amedeo.com/lit.php?id=1178697>
111. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naive patients: a randomized trial. *JAMA* 2004, 292:180-9. <http://amedeo.com/lit.php?id=15249567>
112. Saag MS, Tebas P, Sension M, et al. Randomized, double-blind comparison of two nelfinavir doses plus nucleosides in HIV-infected patients (Agouron study 511). *AIDS* 2001, 15:1971
113. Torti C, Quiros-Roldon E, Regazzi M, et al. Early virological failure after tenofovir + didanosine + efavirenz combination in HIV-positive patients upon starting antiretroviral therapy. *Antivir Ther* 2005, 10:505-13. <http://amedeo.com/lit.php?id=16038476>
114. van der Valk M, Gisolf EH, Reiss P, et al. Increased risk of lipodystrophy when nucleoside analogue reverse transcriptase inhibitors are included with protease inhibitors in the treatment of HIV-1 infection. *AIDS* 2001, 15:847-55.

115. van Heeswijk RP, Veldkamp AI, Mulder JW, et al. The steady-state pharmacokinetics of nevirapine during once daily and twice daily dosing in HIV-1-infected individuals. *AIDS* 2000, 14:F77-82. <http://amedeo.com/lit.php?id=10853971>
116. van Leeuwen R, Katlama C, Murphy RL, et al. A randomized trial to study first-line combination therapy with or without a protease inhibitor in HIV-1-infected patients. *AIDS* 2003, 17:987-99. <http://amedeo.com/lit.php?id=12700448>
117. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004, 363:1253-63. <http://amedeo.com/lit.php?id=15094269>
118. van Lunzen J, Schewe K, Kuhlmann B, et al. High rate of virological failure during once daily therapy with tenofovir + didanosine 250 mg + efavirenz in antiretroviral-naive patients--results of the 12-week interim analysis of the TEDDI trial. Abstract TuPp0306, 3rd IAS 2005, Rio de Janeiro.
119. Veldkamp AI, Harris M, Montaner JS, et al. The steady-state pharmacokinetics of efavirenz and nevirapine when used in combination in HIV type 1-infected persons. *J Infect Dis* 2001, 184: 37-42. <http://amedeo.com/lit.php?id=11398107>
120. Vibhagool A, Cahn P, Schechter M, et al. Triple nucleoside treatment with abacavir plus the lamivudine/zidovudine combination tablet (COM) compared to indinavir/COM in antiretroviral therapy-naive adults: results of a 48-week open-label, equivalence trial (CNA3014). *Curr Med Res Opin* 2004, 20:1103-14. <http://amedeo.com/lit.php?id=15265255>
121. Walmsley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med* 2002, 346:2039-46. <http://amedeo.com/lit.php?id=12087139>
122. Williams I, Asboe D, Babiker A, et al. A virological benefit from an induction/maintenance strategy compared with a standard 3-drug regimen in antiretroviral naive patients: the FORTE trial. Abstract 564, 11th CROI 2004, San Francisco.
123. Louie M, Hogan C, Di Mascio M, Hurley A, et al. Determining the relative efficacy of highly active antiretroviral therapy. *J Infect Dis* 2003, 187:896-900.

## 7. When to change HAART

Christian Hoffmann, Fiona Mulcahy

HAART is changed for three main reasons:

1. Acute side effects
2. Long-term toxicity (or concern regarding this)
3. Virological treatment failure

Changes in antiretroviral therapy are very common, especially within the first or second year. Treatment modification is required in approximately 50 % of patients within the first year. In an English cohort, 44 % of patients had had their regimen modified by 14 months (Mocroft 2001); in a German study, 53 % of patients had changed drugs after one year (Fätkenheuer 2001). The reasons were mainly due to adverse drug events. If side effects do not occur, the rate of switching drugs is significantly less. In an Italian cohort, it was less than 10 % within the first year (d'Arminio Monforte 2000).

### Change due to acute side effects

Not every acute side effect requires immediate modification of HAART. A bit of nausea or diarrhea in the beginning can and should be tolerated. One should always remember that the number of available drugs is limited. Gastrointestinal side effects that occur during the first weeks are not dangerous and often improve spontaneously or can be treated symptomatically. The same is true for some allergic reactions and for relatively mild CNS disorders with efavirenz (mild allergies). However, certain adverse drug events almost always require discontinuation or changing of HAART. These include:

#### Side effects that almost always require discontinuation or changing of HAART

- Severe diarrhea, which persists despite loperamide even after several weeks (usually due to nelfinavir, lopinavir, saquinavir)
- Severe nausea, which persists despite metoclopramide, which requires continuous treatment or leads to significant weight loss (usually AZT, ddI)
- Polyneuropathy (d4T, ddC, ddI, possibly also 3TC – often resolves very slowly, therefore change treatment quickly!)
- Severe anemia (AZT)
- Severe, progressive muscular weakness (d4T!, ddI!)
- Pancreatitis (ddI, ddI+TDF!, d4T+ddI+HU! In rare cases lopinavir/r)
- Lactic acidosis (most often d4T+ddI, but also all other NRTIs)
- Severe allergies with involvement of mucous membranes, fever (typically abacavir, NNRTIs, more rarely fosamprenavir)
- Renal failure (tenofovir, indinavir)
- Nephrolithiasis or recurring renal colic (indinavir)
- Hepatotoxicity with transaminases > 5 x normal values (nevirapine, tipranavir)
- Jaundice (nevirapine, atazanavir, indinavir, tipranavir)
- Severe repetitive onychitis (indinavir, possibly also 3TC)
- Psychosis (efavirenz, possibly also AZT)



## Change due to concern over long-term toxicity

In the last few years, many clinicians have started to change virologically successful combinations out of concern for cumulative long-term toxicities (especially lipodystrophy and dyslipidemia). In particular PI- and d4T-containing combinations are sometimes replaced with NNRTIs and other nucleoside analogs. A large number of switch studies have appeared in the last few years on this topic. The most important studies are discussed below.

### PI replacement

One main conclusion can be drawn from the studies on PI-switch: switching to NNRTI-containing regimens for reasons of existing or possible long-term toxicity is virologically safe, if the viral load is well suppressed (see Table 7.1).

However, one meta-analysis indicated that switching to an NNRTI may have some immunological disadvantages, as CD4+ T-cells possibly increase slightly less on non-PI regimens (Owen 2004).

Lipid levels are most likely to improve after switching to abacavir, and least likely to do so on efavirenz. Whether lipodystrophy really improves after stopping a PI is still unclear. There seem to be subjective improvements, but these are difficult to quantify.

Switching from a PI to abacavir poses an increased risk of virological failure, particularly with prior nucleoside analog treatment and the associated resistance mutations. Potential side effects also need to be considered with every switch: a rash or hepatotoxicity can be expected with nevirapine, and efavirenz may be associated with adverse CNS events. There is the risk of a hypersensitivity reaction with abacavir, the frequency of which reached a considerable 10 % in the TRIZAL Study (Katlama 2003).

Quality of life improved significantly in the switch arms of most studies, probably due to the reduced pill burden.

### d4T replacement

The thymidine analog d4T, which plays a leading role in mitochondrial toxicity (see corresponding chapter), is also frequently replaced with other nucleoside analogs. Such switch studies have however been smaller, and often inconsistent – sometimes PIs were replaced at the same time (see Table 7.2).

Despite their heterogeneity, most studies show that lipodystrophy improves if d4T is replaced by abacavir, for example. In particular, the subcutaneous fat of the limbs increases, although at first the improvement is often unrecognizable clinically and can only be detected in DEXA scans (Martin 2004). Histological investigations have shown that the elevated rate of apoptosis in adipocytes normalizes when d4T has been replaced (Cherry 2005, McComsey 2005).

Based on the available data, it seems to be advisable to replace d4T with another nucleoside analogs.

With abacavir, however, the HSR remains a problem, occurring in 10 % of patients in the Mitox Study (Carr 2002). It should also be noted that it is never certain

whether the viral suppression will be sufficient under a new regimen. Particular caution has to be taken when there has been long-term pretreatment. One example of what could happen when the drug is changed for strategic reasons is shown in Table 7.3.

Table 7.1: Randomized studies on switching from PIs to other drugs

Source	N	Wk	VL Effect	Effect of switch on lipids (L) or lipodystrophy (LD)
<b>PI → NVP</b>				
Barreiro 2000	138	24	Advantage	L unchanged, LD better
Ruiz 2001	106	48	n.s.	L possibly better, LD unchanged
Arranz-Caso 2005	160	48	n.s.	L better, LD better
<b>PI → EFV</b>				
Katlama 2000	134	48	n.s.	L unchanged, LD n.a.
Becker 2001	346	48	Advantage	L unchanged
Molina 2005	355	48	Advantage	L/LD n.a., side effects similar
<b>PI → ABC</b>				
Clumeck 2001	211	24	Advantage	L better, LD subjectively better
Keiser 2002	104	28	n.s.	L better
Opravil 2002	163	84	Disadvantage (trend)	L better, LD unchanged
Lafeuillade 2003	209*	48	n.s.	L better, LD better
<b>PI → EFV v NVP</b>				
Negredo 2002	77	48	n.s.	L only better on NVP, LD unchanged
Calza 2005	130	48	n.s.	L actually worse, if the PI-arm contained lipid reducer
<b>PI → EFV v NVP v ABC</b>				
Martinez 2003	460	48	Trend against ABC	L only better on ABC. LD probably unchanged

In all studies (except Martinez 2003), randomization was against continuing PIs. All had an open-label design and all patients had been on PIs for several months at the time of the switch, with undetectable viral load. VL = viral load in the switch arm versus the continuing arm. Wk = weeks, LD = lipodystrophy, L = lipids, n.a. = not available, n.s. = not significant.

\*Here only 62 % of patients were taking a PI, the rest were on NNRTIs or triple nuke.

Table 7.2: Randomized studies on switching from d4T to other drugs

Source	N	Switch	Wk	Effect of switch
Carr 2002 Martin 2004	106	ABC instead of d4T or AZT	104	LA better, lipids unchanged
John 2003	37	AZT instead of d4T and ABC instead of PI	48	LA of limbs slightly better, lipids and abdominal fat unchanged
Moyle 2003	30	ABC instead of d4T or PI/NNRTI, or AZT+ABC instead of d4T+PI	48	LA better (when replacing d4T) Lipids better (when replacing PI)
McComsey 2004*	118	AZT or ABC instead of d4T	48	LA better, lactate better
Moyle 2005	105	TDF or ABC instead of d4T or AZT	48	LA better, lipids better on TDF
Murphy 2006	101	ABC or NS instead of d4T or AZT	48	LA better

No study showed any difference with respect to virological failure. Wk = weeks, LA = lipoatrophy, NS = nuke sparing. In McComsey 2004 and Moyle 2005: only patients with LA were investigated.

\* The study was not randomized.

Table 7.3: Example of what could happen on switching drugs. (n.k. = not known)

Date	(HA)ART	CD4 cells	Viral load
1996-98	AZT+ddC	n.k.	n.k.
Since 1998	AZT+3TC+NfV (always under the detection limit)	n.k.	n.k.
Nov. 2002	Findings: significant lipoatrophy. Decision to switch	688	< 50
Feb. 2003	<b>ABC</b> +3TC+NfV	788	< 50
Apr. 2003	<b>ABC+TDF+NVP</b> (= targeted regimen, s. notes below)	871	< 50
May 2003	Severe rash, ALT/AST > 500 U/l	n.k.	< 50
Jun. 2003	<b>ABC+TDF+3TC</b>		
Aug. 2003	Resistance: M41L+D67N+M184V+L210W+T215Y	679	37,400
Sep. 2003	<b>AZT</b> +3TC+NfV	n.k.	59,100
Oct. 2003		n.k.	< 50
Oct. 2004		743	< 50

Notes: On account of possible allergies to both ABC and NVP, HAART was changed in February 2003 in two steps. Rash with hepatic involvement did indeed occur on NVP, so that in July 2003, NVP was replaced by 3TC – triple nuke! The resistances that were then detected were almost certainly present under the earlier treatment with AZT+ddC, but sufficiently suppressed by PI therapy. This case shows how careful one must be when switching drugs, if there is a past history of inadequate (duotherapy!) treatment. The ice is thin!

### Switching to tenofovir

Studies on therapy-naïve patients have shown that the short-term toxicity of tenofovir is lower than of d4T or AZT. In the 903 Study tenofovir was tolerated significantly better than d4T (Gallant 2004) – in 934 it was tolerated better than AZT (Gallant 2006). Can switching to tenofovir help to reduce side effects?

First attempts at this have been fairly positive (Haberl 2003, Domingo 2004). In the 903 Study, lipids improved in patients that were switched from d4T to tenofovir (Suleiman 2004). In a retrospective study, replacing d4T with tenofovir improved both lipids and liver enzymes (Schewe 2006). Even the mitochondrial DNA that was depleted by d4T seems to improve (Ribera 2003).

However, so far only a few randomized studies have been performed on switching thymidine analogs to tenofovir. One such study on 105 patients with lipoatrophy, who had the thymidine analog replaced by either tenofovir or abacavir, showed that the lipoatrophy improved to the same extent with tenofovir as with abacavir. After 48 weeks, the clinical changes in both arms were similarly pronounced, but the lipid changes were more significantly improved on tenofovir.

However, in view of the problematic data on triple nuke therapy containing tenofovir (see corresponding section), one should be cautious when making such a switch. The weak efficacy of tenofovir-containing triple nuke regimens are not only noticeable in primary therapy, but also in patients who just simplify their sufficient therapy (Hoogewerf 2003, Perez-Elias 2005). One example of how such an action can go wrong is shown in table 7.3.

In practice, changes are often made, which go further than PI and d4T/AZT simply due to concerns over long-term toxicity. Such switching (e.g. abacavir or tenofovir instead of ddI) is based on laboratory studies showing a certain hierarchy with respect to mitochondrial toxicity (Kakuda 2000, see also chapter on mitochondrial toxicity). In addition, there are an increasing number of reports on simplification of therapy, in which mono- or nuke-sparing strategies are being used (see below).

So far, there is no clear clinical evidence to show that this procedure has any benefit for the patient. Therefore, patients are being subjected, on the basis of theoretical thoughts, to unnecessary risks of increasing viral load and possible resistances.

Therefore, it is currently advisable to wait for the results of the corresponding clinical studies.

## **Virological treatment failure**

Every change in treatment due to virological failure requires experience and a certain degree of finesse. But also decisiveness! There are many possibilities for mistakes here. It is important to explain to the, often skeptical, patient (“Shouldn’t I save other drugs for later?”) when and why changes have to be made.

HAART should be rapidly changed in the case of insufficient viral suppression and/or after an increase in plasma viremia, as suboptimal therapy always carries the risk of new resistance mutations, which may eliminate future treatment options via cross-resistance. First-line therapy with AZT+3TC+indinavir is a good example. If this regimen fails but continues to be taken, the virus may generate typical mutations such as 41L, 67N, 210W, 215F, 184V, 82T, 84V, 46L, 90M – and this eliminates all currently available drugs with the exception of NNRTIs and ddI (and T-20). If an NNRTI is added, it is easy to have no options left at all. Even individual mutations may create significant problems: K65R, which very frequently occurs on failing tenofovir-containing triple nuke therapies, leads to considerable loss of efficacy for ABC, 3TC, FTC and probably ddI.

Viral replication in the presence of insufficient plasma levels is ideal for the development of resistance mutations.

In the case of clear virological failure, action must be taken without delay – the longer one waits, the more difficult things become! Insufficient viral suppression means a viral load above the level of detection of 50 copies/ml. Some clinicians, however, tolerate values up to 500 or even 1,000 copies/ml. In patients with good options for subsequent regimens and good compliance, we consider this delay unwise (with the few exceptions described below). The patient’s frequent argument “But I’m fine!” makes no difference here!

When the first important resistances appear and the child has fallen into the well, the situation suddenly looks different. Currently, several trials are underway to investigate two randomized strategies in patients, in whom several HAART combinations have failed: either change immediately, or when the viral load reaches a certain level (“early versus deferred switch”). The preliminary results indicate that even in such cases, one can wait a short time (Nasta 2006, Riddler 2006).

In cases of clinical treatment failure (disease progression) or immunological failure (stagnation or decrease in the level of CD4+ T-cells), in which the viral load is below 50 copies/ml, the value of a change in therapy is uncertain. Some combinations such as TDF+ddI, however, are rather unfavorable for immunological reconstitution (Negredo 2004); such combinations should be changed.

It is important that when virological failure occurs, the individual situation of the patient is carefully analyzed. In particular, several questions need to be addressed:

#### **What are the reasons for the measurable viral load?**

A viral load above 50 copies/ml does not necessarily mean that resistance mutations have developed. It may also indicate insufficient plasma drug levels (measure these if possible!). This may be due to: drug malabsorption, drug interactions or simply insufficient dosing (e.g. in very big, heavy patients). Compliance is also critical. Any possible difficulties associated with the regimen should be openly addressed: Is it the number of pills? Do restrictions in food intake cause problems? Would once-daily treatment be better? Are there other reasons, such as depression? The risks of resistance developing as a result of non-compliance should be reiterated. If plasma levels are sufficient and viral load remains detectable (monitor blips at short intervals – within a few weeks!), treatment should definitely be changed as soon as possible.

#### **How vulnerable is the present combination?**

NNRTI regimens are extremely sensitive, as cross-resistance can develop particularly rapidly for the whole class. Thus, a prompt change in therapy is even more vital than with the other drug classes. Delaying this by even a few days or weeks may be too long! Rapid development of resistance can also be expected with 3TC (and probably FTC). A PI-containing regimen without an NNRTI may allow a little more time, but the credo still applies: the higher the viral load at the time of modification, the lower the chances of success. One should not wait too long.

**What options does the patient have, and what are the consequences of the change in therapy?**

The more options that remain available, the sooner they should be utilized. Therapy can often be intensified quite easily (e.g. adding abacavir plus an NNRTI). In such cases, the decision to change or intensify a regimen is less difficult.

On the other hand, it may be advisable in certain circumstances to continue therapy in a patient, even if the plasma viremia is not completely suppressed. Often, the viral load does not rise above the baseline value, and the CD4+ T-cells remain stable or even increase. Some experts advocate waiting in these cases. Resistances to nucleoside analogs are to be expected, and therefore NNRTIs and PIs can be saved from the start.

Even when multiple resistances are already present, one is probably able to wait initially (see above).

Intensification of therapy may not be feasible in all cases. A patient on triple-class therapy as well as extensive pre-treatment usually has few options left. These are often reduced even further by side effects. In such cases, the goal of achieving a viral load below the level of detection may have to be abandoned (see also “Salvage Therapy” chapter).

**References**

See at the end of the next chapter.

## 8. How to change HAART

Christian Hoffmann, Fiona Mulcahy

The approach to changing a regimen that is successful but intolerable due to side effects is usually straightforward. The suspected drug is replaced with another drug of the same class. Difficulties can arise if alternate drugs are contraindicated because of potential toxicity or if resistance mutations against these drugs are suspected. In such cases, changes have to be individualized according to the situation of the patient.

This chapter discusses two other important reasons for switching, where certain principles should apply: changing due to virological failure, and changing HAART to simplify the regimen. Switching out of concern for lipodystrophy has been discussed in previous chapters.

### Change due to virological failure

The same principles apply as when initiating therapy: compliance, dosing issues, concurrent diseases, comedications and drug interactions. It is also essential to consider treatment history and possible existing resistance mutations. Although desirable before any change in treatment, resistance tests are not always practical. It is therefore useful to become familiar with the most important resistance mutations, particularly for nucleoside analogs (see Table 8.1). The basic principles for changing therapy in cases of virological failure apply: the faster the change, the better; the virus should be given as little time as possible to generate more resistance mutations. In addition: the more drugs that are changed, the higher the likelihood of success for the new regimen.

Table 8.1: Expected resistance mutations with different nuke backbones

Failing nuke backbone	Mutations
AZT/d4T+3TC AZT+3TC+ABC	M184V and then successive TAMs, the longer one waits
TDF+3TC/FTC	K65R and/or M184V
ABC+3TC	L74V > K65R and/or M184V
AZT/d4T+ddI	TAMs, Q151M, T69ins
TDF+ABC/ddI	K65R

The situation with NNRTIs is more straightforward: there is usually complete cross-resistance. Continuation in the presence of these resistance mutations is of no use, as they have no impact on the replicative fitness of the virus.

There are also relevant cross-resistance mutations for PIs. Resistance testing is therefore recommended here. In many cases it may be possible to treat with lopinavir/r after failure of the first PI. This is now the area of salvage, discussed in more detail in the next chapter.

Table 8.2 provides a rough guide on how to proceed without knowledge of resistance mutations.

Table 8.2: Changing first-line therapy without knowledge of resistance mutations\*

Failing initial therapy	Potentially successful change
3 Nukes	2 new nukes plus NNRTI or PI 2 new nukes plus NNRTI plus PI
2 Nukes + 1 NNRTI	2 new nukes plus PI
PI + NNRTI	2 nukes + PI
2 Nukes + 1 PI	2 new nukes plus NNRTI plus possibly new boosted PI, or boost present PI, if this was not already the case

\* Note: there is insufficient data available on all these changes. In individual cases, other modifications or simply waiting may be advisable. Apart from nelfinavir, all PIs should be boosted.

If the increase in viral load is minimal, treatment success may also be achieved with simple changes – if one acts quickly. In the case of two nukes plus an NNRTI, for example, treatment may possibly be intensified simply by the addition of abacavir (Degen 2000, Katlama 2001 Rozenbaum 2001). In a placebo-controlled study, 41 % of patients on stable ART with a viral load between 400 and 5,000 copies/ml achieved a viral load below 400 copies/ml at 48 weeks after addition of abacavir alone (Katlama 2001). Such results could possibly be even better with “more rigorous” entry levels (for example, not waiting to change therapy until 5,000 copies/ml are reached, but acting already at 500 copies/ml).

Addition of tenofovir – one extra tablet a day – also seems possible in certain cases (Khanlou 2005). Tenofovir reduced the viral load under stable HAART by 0.62 log (Schooley 2002). Our experience with this approach has been good in cases with minimal increases in the viral load (up to 500 copies/ml) and in the absence of TAMs.

In patients who have been treated exclusively (and over a prolonged period) with nukes, this strategy is not promising. Extensive resistance mutations usually exist, so that a complete change of HAART is necessary. At least two randomized studies (some blinded) have shown that most benefit is achieved by switching to an NNRTI plus a PI plus at least one new nucleoside analog. This has been shown for both nelfinavir plus efavirenz and indinavir plus efavirenz (Albrecht 2001, Haas 2001). In patients previously treated with NRTIs or NNRTIs, a boosted PI must be used.

## Change to simplify – do “maintenance therapies” work?

Can HIV infection be treated in a similar fashion to some hematological diseases or tuberculosis, with a sequence of intense induction therapy followed by less toxic (and less expensive) maintenance therapy? The idea is appealing, and has circulated almost since the existence of HAART. Between 1998 and 2003, the answer was clearly that maintenance therapies do not work. By 1998, three randomized studies (Trilège, ADAM, ACTG 343) had already destroyed all hope that HAART might be reduced to two or even one drug.

In the French Trilège Trial, 279 patients adequately treated with HAART were randomized to three arms of different intensity (Pialoux 1998, Flander 2002). At 18 months, the viral load had increased to above 500 copies/ml in 83 patients – 10 on AZT+3TC+indinavir, but 46 on AZT+3TC and 27 on AZT+indinavir. However, temporary dual therapy had no negative effect, and resistance did not develop (Descamps 2000). In the ADAM Trial (Reijers 1998), patients who had been treated



with d4T+3TC plus saquinavir+nelfinavir for several months either stopped or continued their nucleoside analogs. The study was already doomed at interim analysis: in 9/14 (64 %) patients, simplifying therapy already had a detectable viral load at 12 weeks, versus 1/11 (9 %) of those continuing on the previous regimen. The third study, finally led to the end of the notion of maintenance therapy was ACTG 343. 316 patients, with a viral load below 200 copies/ml for at least two years, either continued to take AZT+3TC+indinavir or a simplified regimen of AZT+3TC or indinavir. The rate of treatment failure (viral load above 200 copies/ml) was 23 % in the two maintenance arms compared to only 4 % in patients on continued therapy (Havlir 1998).

In the last few years, newer better drugs have been licensed. In particular, lopinavir with its antiviral potency and concurrent high resistance barrier casts a different light on the negative image of maintenance therapies.

In several pilot studies, patients with good viral load suppression were able to successfully simplify therapy with “lopinavir monotherapy” (see Table 8.3).

Table 8.3: Newer studies on maintenance therapies (either mono- or nuke sparing)

Source	n	“Maintenance”	Week	Less than 50 copies?
Ruane 2004	18	LPV/r	24	73 %, a few blips, no resistance
Arribas 2005 (OK Study)	42	LPV/r (randomized against +2NA)	48	81 versus 95 % (p=0.34). Pts with failure of therapy “worse adherence”, no resistance found
Campo 2005	6	LPV/r	24	66 %, 2 pts “non-compliant”, no resistance
Kahlert 2004	12	IDV/r	48	92 %, 1 dropout, no failure
Vernazza 2005 (ATARITMO)	28	ATV/r	24	92 %, no resistance or failure
Swindells 2006 (ACTG 5201)	34	ATV/r	24	91 %, no resistance
Girard 2004 (COOL Trial)	45	EFV+TDF (randomized against 3TC)	24	A few SAEs on efavirenz, so far, no virological failure

All patients had less than 50 copies/ml for at least six months (Ruane: 75). SAE = serious adverse events.

Virological failure with documented resistance has so far not been observed. However, patient numbers were low and observation periods were short. In view of these studies, it now appears to be time to set up larger randomized studies.

There is also data on boosted saquinavir/r: in the Prometheus Study, PI- and d4T-naïve (including some completely treatment-naïve) patients were randomized to a regimen of saquinavir/r plus/minus d4T. After 48 weeks, 88 versus 91 % of patients in the on-treatment analysis were below 400 copies/ml. However, particularly patients with high viral loads were not stable on this treatment (Gisolf 2000).

Another drug that might be suitable for such mono-maintenance therapy is fosamprenavir/r, which, like lopinavir/r, also seems to have a relatively high genetic barrier. In the SOLO Study, no resistance was observed on boosted fosamprenavir

even after 48 weeks (MacManus 2004). However, there is no data available yet on fosamprenavir maintenance therapy.

An approach taken in the French COOL Study is also interesting. 140 patients were randomized to TDF+3TC+efavirenz or TDF+efavirenz for 48 weeks. Inclusion criterion is HAART with a viral load below 50 copies/ml for at least three months; patients with prior treatment failure were excluded. There were no restrictions on CD4+ T-cell counts. An interim analysis of 45 patients who had been followed for 24 weeks was presented at the World AIDS Conference in Bangkok: the risk of virological failure appeared to be low (Girard 2004).

## Conversion in order to simplify – triple nuke revisited

Triple nuke therapy, though now fairly obsolete for first-line therapy (see chapter “Which HAART to start with”), seems to also be justifiable for maintenance therapy. At least three randomized studies could not detect any virological disadvantage (Katlama 2003, Bonjoch 2005, Markowitz 2005).

In the ESS40013 Study, a total of 448 patients were treated with AZT+3TC+ABC plus efavirenz. After 36 or 44 weeks, 282 patients with undetectable viral load at this time were randomized to continue with the same therapy or to stop efavirenz. After 96 weeks, 79 versus 77 % of patients were still below 50 copies/ml, proving that triple nuke was not inferior (Markowitz 2005).

In a Spanish study, 134 patients with an undetectable viral load for at least 24 weeks were randomized to receive either Trizivir™ or Combivir™ plus nevirapine (Bonjoch 2005). At 48 weeks, the percentage of patients with an undetectable viral load was comparable across both arms (71 versus 73 % in the ITT analysis). Similar results were also seen in the TRIZAL study, in which 209 patients were randomized (Katlama 2003).

## References on changing and simplifying therapy

1. Albrecht MA, Bosch RJ, Hammer SM, et al. Nelfinavir, efavirenz, or both after the failure of nucleoside treatment of HIV infection. *N Engl J Med* 2001, 345:398-407. <http://amedeo.com/lit.php?id=11496850>
2. Arranz Caso JA, Lopez JC, Santos I, et al. A randomized controlled trial investigating the efficacy and safety of switching from a protease inhibitor to nevirapine in patients with undetectable viral load. *HIV Med* 2005, 6:353-9. <http://amedeo.com/lit.php?id=16156884>
3. Arribas JR, Pulido F, Delgado R, et al. Lopinavir/ritonavir as single-drug therapy for maintenance of HIV-1 viral suppression: 48-week results of a randomized, controlled, open-label, proof-of-concept pilot clinical trial (OK Study). *J AIDS* 2005, 40:280-7.16249701
4. Barreiro P, Soriano V, Blanco F, et al. Risks and benefits of replacing protease inhibitors by nevirapine in HIV-infected subjects under long-term successful triple combination therapy. *AIDS* 2000, 14: 807-12. <http://amedeo.com/lit.php?id=10839588>
5. Becker S, Rachlis A, Gill J, et al. Successful Substitution of Protease Inhibitors with Efavirenz in patients with undetectable viral loads - A prospective, randomized, multicenter, open-label study (DMP 049). Abstract 20, 8th CROI 2001, Chicago. <http://hiv.net/link.php?id=206>
6. Bonjoch A, Paredes R, Galvez J, et al. Antiretroviral treatment simplification with 3 NRTIs or 2 NRTIs plus nevirapine in HIV-1-infected patients treated with successful first-line HAART. *J AIDS* 2005, 39:313-6.
7. Calza L, Manfredi R, Colangeli V, et al. Substitution of nevirapine or efavirenz for protease inhibitor versus lipid-lowering therapy for the management of dyslipidaemia. *AIDS* 2005, 19:1051-8. <http://amedeo.com/lit.php?id=15958836>
8. Campo RE, Lalanne R, Tanner TJ, et al. Lopinavir/ritonavir maintenance monotherapy after successful viral suppression with standard highly active antiretroviral therapy in HIV-1-infected patients. *AIDS* 2005, 19:447-9.

9. Carr A, Workman C, Smith DE, Hoy J, Abacavir substitution for nucleoside analogs in patients with HIV lipatrophy: a randomized trial. *JAMA* 2002;288:207-15. <http://amedeo.com/lit.php?id=12095385>
10. Cherry CL, Lal L, Thompson KA, et al. increased adipocyte apoptosis in lipatrophy improves within 48 weeks of switching patient therapy from stavudine to abacavir or zidovudine. *J AIDS* 2005, 38:263-267.
11. Clumeck N, Goebel F, Rozenbaum W, et al. Simplification with abacavir-based triple nucleoside therapy versus continued protease inhibitor-based HAART in HIV-1-infected patients with undetectable plasma HIV-1 RNA. *AIDS* 2001, 15: 1517-26. <http://amedeo.com/lit.php?id=11504984>
12. d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. *AIDS* 2000, 14:499-507.
13. Degen O, van Lunzen J, Stellbrink HJ. Intensification of background antiretroviral therapy with abacavir during low-level failure may restore optimal suppression. *Antivir Ther* 2000;5:91-4.
14. Descamps D, Flandre P, Calvez V, et al. Mechanisms of virologic failure in previously untreated HIV-infected patients from a trial of induction-maintenance therapy. *Trilege*. *JAMA* 2000, 283: 205-11. <http://amedeo.com/lit.php?id=10634336>
15. Domingo P, Labarga P, Palacios R, et al. Improvement of dyslipidemia in patients switching from stavudine to tenofovir: preliminary results. *AIDS* 2004, 18:1475-8.
16. Fätkenheuer G, Römer K, Cramer P, Franzen C, Salzberger B. High rate of changes of first antiretroviral combination regimen in an unselected cohort of HIV-1 infected patients. Abstract 50, 8th ECCAT 2001, Athens, Greece.
17. Flander P, Raffi F, Descamps D, et al. Final analysis of the Trilege induction-maintenance trial: results at 18 months. *AIDS* 2002, 16:561-8. <http://amedeo.com/lit.php?id=11872999>
18. Gallant JE, DeJesus E, Arribas JR, et al. Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV. *N Engl J Med* 2006, 354:251-60. <http://amedeo.com/lit.php?id=16421366>
19. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA*. 2004, 292: 191-201. <http://amedeo.com/lit.php?id=15249568>
20. Girard PM, Cabie A, Michelet C, et al. EFV/TDF vs EFV/3TC/TDF as maintenance regimen in virologically controlled patients under HAART: a 6-month analysis of the COOL Trial. Abstract TuPeB4597, 15th Int Conf AIDS 2004, Bangkok.
21. Gisolf EH, Jurriaans S, Pelgrom J, et al. The effect of treatment intensification in HIV-infection: a study comparing treatment with ritonavir/saquinavir and ritonavir/saquinavir/stavudine. *Prometheus Study Group*. *AIDS* 2000, 14:405-13. <http://amedeo.com/lit.php?id=10770543>
22. Haas DW, Fessel WJ, Delapenha RA, et al. Therapy with efavirenz plus indinavir in patients with extensive prior nucleoside reverse-transcriptase inhibitor experience: a randomized, double-blind, placebo-controlled trial. *J Infect Dis* 2001,183:392-400. <http://amedeo.com/lit.php?id=11133370>
23. Haberl A, Müller A, Mölsch M. Switch to tenofovir in patients with suppresses HI-viremia. Abstract 9.8/4, 9th EACS 2003, Warsaw, Poland.
24. Havlir DV, Marschner IC, Hirsch MS, et al. Maintenance antiretroviral therapies in HIV infected patients with undetectable plasma HIV RNA after triple-drug therapy. ACTG 343 Team. *N Engl J Med* 1998, 339:1261-8. <http://amedeo.com/lit.php?id=9791141>
25. Hoogewerf M, Regez RM, Schouten WE, Weigel HM, Frissen PH, Brinkman K. Change to abacavir-lamivudine-tenofovir combination treatment in patients with HIV-1 who had complete virological suppression. *Lancet* 2003; 362:1979-80. <http://amedeo.com/lit.php?id=14683659>
26. John M, McKinnon EJ, James IR, et al. Randomized, controlled, 48 week study of switching stavudine and/or protease inhibitors to Combivir/abacavir to prevent or reverse lipatrophy in HIV-infected patients. *JAIDS* 2003, 33: 29-33. <http://amedeo.com/lit.php?id=12792352>
27. Kahlert C, Hupfer M, Wagels T, et al. Ritonavir boosted indinavir treatment as a simplified maintenance „mono“-therapy for HIV infection. *AIDS* 2004 , 18:955-7.
28. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. *Clin Ther* 2000, 22:685-708. <http://amedeo.com/lit.php?id=10929917>
29. Katlama C, Clotet B, Plettenberg A, et al. Intensification of stable background therapy with abacavir in antiretroviral therapy experienced patients: 48-week data from a randomized, double-blind trial. *HIV Med* 2001, 2:27-34. <http://amedeo.com/lit.php?id=11737373>
30. Katlama C, Fenske S, Gazzard B, et al. TRIZAL study: switching from successful HAART to Trizivir (abacavir lamivudine-zidovudine combination tablet): 48 weeks efficacy, safety and adherence results. *HIV Med* 2003;4:79-86. <http://amedeo.com/lit.php?id=12702127>
31. Keiser P, Senson M, DeJesus E, et al. Simplification of protease inhibitor (PI)-based highly active antiretroviral regimens with abacavir (ABC) improves hyperlipidemia and maintains viral suppression in HIV-1 infected adults (ESS40003). Abstract WePeC6267, XIV Int AIDS Conf 2002, Barcelona.

32. Keiser PH, Sension MG, DeJesus E, et al. Substituting abacavir for hyperlipidemia-associated protease inhibitors in HAART regimens improves fasting lipid profiles, maintains virologic suppression, and simplifies treatment. *BMC Infect Dis* 2005, 5:2.
33. Khanlou H, Guyer B, Farthing C. Efficacy of tenofovir as intensification of zidovudine/lamivudine/abacavir fixed-dose combination in the treatment of hiv-positive patients. *J AIDS* 2005;38:627-628.
34. Lafeuillade A, Clumeck N, Mallolas J, et al. Comparison of metabolic abnormalities and clinical lipodystrophy 48 weeks after switching from HAART to Trizivir versus continued HAART: the Trizal study. *HIV Clin Trials* 2003;4:37-43. <http://amedeo.com/lit.php?id=12577195>
35. MacManus S, Yates PJ, Elston RC, White S, Richards N, Snowden W. GW433908/ritonavir once daily in antiretroviral therapy-naive HIV-infected patients: absence of protease resistance at 48 weeks. *AIDS* 2004, 18:651-5. <http://amedeo.com/lit.php?id=15090770>
36. Markowitz M, Hill-Zabala C, Lang J, et al. Induction with abacavir/lamivudine/zidovudine plus efavirenz for 48 weeks followed by 48-week maintenance with abacavir/lamivudine/zidovudine alone in antiretroviral-naive HIV-1-infected patients. *J AIDS* 2005, 39:257-64. 15980684
37. Martin A, Smith DE, Carr A, et al. Reversibility of lipodystrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS* 2004, 18:1029-36.
38. Martinez E, Arnaiz JA, Podzamczar D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with HIV infection. *N Engl J Med* 2003; 349:1036-46. <http://amedeo.com/lit.php?id=12968087>
39. McComsey GA, Paulsen DM, Loneragan JT, et al. Improvements in lipodystrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine. *AIDS* 2005, 19:15-23.
40. McComsey GA, Ward DJ, Hesselthaler SM, et al. Improvement in lipodystrophy associated with highly active antiretroviral therapy in human immunodeficiency virus-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. *Clin Infect Dis* 2004, 38:263-270. <http://amedeo.com/lit.php?id=14699460>
41. Mocroft A, Phillips AN, Miller V, et al. The use of and response to second-line protease inhibitor regimens: results from the EuroSIDA study. *AIDS* 2001, 15:201-9. <http://amedeo.com/lit.php?id=11216928>
42. Mocroft A, Youle M, Moore A, et al. Reasons for modification and discontinuation of antiretrovirals: results from a single treatment centre. *AIDS* 2001, 15:185-94. <http://amedeo.com/lit.php?id=11216926>
43. Molina JM, Journot V, Morand-Joubert L, et al. Simplification therapy with once-daily emtricitabine, didanosine, and efavirenz in HIV-1-infected adults with viral suppression receiving a protease inhibitor-based regimen: a randomized trial. *J Infect Dis* 2005, 191:830-9. <http://amedeo.com/lit.php?id=15717256>
44. Moyle G, Baldwin C, Langroudi B, Mandalia S, Gazzard BG. A 48 week, randomized, open label comparison of three abacavir-based substitution approaches in the management of dyslipidemia and peripheral lipodystrophy. *J AIDS* 2003, 33: 22-28. <http://amedeo.com/lit.php?id=12792351>
45. Moyle G, Sabin C, Carteledge J, et al. A 48-week, randomised, open-label comparative study of tenofovir DF vs. abacavir as substitutes for a thymidine analog in persons with lipodystrophy and sustained virological suppression on HAART. Abstract 44B, 12th CROI 2005, Boston.
46. Murphy E, Zhang J, Hafner R, et al. Peripheral and visceral fat changes following a treatment switch to a nonthymidine analogue or nucleoside-sparing regimen in patients with peripheral lipodystrophy: 48-week final results of ACTG a5110, a prospective, randomized multicenter clinical trial. Abstract 755, 13th CROI 2006, Denver.
47. Nasta P, Matti A, Cocca G, et al. Early vs deferred HAART switch in heavily pre-treated HIV patients with low viral load level and stable CD4 cell count. Abstract 523, 13th CROI 2006, Denver.
48. Negro E, Cruz L, Paredes R, et al. Virological, immunological, and clinical impact of switching from protease inhibitors to nevirapine or to efavirenz in patients with HIV infection and long-lasting viral suppression. *Clin Infect Dis* 2002, 34:504-10. <http://amedeo.com/lit.php?id=11797178>
49. Negro E, Moltó J, Burger D, et al. Unexpected CD4 cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load. *AIDS* 2004, 18:459-463. <http://amedeo.com/lit.php?id=15090798>
50. Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in HIV infection. *J Infect Dis* 2002, 185: 1251-60. <http://amedeo.com/lit.php?id=12001042>
51. Owen C, Kazim F, Badley AD. Effect on CD4 T-cell count of replacing protease inhibitors in patients with successful HIV suppression: a meta-analysis. *AIDS* 2004, 18:693-5.
52. Perez-Elias MJ, Moreno S, Gutierrez C, et al. High virological failure rate in HIV patients after switching to a regimen with two nucleoside reverse transcriptase inhibitors plus tenofovir. *AIDS* 2005;19:695-8.
53. Pialoux G, Raffi F, Brun-Vezinet F, et al. A randomized trial of three maintenance regimens given after three months of induction therapy with zidovudine, lamivudine, and indinavir in previously untreated

HIV-1-infected patients. *Trilege*. *N Engl J Med* 1998, 339: 1269-76.  
<http://amedeo.com/lit.php?id=9791142>

54. Reijers MH, Weverling GJ, Jurriaans S, et al. Maintenance therapy after quadruple induction therapy in HIV-1 infected individuals: ADAM study. *Lancet* 1998, 352: 185-90.  
<http://amedeo.com/lit.php?id=9683207>
55. Ribera E, Sauleda S, Paradoineiro JC, et al. Increase in mitochondrial DNA in PBMCs and improvement of lipidic profile and lactate levels in patients with lipotrophy when stavudine is switched to tenofovir. Abstract F16/4, 9th EACS 2003, Warsaw.
56. Riddler S, Jiang H, Deeks S, et al. A randomized pilot study of delayed ART switch in subjects with detectable viremia on HAART. Abstract 522, 13th CROI 2006, Denver.
57. Rozenbaum W, Katlama C, Massip P, et al. Treatment intensification with abacavir in HIV-infected patients with at least 12 weeks previous lamivudine/zidovudine treatment. *Antiviral Therapy* 2001, 6:135-42. <http://amedeo.com/lit.php?id=11491418>
58. Ruane P, Lubner A, Gaultier C et al. Maintenance therapy using Lopinavir/ritonavir (LPV/r) alone with well-controlled HIV Infection. Abstract TuPeB4577, XV Int AIDS Conf 2004, Bangkok.
59. Ruiz L, Negro E, Domingo P, et al. Antiretroviral treatment simplification with nevirapine in protease inhibitor-experienced patients with HIV-associated lipodystrophy: 1-year prospective follow-up of a multicenter, randomized, controlled study. *J Acquir Immune Defic Syndr* 2001, 27: 229-36.  
<http://amedeo.com/lit.php?id=11464141>
60. Schewe CK, Maserati R, Wassmer G, Adam A, Weitner L. Improved lipid profiles and maintenance of virologic control in heavily pretreated HIV-infected patients who switched from stavudine to tenofovir treatment. *Clin Infect Dis* 2006, 42:145-7.
61. Schooley RT, Ruane P, Myers RA, Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS* 2002, 16:1257-63.  
<http://amedeo.com/lit.php?id=12045491>
62. Suleiman JMA, Lu B, Enejosa J, Cheng A, for the 903E study team. Improvement in lipid parameters associated with substitution of stavudine (d4T) to tenofovir DF (TDF) in HIV-infected patients participating in GS 903. Abstract H-158, 44th ICAAC 2004, Washington.
63. Swindells S, Wilkin T, DiRienzo G, et al. A prospective, open-label, pilot trial of regimen simplification to atazanavir/ritonavir alone as maintenance antiretroviral therapy after sustained virologic suppression (ACTG 5201). Abstract 108 LB, 13th CROI 2006, Denver.
64. Vernazza P, Daneel S, Schiffer V, et al. Viral suppression in CSF and genital tract in ritonavir-boosted „atazanavir-only“ maintenance therapy (ATARITMO Study). Abstract WeOa0204, 3rd IAS 2005, Rio de Janeiro.

## 9. Salvage therapy

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### Background

The term “salvage therapy” is not clearly defined in HIV medicine. It is currently used to refer to varying situations. Some speak of salvage only if all drug classes have failed, whereas others employ the term from second-line therapy onward. As yet, no consensus on the definition of “salvage” has been reached. Here, we define salvage as the therapeutic approach when at least one PI-containing regimen has failed. Moreover, the concept is constantly being shifted further back in the therapy career of patients. Today, many clinicians talk about salvage when there is resistance to at least two or three antiretroviral drug classes. Viruses with multiple resistances are in turn termed MDR (“multi-drug resistant”) viruses.

In the last few years, significant progress has been made for these patients. Now we have drugs, such as lopinavir, T-20, tipranavir and darunavir, which still have an effect in the presence of numerous resistances. Furthermore, completely new classes of drugs such as coreceptor antagonists or integrase inhibitors are waiting in the wings (see chapter entitled “HAART 2006/2007”). That provides confidence for the future.

Nevertheless, there are many problems. One of these is the difficulty in finding homogenous patient populations for prospective studies of new salvage strategies. Although the risk of MDR is declining with newer regimens (Lohse 2005), there remain many patients with MDR viruses. But: each one has an individual history of therapy; each has a different constellation of resistances and therefore varying prerequisites for a potential salvage regimen. In large HIV centers, often more than 50 different combinations are used. This makes it difficult to test new salvage substances in Phase II/III trials. The correct study design is also crucial: as the single use of an experimental drug in a failing regimen is ethically questionable, the appropriate ART must always be optimized (=OBT, optimized background therapy). If the OBT is too good, the effect of the new drug may be hidden, as many patients achieve a good viral suppression just on OBT. If the OBT is too poor, the effect of the new drug may only be temporary or too weak – the window through which the efficacy of a new salvage drug can be seen is small.

First a few words about the daily practice: it should not be forgotten that patients with MDR viruses, who often have a long therapeutic history, and who now presumably find themselves once again on a precipice, need encouragement. It is important not to take hope away from these patients. Although some studies have shown that patients with MDR viruses have a worse prognosis than patients without resistances (Hogg 2005, Zaccarelli 2005), data are not unequivocal. In the GART Study, the risk of progression for patients with more than six resistances was not increased in contrast to patients with less than two resistances, when compared over 15 months (Lucas 2004). With good CD4+ T-cell counts, even despite MDR viruses, the risk of developing AIDS is relatively small (Ledergerber 2004). MDR

viruses have a weaker ability to replicate and are probably less aggressive (Prado 2005). Furthermore, progress is continuing. New classes of drugs will arrive. So, for MDR, simply - be patient! It usually takes years to progress from virological treatment failure to immunological, and finally clinical failure (see also “Principles of Therapy”). Fortunately, these patients, who are used to every outpatient department or specialist practice – most having been treated for ten or fifteen years, and have lived through and suffered a lot – are often not nearly as nervous as the (frequently) young HIV doctor: they have learned that there is (almost) always more to come...

It is, however, important that patients with MDR viruses are very carefully observed and undergo regular (monthly) full body examination – something that is often neglected today in the long discussions about blood values and resistance testing for many HIV patients. Loss of weight, B-symptoms, oral candidiasis, OHL, and cognitive worsening are early signs of disease progression that should not be missed.

The following is a discussion about a few salvage therapy strategies, which when used alone or in combination, are promising.

- Salvage with lopinavir/r, tipranavir/r, darunavir/r and T-20
- Double PI salvage regimens
- Mega-HAART, with or without treatment interruptions
- Utilizing NNRTI “hypersusceptibility”
- Salvage through recycling
- Just waiting, and even simplifying ART
- Experimental salvage drugs

### Salvage with lopinavir/r, tipranavir/r, darunavir/r and T-20

The introduction of the three boosted PIs lopinavir/r (Kaletra™), tipranavir (Aptivus™) and darunavir (Prezista™, since spring 2006 in an expanded access program) has significantly improved salvage therapy. The resistance barriers for these drugs are high, so that the response, even in the presence of multiple PI resistances, is often still good. Although the occurrence of dyslipidemia is sometimes disturbing, the three substances are very valuable in salvage therapy, and should be considered following failure of the first PI.

**Lopinavir/r:** was the first important salvage drug. The higher the plasma levels of lopinavir, the better (Boffito 2002). So, because once-daily administration results in trough levels that are too low (la Porte 2005), lopinavir/r should be given twice daily where possible, at least in pretreated patients. A minimum of 5-7, if not 8 PI mutations are necessary for failure of lopinavir/r (Kempf 2001, Masquelier 2002). In 70 patients on a failing PI regimen, the decrease in viral load was an impressive 1.4 logs at two weeks after simple substitution of the PI with lopinavir/r (Benson 2002). However, two large randomized studies have also shown that the effect of lopinavir/r on PI-resistant viruses is only marginally better than boosted PIs such as atazanavir/r and fosamprenavir/r – a virological difference could only, if at all, be

seen in patients with multiple PI resistances (Elston 2004, Johnson 2006). An example of the salvage effect of lopinavir/r is shown in Table 9.1.

Table 9.1: Patient example of the success of lopinavir/r in salvage therapy

Date	(HA)ART	CD4+ T-cells	Viral load
Mar 1993	AZT	320	N/A
Jan 1995	AZT+ddC	190	N/A
May 1996	AZT+3TC+SQV	97	N/A
Feb 1997	d4T+3TC+IDV	198	126,500
Aug 1997	d4T+3TC+NFV	165	39,500
Mar 1998	d4T+ddl+SQV/RTV+HU	262	166,000
Sep 1998		238	44,000
Jul 2000	AZT+3TC+NVP+LPV/r	210	186,000
Oct 2000		385	< 50
Oct 2004		569	< 50

This case illustrates several phenomena: insufficient responses to new regimens after failure of the first PI; insufficient viral suppression over two years with surprisingly stable CD4+ T-cell levels; and finally a durable response to lopinavir/r – after more than four years of suboptimal PI-treatment! NNRTI hypersusceptibility may have possibly been present in this case (see below). On switching to lopinavir/r, the patient had genotypic and phenotypic resistance to various nucleoside analogs (and PIs).

**Tipranavir/r:** In the two Phase III studies RESIST-1 (USA) and -2 (Europe), 1,483 intensively pre-treated patients with an OBT received either tipranavir/r or a boosted comparison PI, mainly lopinavir/r (Lazzarin 2005). The patients had a viral load of at least 1,000 copies/ml and at least one primary PI mutation (although no more than two mutations on the codons 30, 82, 84 and 90). After 24 weeks, 24 % in the tipranavir/r arm reached less than 50 copies/ml versus 9 % in the comparison PI arm. The difference remained significant when only the patients on lopinavir/r in the comparison arm were analyzed (Cooper 2005). However, this difference obviously only occurred because some patients in the randomization had already been pre-treated with lopinavir/r. In lopinavir/r-naïve patients, there was no significant difference between tipranavir/r and lopinavir/r. In other words, if lopinavir/r is still effective, tipranavir/r is not much better, but when the lopinavir/r card has been played, tipranavir/r can still be effective.

**Darunavir/r:** Similar to the RESIST studies, two other salvage studies yielded to encouraging results in 2005: POWER-1 (Europe) and -2 (USA). Using 600 pre-treated patients (three classes and an average of 11 drugs), various doses of darunavir were tested against a similarly boosted comparison PI (Katlama 2005). Despite considerable resistances at the baseline, the viral load sank after 24 weeks to less than 50 copies/ml in 47 % of patients in the 600 mg group – a significantly better result than the control PI (14 %), and an extraordinary success for such a patient group. The effect of darunavir is of course not limitless. The first resistances have already been described, situated on V321, I47V and I54M (De Meyer 2006). An EAP will be available in many countries from spring 2006.

For all three PIs, it has become clear that the success of therapy is bigger, the greater the number of active substances additionally available. In particular, the administration of T-20 can significantly improve the effect. In the TORO Studies,



patients on T-20 profited markedly from lopinavir/r (Lalezari 2003, Lazzarin 2003); in the RESIST studies, the proportion of patients on tipranavir, who were below the level of detection of 50 copies/ml after 24 weeks, increased to 32.8 % when T-20 was given (Lazzarin 2005). In the POWER Studies, the proportion also increased significantly to 63 %. Therefore, if tipranavir or darunavir are being considered, T-20 should also be contemplated.

## Double PI salvage regimens

Not only lopinavir but also other PIs can be boosted with low doses of ritonavir (as contained in Kaletra™). The introduction of tipranavir and darunavir has meant that this double PI strategy has lost some of its standing in salvaging. It does, however, remain important in cases in which NRTIs are being avoided (see also “Nuke Sparing”) in order to prevent mitochondrial toxicity.

**Lopinavir/r + saquinavir/r:** in vitro data indicate that there is synergy between these drugs (Molla 2002). The ritonavir dose in Kaletra™ suffices for 1,000 mg bid saquinavir (Stephan 2004). There do not seem to be any unfavorable interactions between saquinavir and lopinavir/r (Ribera 2004).

The efficacy of lopinavir/r + saquinavir was more closely examined in the LopSaq Study (Staszewski 2004). The largest study of its kind, it enrolled 163 heavily treatment-experienced patients for different reasons (resistance, toxicity) to be treated with a nuke-free combination consisting of lopinavir/r (400/100 mg bid) plus saquinavir (1,000 mg bid). 88 patients interrupted therapy prior to starting this regimen. At the last follow up, 115 patients were evaluated by week 48. Of these, 77 patients (61 %), a considerable proportion, showed good virological response, and 50 patients even reached a viral load below 50 copies/ml. However, the response in patients with numerous PI resistance mutations and low CD4+ T-cell counts was poor (Staszewski 2004). In a small study, 14/16 patients achieved a viral load below the level of detection after 48 weeks (Hellinger 2005).

**Atazanavir/r + saquinavir/r:** saquinavir does not seem to influence atazanavir levels, and the levels of both PIs can be improved by addition of ritonavir. On a once-daily combination of 300 mg atazanavir, 100 mg ritonavir and 1,600 mg saquinavir, the PK parameters for saquinavir were significantly improved by atazanavir, and trough levels of saquinavir increased by over 110 % (Boffito 2004). The reason for this interaction between saquinavir and atazanavir is still unclear, but could be related to gastrointestinal transport mechanisms. It is interesting to note that intracellular levels of saquinavir are also significantly elevated (Ford 2004). The regimen was well tolerated, although hyperbilirubinemia frequently occurred. Indirect bilirubin was increased 5-fold on average.

In the ATSAQ study (Rottmann 2004), 40 heavily treatment-experienced patients were treated with a nuke-free combination of 300 mg atazanavir, 100 mg ritonavir and 2 x 1,000 mg saquinavir. After a median of 32 weeks, 85 % of patients had reached a viral load below 400 copies/ml.

Three further studies are currently underway, testing different doses of this combination. Despite the fact that saquinavir levels are elevated by atazanavir, this combination is probably not useful without ritonavir. In the BMS A1424-045 Study,

saquinavir and atazanavir did less well than boosted atazanavir or lopinavir (Johnson 2006). In the AI424-009 Study, the unboosted combination was also relatively weak (Haas 2003). It should therefore not be used.

**Saquinavir/r + fosamprenavir:** the combination of saquinavir and amprenavir was tested early on (Eron 2001). Newer studies have focused more on the combination of saquinavir with fosamprenavir. As with amprenavir, saquinavir levels dropped significantly in 18 patients treated with a combination of 1,000 mg saquinavir, 100 mg ritonavir and 700 mg fosamprenavir (all bid). However, this negative interaction can be compensated by an increase in the ritonavir dose to 200 mg bid (Bofito 2004). Since the resistance profiles of these two drugs only partially overlap, use of this combination is interesting, particularly now that the new 500 mg saquinavir tablets are on the market, which reduce the pill burden.

**Lopinavir/r + indinavir:** In vitro, lopinavir and indinavir work synergistically. This combination has been tested with different doses of indinavir. In the Crix-Lop Study from Frankfurt, 28 highly treatment-experienced patients were enrolled (Staszewski 2003), and 17 of these remained on treatment even after 46 weeks (2 x 800 mg indinavir/400 mg lopinavir). It was shown once again that the low ritonavir dose is sufficient to boost both PIs (von Hentig 2003, Isaac 2004). However the data is not completely clear-cut, and case numbers are fairly low. An additional ritonavir dose is possibly necessary, and TDM is recommended. Indinavir and lopinavir do not usually seem to require dose adjustment.

**Lopinavir/r + fosamprenavir:** the resistance profile is very promising, and the lopinavir and (fos)amprenavir combination is probably the most extensively investigated double PI strategy. Unfortunately, the unfavorable PK data that is emerging is likely to prevent widespread use of this combination. A complex interaction has already been described between lopinavir and amprenavir, which causes levels of both drugs to drop significantly (Khanlou 2002, Mauss 2002, Raguin 2004). Increasing the ritonavir boosting dose is not beneficial (Mauss 2004, Taburet 2004). Similar unfavorable interactions seem to apply also to fosamprenavir (Kashuba 2005). Taking the two PIs at different intervals to each other does not prevent low fosamprenavir levels (Corbett 2004).

As a result, this combination cannot be recommended until further data becomes available. If treatment with lopinavir/r and fosamprenavir is nevertheless attempted based on the individual resistance profile, significant dose adjustment will be required – based on TDM.

**Other double PI combinations:** the double PI combination of atazanavir and indinavir should be avoided as both drugs cause hyperbilirubinemia. Severe diarrhea is to be expected when combining lopinavir/r and nelfinavir, and a pilot study found further decreased lopinavir levels (Klein 2003). Indinavir and nelfinavir have relatively weak activity in combination (Schranz 2000, Riddler 2003).

Tipranavir seems to have negative interactions with other PIs. In one study, levels of lopinavir, saquinavir and amprenavir all dropped significantly, which is why a double PI regimen with tipranavir is currently not advisable (Walmsley 2004). In contrast, interactions between tipranavir and indinavir may not be as relevant (Leen 2004).

Initial pilot studies have shown that favorable interactions seem to exist between atazanavir and fosamprenavir (Khanlou 2004, Zilly 2005). This also applies to lopinavir and atazanavir (Langman 2005). The combination is currently being investigated in the German LORAN Study.

It should be noted that double PI combinations should only be considered in salvage patients experiencing NRTI side effects (mitochondrial toxicity), and should be administered by experienced clinicians with access to therapeutic drug monitoring, so that dose adjustment is possible if required.

Table 9.2: Double PI combinations with sufficient supporting data

Combination	Daily Dose/comment	Source
<b>More favorable</b>		
Lopinavir/r + saquinavir	800/200/2,000	Staszewski 2004
Atazanavir/r + saquinavir	300/200/2,000	Boffito 2004
Lopinavir/r + atazanavir	800/200/300	Langman 2005
Saquinavir/r + fosamprenavir	2,000/200/1,400 bid	Boffito 2004
Lopinavir/r + indinavir	800/200/1,600 bid	Staszewski 2003
<b>Less favorable</b>		
Lopinavir/r + fosamprenavir	Poor PK data	Kashuba 2005
Atazanavir + saquinavir	Poor activity	Johnson 2005
Tipranavir + LPV/APV/SQV	Poor PK data	Walmsley 2004
Lopinavir/r + nelfinavir	Poor PK data, diarrhea	Klein 2003
Atazanavir + indinavir	Elevated bilirubin	
Indinavir + nelfinavir	Relatively poor activity	Riddler 2002

## Mega-HAART with and without treatment interruptions

Intensified treatment combinations with more than three or four drugs – often described as “mega”- or “giga”-HAART – may indeed be effective. The success of the mostly uncontrolled studies is debatable. On five- or six-drug regimens, sufficient suppression of viral load was achieved only in a variable percentage of patients (22-52 %; Miller 2000, Montaner 2001, Piketty 2002). Only well-informed and highly motivated patients can be considered for mega-HAART regimens, and such approaches are often unrealistic in clinical practice. It is important to consider that potential drug interactions are difficult to predict for such combinations, and therefore plasma levels should be measured whenever possible. However, most PIs can be combined quite well without causing significant interactions or toxicity (van Heeswijk 2001, Eron 2001). Nevertheless, mega-HAART will become less important with the introduction of new salvage drugs and new drug classes.

So, do structured treatment interruptions (STI) before initiation of such intensified regimens provide additional benefit? Possibly.

In the GIGHAART Study (Katlama 2002 + 2004), heavily treatment-experienced patients with advanced HIV infection (less than 200 CD4+ T-cells/ $\mu$ l, viral load above 50,000 copies/ml) were randomly allocated to eight weeks of treatment inter-

ruption or not. All 68 patients were subsequently switched to a combination of 7-8 drugs: 3-4 NRTIs, hydroxyurea, 1 NNRTI and 3 PIs (usually amprenavir/r or lopinavir/r plus indinavir, saquinavir or nelfinavir). In the group that underwent treatment interruption, efficacy after 24 weeks was significantly better, and viral load dropped by 1.08 versus 0.29 logs. There was also a significantly greater increase of 51 versus 7 CD4+ T-cells/ $\mu$ l. These effects were still visible after 48 weeks, although less marked. In the multivariate analysis, the following factors were associated with virological response (decrease of  $> 1$  log): STI (ratio 3.2), STI plus reversion to wild-type (12.4), adequate plasma trough levels (5.6) and use of lopinavir (6.0). It has been speculated that the effect occurred because of the occasionally very high PI level (Delaugerre 2005).

However, results from the GIGHAART Study have not remained unquestioned. In the CPRC064 Study, in which patients interrupted treatment for four months prior to the salvage regimen, no differences were found between those patients on STI and those who were not (Lawrence 2003). However, it was disconcerting to see that patients who interrupted treatment not only had worse CD4+ T-cell counts, but also a significantly higher frequency of severe clinical events during the follow-up period (22/138 versus 12/132). The study was even stopped prematurely as a result. Two other randomized studies (CCTG 578 and Retrogene) did not find any virological benefit in interrupting treatment prior to starting an intensified salvage regimen (Haubrich 2003, Ruiz 2003).

Despite all the discussions concerning mega- or giga-HAART, the primary treatment goal of achieving an “undetectable viral load” must be abandoned in some patients. This is particularly true if, despite the best compliance, significant side effects are the only result of treatment, due to toxicity and drug interactions. Here, more is clearly not always better. Quality of life is important to keep in mind. In such cases, it could be wiser to lower the bar and wait for new options (see below). Such patients should be monitored in larger centers where new options become available sooner and where clinicians have experience with intensified regimens. Using up a single new drug at a time should be avoided; if possible, two or more effective drugs should be used!

## Utilizing NNRTI “hypersusceptibility”

NNRTI-naïve patients (no prior therapy with nevirapine or efavirenz) often still respond surprisingly well to NNRTI-containing salvage regimens. In a small, randomized study on 56 NNRTI-naïve patients, the proportion of patients with less than 200 copies/ml after 36 weeks increased from 22 to 52 %, if nevirapine was given in addition to two new nucleoside analogs and nelfinavir (Jensen-Fangel 2001). In ACTG 359, addition of delavirdine to a new PI regimen increased the virological response rate from 18 to 40 % (Gulick 2002). The phenomenon of “NNRTI hypersusceptibility” may have been responsible for this. Viral strains are considered “hypersusceptible” to certain drugs if the IC<sub>50</sub> (50 % inhibitory concentration) for the drug is lower than that of the wild-type in phenotypic resistance tests. This phenomenon, for which the biochemical correlate is still the subject of debate (Delgado 2005), generally occurs very rarely with nucleoside analogs, but

quite frequently with NNRTIs, and mostly in viruses that have developed resistance mutations against nucleoside analogs.

NNRTI hypersusceptibility was first described in January 2000 (Whitcomb 2000). Several prospective studies have since described this phenomenon more closely (Albrecht 2001, Haubrich 2002, Katzenstein 2002, Mellors 2002). In an analysis of more than 17,000 blood samples, the prevalence of hypersusceptibility in NRTI-naïve patients to delavirdine, efavirenz and nevirapine was 5 %, 9 % and 11 %, respectively. In NRTI-experienced patients, it was notably 29 %, 26 % and 21 % (Whitcomb 2002). There seems to be some evidence that patients with NNRTI hypersusceptibility have better virological responses. Of 177 highly treatment-experienced (but NNRTI-naïve) patients, 29 % exhibited this type of lowered IC50 for one or several NNRTIs (Haubrich 2002). Of the 109 patients who received a new NNRTI-containing regimen, those with NNRTI hypersusceptibility achieved better results. Viral load was significantly lower even after 12 months (-1.2 versus -0.8 logs), and the CD4+ T-cell count was also higher.

Recent studies have demonstrated that NRTI mutations, predominantly at codons 215, 208 and 118, are independently associated with NNRTI hypersusceptibility (Shulman 2004). The replicative fitness does not seem to be important here (Schulman 2006). In another study, mutations were mainly at codons 41, 184, 210, 215. Even if the real significance and molecular correlate for NNRTI hypersusceptibility remain uncertain, the consequence is clear: patients with NRTI mutations and without NNRTI resistance should always receive an NNRTI in their new regimen if at all possible.

## **Salvage through recycling of older drugs**

One can occasionally also make use of drugs that have already been used in the past, as in the Jaguar Study, for example (Molina 2003). 168 patients with more than 1,000 copies/ml and a median 4 NRTI mutations on stable HAART received either ddI or placebo in addition. The viral load was reduced by 0.60 logs after 4 weeks. 68 % of patients had previously received ddI, and even in these patients, viral load was still reduced by 0.48 logs.

## **“Watch and wait” or even simplifying ART**

Sometimes even the most intensified salvage protocol is not effective. Viral load cannot be suppressed to undetectable levels, despite the use of T-20 and darunavir and other antiretroviral drugs. What should be done with such patients? The answer is: keep going, as long as the patient tolerates therapy! Multidrug-resistant viruses are typically slightly less aggressive than the wild-type, at least for a certain period of time. A drug such as 3TC also has a positive effect on the viral load even in the presence of a confirmed M184V resistance. In a small study, in which 6 patients with MDR viruses stopped only 3TC, the viral load increased 0.6 logs (Campbell 2005). Therefore, if possible, HAART should not be stopped completely in very immunocompromised patients who are then at risk of developing opportunistic infections. In fact, all efforts should be made, particularly in such cases, to at least

partially control the virus. “Just waiting” even on a suboptimal regimen is therefore a strategy that can be used to gain valuable time until new drugs become available. In such cases, HAART is not being taken in vain: suboptimal HAART is better than none at all, and some suppression of viral load still better than none. Patients benefit even with only a slight reduction in viral load (Deeks 2000). In a large cohort study, CD4+ T-cell counts did not drop as long as the viral load remained below 10,000 copies/ml, or at least 1.5 logs below the individual set point (Lederberger 2004).

One important question relates to how intensively treatment should be continued: some drugs can certainly be discontinued. NNRTIs such as nevirapine or efavirenz can be stopped if resistance mutations have been found, because replicative fitness is not influenced by the NNRTI mutations (Piketty 2004).

What about PIs? Initial data from a small pilot study on this issue gained some attention in February 2003, and was published recently (Deeks 2005). Although not always predictable from the design and analysis, the results were interesting: 18 patients, in whom the viral load remained high despite more than 6 months on HAART (good compliance, appropriate efficacy), had the PIs removed from their respective HAART regimens, whilst the NRTIs were continued. Within the first two weeks, none of the patients had an increase of more than 0.5 logs, and even after 16 weeks, no increase was observed in most patients (in only 5/18 patients, there was an increase of between 0.5 and 1.0 logs; in the others, there was no increase, or even a fall). A negative immunological effect was also seen in a few patients, but this was only moderate. Repeated resistance tests showed that all PI mutations persisted in all patients in the first 12 weeks, although PIs were not being taken. One retrospective study on HIV-infected children, in which the PIs had been discontinued, was based on the same ideas as the Deeks Study. Here, it was also seen that under continuous NRTI therapy, there was an increase in viral load over a long period of time (LeGrand 2005).

Results from one of our own patients (we now have several) where this approach has been successful for almost three years are shown in Table 9.3. Resistance testing after two years showed that there were no changes in the MDR virus.

The approach of “watch and wait” on a simple nucleoside regimen thus seems feasible in some patients for a certain period of time. The reasons for this phenomenon, however, are still not understood, but it is possible that multiresistant viruses cannot easily mutate back. With protease inhibitor therapy alone, this does not appear to be effective – in 5/5 patients, in whom only the nucleoside analog was stopped, the viral load rapidly increased significantly (Deeks 2005).

An Italian study took another innovative approach, enrolling 50 patients with a viral load of at least 1,000 copies/ml on a 3TC-containing regimen, with evidence of the M184V mutation and at least 500 CD4+ T-cells/ $\mu$ l (Castagna 2004). Patients were randomized to completely interrupt treatment or to continue with 300 mg 3TC alone. The rationale: the M184V mutation reduces the replicative fitness of HIV. And indeed – patients on 3TC had a significantly lower increase in viral load (0.6 versus 1.2 logs) and lost significantly less CD4+ T-cells (73 versus 153/ $\mu$ l). The M184V mutation was maintained in all patients on 3TC, and no other mutations accumulated. In contrast, a shift to wild-type was observed in all patients without 3TC.

Table 9.3: Example of a successful “wait and watch”-strategy over almost three years

Date	(HA)ART	CD4+ T cells	Viral load
until 1997	AZT, AZT+ddC, AZT+ddl	40 (nadir)	107,000
Mar 97	AZT+3TC+SQV-HGC	84	259,000
Oct 97	d4T+3TC+SQV+NfV	211	67,000
Jun 98	d4T+3TC+NVP+IDV/r	406	1,200
Jan 00	AZT+3TC+ABC+NVP+IDV/r	370	1,030
Mar 02	AZT+3TC+ABC+TDF+NVP+IDV/r	429	3,350
Sep 02	d4T+ddl+3TC+NVP+LPV/r	283	5,000
Nov 02*		348	7,600
Jan 03		315	16,400
Feb 03	AZT+3TC+ABC	379	6,640
May 03		241	2,400
Dec 04	AZT+3TC+ABC+TDF**	298	4,200
Jan 06		323	5,800

\*Resistance testing showed a total of 20 mutations, with genotypic resistance against all drugs tested. Compliance of the patient is very good, and plasma levels were always adequate.

\*\*TDF was added because of chronic hepatitis B infection.

As patient numbers are still very small in the data presented to date, many observers understandably remain skeptical. The main question is how long and in which patients these strategies could remain successful. It is thus advisable to monitor CD4+ T-cells at short intervals. Nevertheless, if such approaches could be confirmed in larger studies, they would be very attractive.

In addition to better tolerability and simpler dosing, the approach with nucleoside analog therapy would have the advantage of not exerting selective pressure to generate further PI or NNRTI mutations. Drugs such as tipranavir or darunavir, which do not have unlimited efficacy for salvage, would not be compromised. At the same token, it is essential to discontinue NNRTIs immediately, as replicative fitness is not influenced by NNRTI mutations. Otherwise, there is risk of eliminating future NNRTI options such as etravirine.

### Specific New Salvage Drugs

Integrase inhibitors as well as CCR5-antagonists, attachment- or maturation inhibitors are the new classes of drugs that have already been shown to decrease the viral load in HIV patients. The development of these classes will continue: see also the chapter entitled “HAART 2006/2007”.

In addition, new NRTIs and second generation NNRTIs such as SPD-754, etravirine or rilpivirine, are relatively far in their development.

Some of these drugs will be made available in expanded access programs within the next one or two year, or will be tested in Phase III trials. Where possible, patients with MDR viruses should be included in these studies.

## Practical tips for therapy of MDR viruses

1. First question: which previous treatment has been used, with what level of success and for how long?
2. Perform resistance testing (not during treatment interruption!).
3. After addressing point 1+2, choose as many new (active) drugs as possible when changing therapy, but remember to consider potential side effects!
4. Don't wait too long to switch, thus giving the virus the opportunity to develop further resistance mutations – the higher the viral load at the time of switch, the worse the chances for success.
5. Use lopinavir/r, and especially tipranavir or darunavir! In addition, simultaneous therapy with T-20 should be considered.
6. Has the patient ever taken NNRTIs? If not, it's high time! If so, and if there is NNRTI-resistance: stop NNRTIs!
7. Only consider a treatment interruption prior to starting the salvage regimen, if the CD4+ T-cell count and history allow.
8. Don't demand too much from the patient! Not everyone is suitable for mega-HAART.
9. Encourage the patient! New treatments will become available soon, and there is no such thing as having no more therapeutic options. And, just a "watch and wait" approach is possible.
10. Don't immediately exploit a single new drug– if the patient's condition and his or her CD4+ T-cell count allow it, at least wait for a second new drug.
11. Don't allow reversion to wild-type virus – even a "failing" regimen should be continued in the absence of further options.

## References on salvage

1. Albrecht MA, Bosch RJ, Hammer SM, et al. Nelfinavir, efavirenz, or both after the failure of nucleoside treatment of HIV infection. *N Engl J Med* 2001, 345:398-407. <http://amedeo.com/lit.php?id=11496850>
2. Benson CA, Deeks SG, Brun SC, et al. Safety and antiviral activity at 48 weeks of lopinavir/ritonavir plus nevirapine and 2 nucleoside reverse-transcriptase inhibitors in HIV type 1-infected protease inhibitor-experienced patients. *JID* 2002, 185:599-607. <http://amedeo.com/lit.php?id=11865416>
3. Boffito M, Arnaudo I, Raiteri R, et al. Clinical use of lopinavir/ritonavir in a salvage therapy setting: pharmacokinetics and pharmacodynamics. *AIDS* 2002, 16:2081-3. <http://amedeo.com/lit.php?id=12370509>
4. Boffito M, Dickinson L, Hill A, et al. Steady-state pharmacokinetics of saquinavir hard-gel/ritonavir/fosamprenavir in HIV-1-infected patients. *J AIDS* 2004, 37:1376-1384. <http://amedeo.com/lit.php?id=15483467>
5. Boffito M, Kurowski M, Kruse G, et al. Atazanavir enhances saquinavir hard-gel concentrations in a ritonavir-boosted once-daily regimen. *AIDS* 2004, 18:1291-7. <http://amedeo.com/lit.php?id=15362661>
6. Campbell TB, Shulman NS, Johnson SC, et al. Antiviral activity of lamivudine in salvage therapy for multidrug-resistant HIV-1 infection. *Clin Infect Dis* 2005, 41:236-42.
7. Castagna A, Danise A, Carini E, et al. E-184V. Pilot study to evaluate immunological response to lamivudine monotherapy vs treatment interruption in failing HIV-1 infected subjects, harbouring the M184V mutation. Abstract WeOrB1286, 15th Int Conf AIDS 2004, Bangkok.
8. Cooper D, Hicks C, Cahn P, et al. 24-week RESIST study analyses: the efficacy of tipranavir/ritonavir is superior to lopinavir/ritonavir, and the TPV/r treatment response is enhanced by inclusion of geno-



typically active antiretrovirals in the optimized background regimen. Abstract 560, 12th CROI 2005, Boston.

9. Corbett AH, Davidson L, Park JJ, et al. Dose separation strategies to overcome the pharmacokinetic interaction of a triple protease inhibitor regimen containing fosamprenavir lopinavir, and ritonavir. Abstract 611, 11th CROI 2004, San Francisco.
10. Deeks SG, Barbour JD, Martin JN, Swanson MS, Grant RM. Sustained CD4+ T cell response after virologic failure of protease inhibitor-based regimens in patients with HIV infection. *J Inf Dis* 2000, 181:946-53. <http://amedeo.com/lit.php?id=10720517>
11. Deeks SG, Hoh R, Neilands TB, et al. Interruption of Treatment with individual therapeutic drug classes in adults with multidrug-resistant HIV-1 infection. *J Inf Dis* 2005, 192:1537-44. <http://amedeo.com/lit.php?id=16206068>
12. Delaugerre C, Peytavin G, Dominguez S, et al. Virological and pharmacological factors associated with virological response to salvage therapy after an 8-week of treatment interruption in a context of very advanced HIV disease (GigHAART ANRS 097). *J Med Virol* 2005, 77:345-350. <http://amedeo.com/lit.php?id=16173015>
13. Delgado J, Shulman N. Drug resistance. NNRTI hypersusceptibility. *AIDS Read* 2005, 15:28-30. <http://amedeo.com/lit.php?id=15685732>
14. Elston RC, Yates P, Tisdale M, et al. GW433908 (908)/ritonavir (r): 48-week results in PI-experienced subjects: A retrospective analysis of virological response based on baseline genotype and phenotype. Abstract MoOrB1055, XV Int AIDS Conf 2004; Bangkok.
15. Eron JJ Jr, Bartlett JA, Santana JL, et al. Persistent antiretroviral activity of nucleoside analogues after prolonged zidovudine and lamivudine therapy as demonstrated by rapid loss of activity after discontinuation. *J AIDS* 2004, 37:1581-1583.
16. Eron JJ, Haubrich R, Lang W, et al. A phase II trial of dual protease inhibitor therapy: amprenavir in combination with indinavir, nelfinavir, or saquinavir. *J AIDS* 2001, 26:458-61. <http://amedeo.com/lit.php?id=11391165>
17. Ford J, Boffito M, Wildfire A, et al. Effect of atazanavir on intracellular and plasma pharmacokinetics of saquinavir and ritonavir administered once daily in HIV infected patients. Abstract PL6.3, 7th Int Congress Drug Ther HIV Inf 2004, Glasgow.
18. Gulick RM, Hu XJ, Fiscus SA, et al. Durability of response to treatment among antiretroviral-experienced subjects: 48-week results from ACTG Protocol 359. *J Inf Dis* 2002, 186:626-33. <http://amedeo.com/lit.php?id=12195349>
19. Haas DW, Zala C, Schrader S, et al. Therapy with atazanavir plus saquinavir in patients failing highly active antiretroviral therapy: a randomized comparative pilot trial. *AIDS* 2003, 17:1339-49.
20. Haubrich R, Best B, Miller C, et al. Response to LPVr in experienced patients: effect of a treatment interruption. Abstract 565, 10th CROI 2003, Boston. <http://www.retroconference.org/2003/Abstract/Abstract.aspx?AbstractID=1311>
21. Haubrich RH, Kemper CA, Hellmann NS, et al. The clinical relevance of non-nucleoside reverse transcriptase inhibitor hypersusceptibility: a prospective cohort analysis. *AIDS* 2002, 16:F33-40. <http://amedeo.com/lit.php?id=11782591>
22. Hellinger J, Cohen C, Morris A, et al. Pilot study of saquinavir and lopinavir/ritonavir twice daily in protease inhibitor-naive HIV-positive patients. *HIV Clin Trials* 2005, 6:107-17.
23. Hogg RS, Bangsberg D, Alexander C, et al. Drug resistance is associated with an increased risk of death in patients first starting HAART. Abstract 712, 12th CROI 2005, Boston.
24. Isaac A, Taylor S, Cane P, et al. Lopinavir/ritonavir combined with twice-daily 400 mg indinavir: pharmacokinetics and pharmacodynamics in blood, CSF and semen. *J Antimicrob Chemother* 2004, 54:498-502. <http://amedeo.com/lit.php?id=15254024>
25. Jensen-Fangel S, Thomsen HF, Larsen L, et al. The effect of nevirapine in combination with nelfinavir in heavily pretreated HIV-1-infected patients: a prospective, open-label, controlled, randomized study. *J AIDS* 2001, 27:124-9. <http://amedeo.com/lit.php?id=11404533>
26. Johnson M, Grinsztejn B, Rodriguez C, et al. 96-week comparison of once-daily atazanavir/ritonavir and twice-daily lopinavir/ritonavir in patients with multiple virologic failures. *AIDS* 2006, 20:711-718. <http://amedeo.com/lit.php?id=16514301>
27. Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS* 2005, 19:685-694. <http://amedeo.com/lit.php?id=15821394>
28. Kashuba AD, Tierney C, Downey GF, et al. Combining fosamprenavir with lopinavir/ritonavir substantially reduces amprenavir and lopinavir exposure: ACTG protocol A5143 results. *AIDS* 2005, 19:145-52. <http://amedeo.com/lit.php?id=15668539>

29. Katlama C, Carvalho MI, Cooper D, et al. TMC 114/r out performs investigator selected PI(s) in three class-experienced patients: week 24 primary analysis of POWER 1 (TMC 114-C213). Abstract WeOaLB0102, 3rd IAS 2005, Rio de Janeiro.
30. Katlama C, Dominguez S, Duvivier C, et al. Benefits of treatment interruption in patients with multiple therapy failures, CD4 cells <200 /mm<sup>3</sup> and HIV RNA >50 000 cp/ml. Abstract 5887, XIV Int AIDS Conf 2002, Barcelona.
31. Katlama C, Dominguez S, Gourlain K, et al. Benefit of treatment interruption in HIV-infected patients with multiple therapeutic failures: a randomized controlled trial (ANRS 097). *AIDS* 2004, 18:217-26. <http://amedeo.com/p2.php?id=15075539&s=hiv>
32. Kempf DJ, Isaacson JD, King MS, et al. Identification of genotypic changes in HIV protease that correlate with reduced susceptibility to the protease inhibitor lopinavir among viral isolates from protease inhibitor-experienced patients. *J Virol* 2001, 75:7462-9. <http://amedeo.com/lit.php?id=11462018>
33. Khanlou H, Farthing C. Favorable interaction between atazanavir and fosamprenavir with and without ritonavir in the treatment of HIV-infected patients. Abstract P288, 7th Int Congress Drug Ther HIV Inf 2004, Glasgow.
34. Khanlou H, Graham E, Farthing C. Drug interactions between amprenavir and lopinavir/ritonavir in salvage therapy. *AIDS* 2002, 16:797-798.
35. Klein C, Bertz R, Ashbrenner E, et al. Assessment of the multiple-dose pharmacokinetic interaction of lopinavir/ritonavir with nelfinavir. Abstract 536, 10th CROI 2003, Boston.
36. la Porte CJ, Schippers EF, van der Ende ME, et al. Pharmacokinetics of once-daily lopinavir/ritonavir and the influence of dose modifications. *AIDS* 2005, 19:1105-7. <http://amedeo.com/lit.php?id=15958844>
37. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003, 348:2175-85. <http://amedeo.com/lit.php?id=12637625>
38. Langmann P, Zilly M, Winzer R, et al. Efficacy and safety of ATV in combination with LPV/r. Abstract 56, 6th IWCPHT 2005, Quebec.
39. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant HIV. *N Engl J Med* 2003, 349:837-46. <http://amedeo.com/lit.php?id=12944569>
40. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; 348:2186-95. <http://amedeo.com/lit.php?id=12773645>
41. Lazzarin A, Mukwaya G, Clumek N, et al. Tipranavir/ritonavir (TPV/r) demonstrates superior treatment response to lopinavir/r, amprenavir/r or saquinavir/r in PI-experienced patients from the TPV RESIST-1 and RESIST-2 trials. Abstract WePe6.3C07, 3rd IAS 2005, Rio de Janeiro.
42. Ledergerber B, Lundgren JD, Walker AS, et al. Predictors of trend in CD4-positive T-cell count and mortality among HIV-1-infected individuals with virological failure to all three antiretroviral-drug classes. *Lancet* 2004, 364:51-62. <http://amedeo.com/lit.php?id=15234856>
43. Leen CS et al. Pharmacokinetics of indinavir when co-administered with tipranavir/ritonavir. Abstract 299, 7th Int Congress Drug Ther HIV Inf 2004, Glasgow.
44. Legrand FA, Abadi J, Jordan KA, et al. Partial treatment interruption of protease inhibitors augments HIV-specific immune responses in vertically infected pediatric patients. *AIDS* 2005, 19:1575-1585.
45. Lohse N, Obel N, Kronborg G, et al. Declining risk of triple-class antiretroviral drug failure in Danish HIV-infected individuals. *AIDS* 2005, 19:815-22. <http://amedeo.com/lit.php?id=15867496>
46. Lucas GM, Gallant JE, Moore RD. Relationship between drug resistance and HIV-1 disease progression or death in patients undergoing resistance testing. *AIDS* 2004, 18:1539-48. <http://amedeo.com/lit.php?id=15238772>
47. Masquelier B, Breilh D, Neau D, et al. HIV-1 genotypic and pharmacokinetic determinants of the virological response to lopinavir-ritonavir-containing therapy in protease inhibitor-experienced patients. *Antimicrob Agents Chemother* 2002, 46:2926-32. <http://amedeo.com/lit.php?id=12183249>
48. Mauss S, Schmutz G, Kuschak D. Unfavourable interaction of amprenavir and lopinavir in combination with ritonavir? *AIDS* 2002, 16:296-297.
49. Mauss S, Scholten S, Wolf E, et al. A prospective, controlled study assessing the effect of lopinavir on amprenavir concentrations boosted by ritonavir. *HIV Med* 2004, 5:15-7.
50. Mellors J, Bennett FVK, Hellmann NS, et al. Efavirenz hypersusceptibility improves virologic response to multidrug salvage regimens in ACTG 398. Abstract 45, 9<sup>th</sup> CROI 2002, Seattle, USA. <http://www.retroconference.org/2002/Abstract/12985.htm>
51. Miller V, Cozzi-Lepri A, Hertogs K, et al. HIV drug susceptibility and treatment response to mega-HAART regimen in patients from the Frankfurt HIV cohort. *Antivir Ther* 2000, 5:49-55. <http://amedeo.com/lit.php?id=10846593>

52. Molina J, Marcelin AG, Pavie J, et al. Didanosine (ddI) in treatment-experienced HIV-infected patients: results from a randomized double-blind study (AI454-176 Jaguar). Abstract 447, 43rd ICAAC 2003, Chicago.
53. Molla A, Mo H, Vasavanonda S, Han L, et al. In vitro antiviral interaction of lopinavir with other protease inhibitors. *Antimicrob Agents Chemother* 2002, 46:2249-53. <http://amedeo.com/lit.php?id=12069982>
54. Montaner JS, Harrigan PR, Jahnke N, et al. Multiple drug rescue therapy for HIV-infected individuals with prior virologic failure to multiple regimens. *AIDS* 2001, 15:61-9. <http://amedeo.com/lit.php?id=11192869>
55. Piketty C, Gerard L, Chazallon C, et al. Virological and immunological impact of non-nucleoside reverse transcriptase inhibitor withdrawal in HIV-infected patients with multiple treatment failures. *AIDS* 2004, 18:1469-71. <http://amedeo.com/lit.php?id=15199325>
56. Prado JG, Parkin NT, Clotet B, Ruiz L, Martinez-Picado J. HIV type 1 fitness evolution in antiretroviral-experienced patients with sustained CD4+ T cell counts but persistent virologic failure. *Clin Infect Dis* 2005, 41:729-37. <http://amedeo.com/lit.php?id=16080097>
57. Raguin G, Chene G, Morand-Joubert L, et al. Salvage therapy with amprenavir, lopinavir and ritonavir 200 mg/d or 400 mg/d in HIV-infected patients in virological failure. *Antivir Ther* 2004, 9:615-25. <http://amedeo.com/lit.php?id=15456093>
58. Ribera E, Lopez RM, Diaz M, et al. Steady-state pharmacokinetics of a double-boosting regimen of saquinavir soft gel plus lopinavir plus minidose ritonavir in HIV-infected adults. *Antimicrob Agents Chemother* 2004, 48:4256-62. <http://amedeo.com/lit.php?id=15504850>
59. Riddler SA, Havlir D, Squires KE, et al. Coadministration of indinavir and nelfinavir in HIV type 1-infected adults: safety, pharmacokinetics, and antiretroviral activity. *Antimicrob Agents Chemother* 2002, 46: 3877-3882. <http://amedeo.com/lit.php?id=12435691>
60. Rottmann C et al. Atazanavir/ritonavir/saquinavir without any other antiretroviral drugs in protease inhibitor experienced patients with no reverse transcriptase inhibitor options: a 24 week cohort analysis. Abstract P21, 7th Int Congress Drug Ther HIV Inf 2004, Glasgow.
61. Ruiz L, Ribera E, Bonjoch A, et al. Role of structured treatment interruption before a five-drug salvage antiretroviral regimen: the Retrogene Study. *J Infect Dis* 2003, 188:977-985. <http://amedeo.com/lit.php?id=14513417>
62. Schranz J, Fessel WJ. Crixivan-Viracept double PI study (protocol 079): indinavir-nelfinavir + d4T/3TC bid vs indinavir q8h + d4T/3TC. Abstract TuPeB3221, XIII Int AIDS Conf 2000, Durban, South Africa.
63. Shulman N, Mellors J, Clark S, Bosch R, Parkin N. Replicative capacity effect of mutations that are associated with efavirenz hypersusceptibility. Abstract 624, 13th CROI 2006, Denver.
64. Shulman NS, Bosch RJ, Mellors JW, et al. Genetic correlates of efavirenz hypersusceptibility. *AIDS* 2004, 18:1781-5. <http://amedeo.com/lit.php?id=15316338>
65. Staszewski S, Dauer B, Carlebach A, et al. The LOPSAQ salvage study: 48 week analysis of the full cohort treated with lopinavir (LPV/r) plus saquinavir (SQV) without any additional antiretroviral (ART) therapy. Abstract, XV Int AIDS Conf 2004, Bangkok.
66. Staszewski S, Dauer B, Gute P, et al. The Crixilo Cohort Study: preliminary results from a salvage study of HIV-positive patients treated with indinavir and lopinavir/ritonavir without the addition of reverse transcriptase inhibitors. Abstract H-853, 43rd ICAAC 2003, Chicago.
67. Stephan C, Hentig N, Kourbeti I, Dauer B, et al. Saquinavir drug exposure is not impaired by the boosted double protease inhibitor combination of lopinavir/ritonavir. *AIDS* 2004, 18:503-8. <http://amedeo.com/lit.php?id=15090803>
68. Taburet AM, Raguin G, Le Tiec C, et al. Interactions between amprenavir and the lopinavir-ritonavir combination in heavily pretreated patients infected with human immunodeficiency virus. *Clin Pharmacol Ther* 2004, 75:310-23. <http://amedeo.com/lit.php?id=15060509>
69. van Heeswijk RP, Veldkamp A, Mulder JW, et al. Combination of protease inhibitors for the treatment of HIV-1-infected patients: a review of pharmacokinetics and clinical experience. *Antivir Ther* 2001, 6:201-29. <http://amedeo.com/lit.php?id=11782591>
70. Von Hentig N, Dauer B, Moesch M, et al. Indinavir plasma exposure is not affected by ritonavir/lopinavir co-administration in a boosted double PI-only therapy regimen. Abstract F2/4, 9th EACS 2003, Warsaw, Poland
71. Whitcomb JM, Deeks S, Huang W. Reduced susceptibility to NRTI is associated with NNRTI hypersensitivity in virus from HIV-1-infected patients. Abstract 234, 7<sup>th</sup> CROI 2000, San Francisco, USA. <http://www.retroconference.org/2000/abstracts/234.htm>
72. Whitcomb JM, Huang W, Limoli K, et al. Hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in HIV-1: clinical, phenotypic and genotypic correlates. *AIDS* 2002, 16:F41-7. <http://amedeo.com/lit.php?id=12370521>

73. Zaccarelli M, Tozzi V, Lorenzini P, et al. Multiple drug class-wide resistance associated with poorer survival after treatment failure in a cohort of HIV-infected patients. *AIDS* 2005, 19:1081-9.  
<http://amedeo.com/lit.php?id=15958840>
74. Zilly M, Winzer R, Nolte C, et al. Double PI boosting with atazanavir and fos-amprenavir: favourable pharmacokinetics. Abstract 93, 6th Int Workshop Clin Pharmacol HIV Therapy 2005, Quebec.

## 10. When to stop HAART

A current review of treatment interruption

Christian Hoffmann

Hardly a topic in the field of HIV medicine has evoked more heated discussion in the last years than treatment interruption. However, in the discussion over possible risks (AIDS, resistance) or advantages (reduction of toxicity and costs), many issues are confused. It is not only between structured treatment interruptions (STIs), which are made with the knowledge of the treating doctor, and unstructured “drug holidays” that a distinction needs to be drawn. But, the reasons for the interruption of treatment should also be made clear. The reasons can differ greatly.

- At the patient’s request
- To improve compliance and psyche (“life sentence” removed)
- To reduce long-term toxicity
- For immunological reasons
- As a salvage strategy

Many treatment interruptions occur without the clinician’s knowledge. For this reason alone, treatment interruptions are an important constituent of antiretroviral therapies, whether, as a clinician, one approves of them or not. To oppose them means to disregard the realities of treatment. The following chapter provides an overview of the current knowledge in this area. It is limited to patients with chronic HIV infection; (for recommendations on acutely infected patients see the chapter on “Acute HIV Infection”).

### Viral load and CD4+ T-cells during treatment interruption

Almost all patients who stop treatment experience a “rebound” in viral load within a few weeks, even patients in whom this has been undetectable for several years (Davey 1999, Chun 2000). Viral load is usually detectable again within 10-20 days (Davey 1999, Harrigan 1999, Garcia 1999), and its doubling time in the blood is around 1.6 – 2.0 days. The viral load in compartments such as the CNS, as well as the semen and vaginal fluids, changes in parallel to that in the plasma (Garcia 1999, Neumann 1999). The patients should therefore be informed about the higher risk of transmitting HIV.

Frequently, an initial overshooting rebound is observed (De Jong 1997, Birk 2001), and only after a few weeks does the viral load settle to its original, pre-treatment level (Hatano 2000). The rebounding virus evidently does not originate from latent reservoirs; other cell populations must exist, from which these new viruses can be produced so quickly (Chun 2000, Ho 2000, Imamichi 2001).

Treatment interruptions can have serious immunological consequences. Often, CD4+ T-cell counts drop within a short time to pre-treatment levels. The ground that has been gained on HAART is rapidly lost again. The drop is biphasic, and the interval strongest in the first few months (Fagard 2005, Wit 2005, Skiest 2006).

CD4+ T-cell losses vary greatly between patients but may reach 200 or 300/ $\mu$ l within a few weeks. The higher and faster the CD4+ T-cells increased on HAART, the more rapid their decline (Tebas 2002). The CD4 nadir is also important. The lower it was, the more rapidly the cell count drops again (Maggiolo 2004, Skiest 2006). Age is also important – the older the patient, the more extensive the immunological deterioration. The loss of CD4+ T-cells during an interruption may not be regained as quickly. In a prospective study, we saw a significant disadvantage for patients undergoing treatment interruptions. After a follow up of 18 months, CD4+ T-cells were more than 120/ $\mu$ l less in these patients than in matched patients who had not interrupted treatment (Wolf 2005).

### **The risks: resistance, clinical problems, AIDS**

Viral resistance always have to be anticipated whenever there is viral replication in the presence of suboptimal drug levels, and thereby resistant mutants gain a selective advantage over the wild-type virus. As a result, there are concerns that resistances could develop both during the washout phase of medication (increasing viral replication with insufficient plasma levels) and on re-initiation of treatment (continued replication despite sufficient plasma levels).

However, in the case of single treatment interruptions, the probability of this does not appear to be particularly high, as shown in 1999 by the small French COMET Study, one of the first studies on treatment interruption (Neumann 1999). But, there is no certainty as to whether interruptions might not eventually lead to development of resistant isolates, which merely require more time until they are able to dominate the wild-type. Mathematical models show that this risk – at least theoretically – is not low, especially if viral load rises to high levels (Dorman 2000, Bonhoeffer 2000).

The risk of resistance is probably higher for repeated treatment interruptions. In several studies, these have led particularly to NNRTI- or 3TC-resistance (Martinez-Picado 2002, Schweighardt 2002, Ruiz 2005). The risk seems particularly high for strategies involving stopping and starting of HAART at fixed intervals (see below).

Table 10.1 describes the example of a patient who was clinically well and who interrupted treatment. It was probably the repeated stopping and starting of HAART that ultimately led to resistance in this case.

The sharp increase in viral load that may often occur can present as a retroviral syndrome. The symptoms are similar to acute HIV infection, with lymphadenopathy, fever, asthenia and malaise (Colven 2000, Kilby 2000, Zeller 2001, Ruiz 2004). Thrombocytopenia has also been described during interruptions (Ananworanich 2003). The blood count needs to be monitored, especially in patients with a previous history of thrombocytopenia. Finally, attention should also be paid to patients who are co-infected with hepatitis B virus. If the HBV treatment with 3TC, FTC or tenofovir is interrupted, HBV rebound can result in fulminant and life-threatening hepatitis (Sellier 2004). It is therefore advisable to look after these patients very carefully and monitor the liver enzymes at least every two weeks.

Table 10.1: Example of the development of resistance due to repeated treatment interruptions\*

Date	HAART/comments	CD4 <sup>+</sup> T-cells	Viral load
Jun 97	AZT+3TC+SQV	288	67,000
Oct 99	HAART stopped, patient feeling well	540	< 50
Dec 99	Diagnosis of autoimmune hyperthyroidism	400	63,000
Jan 00	AZT+3TC+NVP (+ carbimazole)	260	74,000
Feb 00	Diagnosis of anemia (Hb 7.3 g/dl) HAART stopped again	347	1,500
Mar 00	d4T+3TC+NVP (+ carbimazole)		
Apr 00	Resistance mutations K103N, M184V	360	2,400

\*During the first treatment interruption the patient developed autoimmune hyperthyroidism, the treatment of which led to anemia after re-initiation of HAART, so that HAART was interrupted again. As a result, resistance developed against NNRTIs and 3TC. Autoimmune phenomena in the context of treatment interruption as seen in this patient have not previously been described.

The risk of AIDS seems to be low for single interruptions provided the immune defect is only moderate. In the Swiss Cohort, the risk of progression was not increased (Taffe 2002). In 133 patients who interrupted treatment, we observed no increased risk of AIDS after 24 months, compared to 262 matched controls (Wolf 2005). However, almost all patients in this study were immunologically stable throughout. The risk is probably higher in patients with severe immunodeficiency (Deeks 2001, Lawrence 2003). The CPRC064 Study in which 270 patients with MDR viruses and mostly distinct immunodeficiency (median 144 CD4<sup>+</sup> T-cells/ $\mu$ l) were randomized before a salvage regimen either to a four-month treatment interruption or not, was stopped because of a high risk of progression. In comparison with the control group, a significantly higher number of AIDS illnesses (17 versus 5) occurred in the group interrupting therapy. In a multivariate analysis, two factors were predictive for death or progression: treatment interruption and the CD4<sup>+</sup> T-cell count at the time of interruption. The risk increased by 1.4 with every drop of 50 CD4<sup>+</sup> T-cells demonstrating that severely immunocompromised patients are particularly at risk of developing AIDS during long treatment interruptions of several months. Treatment interruptions should be avoided in such patients. Newer data from the SMART Study, however, show that even with higher CD4<sup>+</sup> T-cells, treatment interruptions can lead to the development of AIDS (see below).

### STI at the patient's wish, and for reduction of toxicity

Interruption of therapy can have psychological advantages (Tuldra 2001). Quality of life improves (Moreno 2003), and many patients are relieved of the burden of continuous, "lifelong" therapy. Clinicians should take the wish for treatment interruption seriously. Presumably most patients expressing such a wish will interrupt sooner or later anyway; so the interruption may as well be structured and controlled. However, the psychological benefit of treatment interruption has not been confirmed by studies – in fact it is striking how few studies have been based on this theme.

Increased transaminases or lipid levels drop quite rapidly after stopping treatment (Hatano 2000, Wolf 2005). It is still not clear whether this is relevant in reducing the risk of cardiovascular disease. In SMART, the risk of cardiovascular and metabolic complications during STIs was actually increased (El Sadr 2006, see below). At present, it seems at least questionable that, through solitary or repeated interruptions, so much HAART can be saved as to improve the cardiovascular risk profile.

What about lipodystrophy and mitochondrial toxicity? At least two studies have shown that, after a few months, mitochondrial DNA can regenerate itself during a treatment break (Cote 2002, Mussini 2005). In contrast, another study showed no effect (Negredo 2006). Whether or not a clinically manifested lipodystrophy improves, remains to be proven. At least short treatment interruptions have not had any effect on morphological changes (Hatano 2000). Resolution of lipodystrophy even after longer interruptions is by no means certain; we have a patient who was treated during seroconversion and developed a “buffalo hump” after one and a half years, which has not resolved even after almost five years of treatment interruption.

Summary: although a treatment interruption, is theoretically substantiated to deal with the worries of long-term toxicity on HAART, a convincing argument has not been provided by the data so far.

## **STI – for immunological reasons**

Hardly any patient has become as famous as the acutely infected homosexual man treated in a Berlin private practice a few years ago who, with a viral load of approximately 80,000 copies/ml, began a HAART regimen consisting of didanosine, indinavir and hydroxyurea. The virus rapidly became undetectable. After several problems – and two short treatment interruptions – HAART was completely stopped after 176 days. Surprisingly, even without drugs, plasma viremia has remained below the level of detection for more than five years. Although virus was still detectable in lymph nodes, thus excluding eradication, the immune system in this case – referred to as the Berlin Patient among experts in the field (Liszewicz 1999) – was obviously capable of durable control of infection. But why? Was it the early initiation of therapy, the hydroxyurea, or the treatment interruptions? To be honest, it must be admitted that no one knows the answer, even today. There may be a completely different explanation: it is possible that certain host factors in this patients that have not yet been investigated could influence the course of disease – completely independently of HAART, STI or hydroxyurea. Nevertheless, STI has been extensively investigated in acutely infected patients (see chapter “Acute HIV infection”).

Attempts to improve HIV-specific immune responses with treatment interruptions in chronically infected patients have been unsuccessful. The theory of “endogenous vaccination” seems plausible: transient increases in viral load could strengthen HIV-specific immune responses, which decline with increasing viral suppression on HAART.

In several pilot studies from 2000/2001, successive interruptions seemed to indeed prolong the time to viral rebound or decrease the rate of rebound, and, in parallel, there were measurable improvements in HIV-specific CD4+ or CD8+ T-cell immune responses (Haslett 2000, Garcia 2001, Lori 2000, Ortiz 1999, Papasavvas



2000, Ruiz 2000). However, almost none of these studies included more than 2-6 patients, and a control group was usually missing. Was this wishful thinking?

STI was finally “put to the test” in the Spanish-Swiss SSITT Study (Oxenius 2002, Fagard 2003): 133 patients were monitored throughout four ten-week treatment cycles, each consisting of eight weeks HAART and two weeks of treatment interruption. After this, HAART was permanently interrupted. Treatment success – defined as a viral load below 5,000 copies/ml without HAART after 52 weeks – occurred in 21/99 patients. However, 5/21 patients had a low viral load even before the initiation of HAART. Most importantly, none of the 32 patients with a pre-HAART viral load above 60,000 copies/ml achieved a viral load of less than 5,000 copies/ml. The viral load set point is lowered in only a few patients, usually those with low initial viral load, despite repeated STIs. In contrast to acute infection, improvement of HIV-specific immune response seems unlikely in the setting of chronic HIV infection. SSIT clearly showed that treatment interruptions on immunological grounds alone are not justified and are dangerous.

In addition, approaches with immunomodulatory drugs, such as hydroxyurea (Foli 2004), mycophenolat (Garcia 2004) or steroids (Ulmer 2005), exist to lengthen the period of STIs. These approaches, whose benefits anyway seem questionable, are still in the experimental phases and not justified outside studies.

### **STI as a salvage strategy for MDR viruses**

In most patients with MDR viruses, treatment interruption leads to a gradual shift back to the wild-type virus and a loss of resistance. Therefore, resistance testing during treatment interruption is often of little use since mutations disappear from the blood as early as two weeks after treatment interruption (Devereux 1999). In modestly immunosuppressed patients, this shift is observed more frequently and faster. In more advanced stages of disease and with a longer duration of treatment, it lasts longer (Miller 2000, Izopet 2000), and sometimes after a longer interruption of therapy, no shift can be seen (Halfon 2005). Providing the shift is visible: PI mutations are the first to disappear, while NNRTI mutations are more protracted because they hardly affect the viral fitness (Deeks 2001, Birk 2001). It is assumed that the wild type merely dominates the resistant mutants. Special PCR methods are still able to detect low quantities of resistant viruses during STI (Izopet 2000), and after treatment is restarted, resistance mutations rapidly dominate again (Delaugerre 2001). Only a few cases have been described in which resistance mutations were apparently flushed out completely. One such patient, from Germany, has been described (Walter 2002), who was not able to attain sufficient viral suppression despite intensified HAART, and who then interrupted treatment. During the following seven months of treatment interruption, there was a gradual reversion to the wild-type virus, and after re-starting HAART (which, according to previous resistance testing, should have had no effect) the viral load has now been successfully suppressed for several years.

Can patients with multi-resistant viruses improve the effect of the salvage regimen, if they have had a previous interruption of treatment? At least two studies to date have shown that the shift resulting from treatment interruptions can be beneficial for salvage strategies. In the Frankfurt Cohort, a shift was associated with improved response to the salvage regimen (Miller 2000). In the GIGHAART Study, there was

still evidence of antiviral efficacy after one year in patients who had interrupted treatment before starting a salvage regimen (Katlama 2004). However, this data is in contrast to that of numerous other studies in which an increased risk of AIDS was seen during treatment interruptions (Lawrence 2003, Ruiz 2003, see above). At the end of 2005, a further work, the Reserve Study, was published, which brought the concept of STI in multiresistance under more scrutiny than before (Ghosh 2005). A total of 23 patients with MDR viruses, on long-term therapy and severely immunosuppressed, interrupted their HAART until at least two drugs became effective again according to genotypic resistance tests. The interval lasted 24 weeks on average, after which an intensive salvage regimen was started (usually at least 6 drugs). The results were sobering: nothing changed during the interruption. After 12 weeks on the salvage regimen, the viral load was practically unchanged in comparison to the baseline value. An even more disturbing side effect: in 15/23 (65 %) of the patients, AIDS illnesses occurred, sometimes even after the interruption.

Summary: in view of the risk of AIDS and the lack of evidence regarding the benefits, treatment interruptions are not justified as salvage strategies outside clinical studies, at least in the severely immunosuppressed.

### **Structured intermittent treatment, fixed intervals**

In the initial phase following interruption of HAART, the viral load usually continues to be very low. Plasma viremia only reaches pre-treatment levels after about four, sometimes even six weeks. The risk of developing resistance is presumably small at lower levels of viral replication (Bonhoeffer 2000). Does this indicate that ultra-short treatment interruptions could be utilized to reduce drugs, costs and long-term toxicity?

In an NIH pilot study on SIT (structured intermittent treatment), 10 chronically infected patients with more than 300 CD4+ T-cells/ $\mu$ l and a viral load below 50 copies/ml were switched to a combination of d4T+3TC+indinavir/r. This combination was administered as seven days of treatment and seven days interruption (7-on-7-off) for a period of at least 44 weeks. The result: neither the viral load nor the proviral DNA increased. CD4+ T-cells and HIV-specific immune responses remained unchanged, suggesting that the immune system is probably unaffected by such ultra-short breaks in treatment. A significant reduction in lipid levels did, however, occur (Dybul 2001). Some patients experienced several blips (temporary increases in viral load) to above 100 copies/ml. The same group has recently reported successful use of the same strategy in eight patients using ddI+3TC+efavirenz. Seven of eight patients have now been followed for more than 60-84 weeks (Dybul 2004). Nevertheless: at this time, it is impossible to predict whether this treatment strategy might result in a higher risk of resistance in the long term. There are still no larger studies, and it has become suspiciously quiet in this area. In addition, patients in the NIH pilot studies were carefully selected, with good immune status and many years of viral suppression. This strategy is probably only applicable to a few patients. A three-armed study from Thailand has already gathered more negative experience with the 7-on-7-off approach (Cardiello 2005). In this study, 19 of 36 patients experienced virological treatment failure within a short period of time, and this treatment arm was consequently stopped prematurely. The main reason for these poor results appears to lie in the fact that the majority of

patients were NRTI-experienced. This means: if nucleoside analogs are unstable, such on-off strategies are problematic.

ART only on weekdays? This approach was taken by the FOTO Study (“Five On, Two Off”), in which HAART was only taken from Monday to Friday and stopped at the weekends (i.e. sparing 28 %). This study enrolled patients on a HAART regimen, who had an undetectable viral load for at least three months. After 48 weeks only one of the 17 NNRTI-treated patients had an increase in viral load, although 2 of 9 PI-treated patients did (Cohen 2005). The authors speculate that the long half-life of efavirenz (none of the 9 patients on efavirenz demonstrated an increase) could be the reason for this difference. Further studies have to be conducted, before such an approach can be recommended.

In contrast, longer interruptions, over several weeks, with fixed intermittent treatment seem to be unfavorable. Results from a randomized NIH study with fixed intervals (each with one month of STI, two months of treatment) were disconcerting (Dybul 2003). The SIT arm contained significantly more patients with virological treatment failure. Resistance mutations developed particularly against NNRTIs and 3TC, so that the study was stopped early. In the Spanish-Swiss SSITT Study (2 weeks STI, 2 months HAART) some resistance was seen (Yerli 2003), likewise in an Italian study (Palmisano 2006). Even though the French WINDOW Study (two months each of STI and therapy) showed no increase in the number of resistances (Marchou 2006), the studies that indicate fixed interruptions as being susceptible to the development of resistances prevail.

### **CD4-driven interruptions: SMART and the consequences**

Beside fixed intervals, whether short or long, there is another approach, whereby interruptions are individualized and based on CD4+ T-cell count. In other words, in patients with a good CD4 count, HAART is interrupted until the CD4 count drops below an immunological cut-off, and only then is it restarted. Over the last few years, many non-randomized studies with differing cut-off points and very heterogeneous patient populations came to the conclusion that this approach is safe and allows for a considerable reduction in drug exposure (Moreno 2003, Boschi 2004, Maggiolo 2004, Skiest 2004, Fernandez 2005, Mussini 2005). In the meantime, a few randomized studies compare such CD4-driven intervals with continuous administration of HAART. The relevant data and results of these studies are given in Table 10.2.

It is clear that the results of these randomized studies differ considerably in part. Whilst TIBET, Staccato or ACTG 5170 produced the verdict that CD4-driven interruptions are safe, two other studies, Trivucan and SMART came to other conclusions.

Table 10.2: Randomized studies in which therapy was continued or interrupted based on CD4 cell count

Source	n	BL-CD4	CD4+ T-cells at restart	Results based on clinical findings in STIs
Ruiz 2005 TIBET	201	> 500 > 6 Mo	< 350 or VL > 100,000	6 % ARS, otherwise STIs clinically safe. Average STI-duration 44 weeks. de novo NNRTI resistances.
El Sadr 2006 SMART	5472	350	< 250	Morbidity and mortality risk low, but significantly raised! See Table 10.3.
Danel 2006 Trivacan	326	> 350	< 250	Morbidity significantly raised (double), due to invasive bacterial infections.
Ananworanich 2006 Staccato	430	> 350	< 350	After 484 PJ: clinically safe (slightly more side effects in HAART arm; more candidiasis in STI arm). No evidence of resistances.
Skiest 2006 ACTG 5170	167	> 350	< 250	In general, safe, with risks only elevated when CD4 nadir was low.

ARS = acute retroviral syndrome; FU = follow up; Mo = months; PJ = patient years; BL = baseline

In particular, the results of the SMART Study, which started in 2002, caused a sensation. In this, the largest randomized HIV study of all time, the cut off levels for stopping HAART were at least 350 cells/ $\mu$ l, and 250 cells/ $\mu$ l for re-instating it. This study was extremely successful worldwide. In the end, 318 centers in 53 countries had recruited a total of 5,472 patients (90 % of the planned 6,000 patients) were included. In January 2006, following an intermediate evaluation, an independent data safety monitoring board concluded that therapeutic interruptions result in an increased risk of AIDS – in the interruption arm, approximately twice as many AIDS illnesses were observed at follow-up, over an average of 15 months. This included severe opportunistic infections as well as malignant tumors. In fact, the overall risk was low, but so significantly elevated that the unusual and far-reaching decision was made to abort the study. In addition, it was surprisingly observed that cardiovascular incidents in the interruption arm did not (as was hoped) become less frequent, but actually increased. The clinical incidents in SMART (details on the SMART website: <http://www.smart-trial.org/news.htm>) are shown in the following table.

Table 10.3. Incidents occurring in SMART, for every 100 patient years (El Sadr 2006)\*\*

	STI (n)	Control (n)	Odds ratio
Progression of disease or death	3.7 (117)	1.5 (47)	2.5 (1.8-3.6)*
Death	1.5 (47)	0.9 (29)	1.9*
Cardiovascular/metabolic events	2.9 (83)	2.5 (73)	1.4*
Grade IV toxicity	5.4 (157)	4.5 (133)	1.2*

\*Significant difference. \*\*In the presentation at the CROI, the numbers were slightly different to those in the abstract, but along the same lines.

The cause of these surprising results can only be speculated about at present. What was conspicuous, however, was that the risk of disease was increased mainly in those patients whose viral load was below the borderline level at the time of interruption. In contrast, an increased risk of AIDS or death was not associated with CD4+ T-cell count at the start of the study. Even the CD4 nadir or a previous diagnosis of AIDS (approximately 24 % of the patients) was astonishingly not predictive. The incidence of AIDS and death also occurred with good CD4+ T-cell counts.

For many experts and observers, SMART laid to rest the concept of interrupting therapy as a method of treatment. However, some points of criticism remain. Much of SMART has not yet been evaluated, and the type of clinical events and the diseased patients have to be looked at more closely. Despite the increased risk of progression, it is important not to lose sight of the proportions. Overall, the risk of becoming ill was low, and in SMART an essential point for stopping and restarting HAART was not noted: the CD4+ T-cell percentage. Only the absolute CD4+ T-cell counts were used as criteria, although the percentage values have been required to be included in therapeutic decisions for many years (Goicoechea 2005, Hulgán 2005). In our opinion, it is still too early to completely dismiss the concept of CD4-driven treatment interruptions. In the first instance SMART has shown that treatment interruptions *such as these, and in this design* are not beneficial. Nothing else. Perhaps patients need to be monitored differently and more effectively during the treatment intervals. However, the danger remains that the results of this study will be generalized.

## Practical tips for treatment interruptions

- Don't try to convince patients to interrupt therapy – if there are no problems with HAART, there is no reason to stop it.
- To reverse resistances or for immunological reasons – i.e., for “strategic” points of view – STIs are not useful.
- A positive effect on cardiovascular incidents or lipodystrophy has not been confirmed. Following the SMART Study, this is highly unlikely.
- Nevertheless, the patient's wish for a break should be respected! The interruption will be made anyway, whether the clinician agrees with it or not.
- A supervised treatment interruption is still always better than one undertaken without the awareness of the clinician.
- Beforehand, information should be provided on clinical (retroviral syndrome, AIDS), immunological (loss of CD4+ T-cells) and virological (resistance) consequences.
- Patients must be aware that the risk of infection increases – even after a longer suppression, viral load returns to initial levels after 4-6 weeks without HAART.
- Beware HBV co-infection (danger of hepatitis flaring up again)!
- CD4+ T-cells (including percentage), viral load, and blood count (thrombocytes!) should be monitored monthly during interruptions.
- Risk of resistance is possibly higher with NNRTIs (choose robust regimens and stop NNRTIs several days earlier if possible – consider the half-life of the drugs).
- Patients who started HAART “too early” according to current standards can probably interrupt quite safely.
- Resistance testing during treatment interruptions is not useful – it usually only measures the wild-type.
- Start with HAART again, in good time after the treatment interruption!

## References

1. Ananworanich J, Gayet-Ageron A, LaBraz M, et al. CD4 guided scheduled treatment interruption compared to continuous therapy: Results of the Staccato Trial. Abstract 102, 13th CROI 2006, Denver.
2. Ananworanich J, Phanuphak N, Nuesch R, et al. Recurring thrombocytopenia associated with structured treatment interruption in patients with HIV infection. *Clin Infect Dis* 2003; 37:723-5. <http://amedeo.com/lit.php?id=12942407>
3. Birk M, Svedhem V, Sonnerborg A. Kinetics of HIV-1 RNA and resistance-associated mutations after cessation of antiretroviral combination therapy. *AIDS* 2001, 15: 1359-68. <http://amedeo.com/lit.php?id=11504957>
4. Bonhoeffer S, Rembiszewski M, Ortiz GM, Nixon DF. Risks and benefits of structured antiretroviral drug therapy interruptions in HIV-1 infection. *AIDS* 2000, 14:2313-22. <http://amedeo.com/lit.php?id=11089619>
5. Cardillo PG, Hassink E, Ananworanich J, et al. A prospective, randomized trial of structured treatment interruption for patients with chronic HIV type 1 infection. *Clin Infect Dis* 2005, 40:594-600. <http://amedeo.com/lit.php?id=15712083>
6. Chun TW, Davey RT Jr, Engel D, Lane HC, Fauci AS. Re-emergence of HIV after stopping therapy. *Nature* 1999, 401:874-5.

7. Chun TW, Davey RT Jr, Ostrowski M, et al. Relationship between pre-existing viral reservoirs and the re-emergence of plasma viremia after discontinuation of HAART. *Nat Med* 2000, 6:757-761. <http://amedeo.com/lit.php?id=10888923>
8. Cohen C, Colson A, Morris A, et al. The FOTO study 48 week results: viral suppression can be maintained when antiretrovirals are taken five consecutive days on, and two days off each week. *WePe12.4C10*, 3rd IAS 2005, Rio de Janeiro.
9. Colven R, Harrington RD, Spach DH, Cohen CJ, Hooton TM. Retroviral rebound syndrome after cessation of suppressive ART in three patients with chronic HIV infection. *Ann Intern Med* 2000, 133: 430-4. <http://amedeo.com/lit.php?id=10975960>
10. Cote HC, Brumme ZL, Craib KJ, et al. Changes in mitochondrial DNA as a marker of nucleoside toxicity in HIV-infected patients. *N Engl J Med* 2002, 346:811-20. <http://amedeo.com/lit.php?id=11893792>
11. Danel C, Moh R, Sorho S, et al. The CD4 guided strategy arm stopped in a randomized structured treatment interruption trial in West African adults: ANRS 1269 Trivacan Trial. Abstract 105LB, 13th CROI 2006, Denver.
12. Davey RT Jr, Bhat N, Yoder C, et al. HIV-1 and T cell dynamics after interruption of HAART in patients with a history of sustained viral suppression. *PNAS* 1999, 96:15109-14. <http://amedeo.com/lit.php?id=10611346>
13. De Jong MD, de Boer RJ, de Wolf F, et al. Transient overshoot of HIV-1 viraemia after early discontinuation of antiretroviral treatment: role of target cell availability. *AIDS* 1997, 11:F79-84. <http://amedeo.com/lit.php?id=9302437>
14. Deeks SG, Wrin T, Liegler T, et al. Virologic and immunologic consequences of discontinuing combination antiretroviral-drug therapy in HIV-infected patients with detectable viremia. *N Engl J Med* 2001, 344: 472-80. <http://amedeo.com/lit.php?id=11172188>
15. Delaugerre C, Valantin MA, Mouroux M, et al. Re-occurrence of HIV-1 drug mutations after treatment re-initiation following interruption in patients with multiple treatment failure. *AIDS* 2001, 15: 2189-91. <http://amedeo.com/lit.php?id=11684940>
16. Devereux HL, Youle M, Johnson MA, Loveday C. Rapid decline in detectability of HIV-1 drug resistance mutations after stopping therapy. *AIDS* 1999, 13: F123-7. <http://amedeo.com/lit.php?id=10630517>
17. Dorman KS, Kaplan AH, Lange K, Sinsheimer JS. Mutation takes no vacation: can structured treatment interruptions increase the risk of drug-resistant HIV-1? *J AIDS* 2000, 25: 398-402. <http://amedeo.com/lit.php?id=11141239>
18. Dybul M, Chun TW, Yoder C, et al. Short-cycle structured intermittent treatment of chronic HIV infection with highly active antiretroviral therapy: effects on virologic, immunologic, and toxicity parameters. *PNAS* 2001, 98: 15161-6. <http://www.pnas.org/cgi/content/full/98/26/15161>
19. Dybul M, Nies-Kraske E, Daucher M, et al. Long-cycle structured intermittent versus continuous HAART for the treatment of chronic infection with HIV: effects on drug toxicity and on immunologic and virologic parameters. *J Infect Dis* 2003, 188:388-96. <http://amedeo.com/lit.php?id=12870120>
20. Dybul M, Nies-Kraske E, Dewar R, et al. A proof-of-concept study of short-cycle intermittent antiretroviral therapy with a once-daily regimen of didanosine, lamivudine, and efavirenz for the treatment of chronic HIV infection. *J Infect Dis* 2004, 189:1974-82. <http://amedeo.com/lit.php?id=15143462>
21. El-Sadr W, Neaton J. Episodic CD4 guided use of antiretroviral therapy is inferior to continuous therapy: Results of the SMART study. Abstract 106LB, 13th CROI 2006, Denver.
22. Fagard C, Bandelier CY, Ananworanich J, et al. Biphasic decline of CD4 cell count during scheduled treatment interruptions. *AIDS* 2005, 19:439-41.
23. Fagard C, Oxenius A, Gunthard H, et al. A prospective trial of structured treatment interruptions in HIV infection. *Arch Intern Med* 2003, 163: 1220-6. <http://amedeo.com/lit.php?id=12767960>
24. Fernandez Guerrero ML, Rivas P, et al. Long-term follow-up of asymptomatic HIV-infected patients who discontinued antiretroviral therapy. *Clin Infect Dis* 2005, 41:390-4. <http://amedeo.com/lit.php?id=16007538>
25. Foli A, Maserati R, Barasolo G, et al. Strategies to decrease viral load rebound, and prevent loss of CD4 and onset of resistance during structured treatment interruptions. *Antivir Ther* 2004, 9:123-32. <http://amedeo.com/lit.php?id=15040544>
26. Garcia F, Plana M, Arnedo M, et al. Effect of mycophenolate mofetil on immune response and plasma and lymphatic tissue viral load during and after interruption of HAART for patients with chronic HIV infection: a randomized pilot study. *J AIDS* 2004, 36:823-830. <http://amedeo.com/lit.php?id=15213566>
27. Garcia F, Plana M, Ortiz GM, et al. The virological and immunological consequences of structured treatment interruptions in chronic HIV-1 infection. *AIDS* 2001, 15: F29-40. <http://amedeo.com/lit.php?id=11416735>

28. Garcia F, Plana M, Vidal C, et al. Dynamics of viral load rebound and immunological changes after stopping effective antiretroviral therapy. *AIDS* 1999, 13: F79-86  
<http://amedeo.com/lit.php?id=10449278>
29. Ghosn J, Wirden M, Ktorza N, et al. No benefit of a structured treatment interruption based on genotypic resistance in heavily pretreated HIV-infected patients. *AIDS* 2005, 19:1643-7.  
<http://amedeo.com/lit.php?id=16184034>
30. Goicoechea M, Haubrich R. CD4 lymphocyte percentage versus absolute CD4 lymphocyte count in predicting HIV disease progression: an old debate revisited. *J Infect Dis* 2005, 192:945-7.
31. Halfon P, Penaranda G, Khiri H, Xerridat B. Long-term persistence of HIV with drug resistance after CD4 cell count-guided structured treatment interruption. *AIDS* 2005, 19:1713-4.
32. Harrigan PR, Whaley M, Montaner JS. Rate of HIV-1 RNA rebound upon stopping antiretroviral therapy. *AIDS* 1999, 13: F59-62. <http://amedeo.com/lit.php?id=10371167>
33. Haslett PA, Nixon DF, Shen Z, et al. Strong HIV-specific CD4+ T cell responses in a cohort of chronically infected patients are associated with interruptions in anti-HIV chemotherapy. *J Infect Dis* 2000, 181: 1264-72. <http://amedeo.com/lit.php?id=10751137>
34. Hatano H, Miller KD, Yoder CP, et al. Metabolic and anthropometric consequences of interruption of HAART. *AIDS* 2000, 14: 1935-42. <http://amedeo.com/lit.php?id=10997397>
35. Hatano H, Vogel S, Yoder C, et al. Pre-HAART HIV burden approximates post-HAART viral levels following interruption of therapy in patients with sustained viral suppression. *AIDS* 2000, 14: 1357-63. <http://amedeo.com/lit.php?id=10930150>
36. Ho DD, Zhang L. HIV-1 rebound after anti-retroviral therapy. *Nat Med* 2000, 6:736-737.  
<http://amedeo.com/lit.php?id=11919491>
37. Hulgian T, Raffanti S, Kheshti A, et al. CD4 lymphocyte percentage predicts disease progression in HIV-infected patients initiating HAART with CD4 lymphocyte counts >350 lymphocytes/mm<sup>3</sup>. *J Infect Dis* 2005, 192:950-7. <http://amedeo.com/lit.php?id=16107946>
38. Imamichi H, Crandall KA, Natarajan V, et al. HIV type 1 quasi species that rebound after discontinuation of HAART are similar to the viral quasi species present before initiation of therapy. *J Infect Dis* 2001, 183: 36-50. <http://amedeo.com/lit.php?id=11106537>
39. Izopet J, Massip P, Souryis C, et al. Shift in HIV resistance genotype after treatment interruption and short-term antiviral effect following a new salvage regimen. *AIDS* 2000, 14: 2247-55.  
<http://amedeo.com/lit.php?id=11089612>
40. Katlama C, Dominguez S, Gourlain K, et al. Benefit of treatment interruption in HIV-infected patients with multiple therapeutic failures: a randomized controlled trial (ANRS 097). *AIDS* 2004, 18:217-26.  
<http://amedeo.com/lit.php?id=15075539>
41. Kilby JM, Goepfert PA, Miller AP, et al. Recurrence of the acute HIV syndrome after interruption of ART in a patient with chronic HIV infection: A case report. *Ann Intern Med* 2000, 133: 435-8.  
<http://amedeo.com/lit.php?id=10975961>
42. Lawrence J, Mayers DL, Hullsiek KH, et al. Structured treatment interruption in patients with multidrug-resistant HIV. *NEJM* 2003; 349: 837-46. <http://amedeo.com/lit.php?id=12944569>
43. Lisiewicz J, Rosenberg E, Lieberman J, et al. Control of HIV despite the discontinuation of antiretroviral therapy. *NEJM* 1999, 340:1683-4.
44. Lori F, Lewis MG, Xu J, et al. Control of SIV rebound through structured treatment interruptions during early infection. *Science* 2000, 290:1591-3. <http://amedeo.com/lit.php?id=11090360>
45. Lori F, Maserati R, Foli A, et al. Structured treatment interruptions to control HIV-1 infection. *Lancet* 2000, 355: 287-8. <http://amedeo.com/lit.php?id=10675080>
46. Maggiolo F, Ripamonti D, Gregis G, Quinzan G, et al. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4 T cells: a controlled, prospective trial. *AIDS* 2004, 18:439-46.  
<http://amedeo.com/lit.php?id=15090796>
47. Marchou B, Tangre P, Charreau I, et al. Structured treatment interruptions in HIV-infected patients with high CD4 cell counts and virologic suppression: results of a prospective, randomized, open-label trial (Window - ANRS 106). Abstract 104, 13th CROI 2006, Denver.
48. Martinez-Picado J, Morales-Lopez K, Wrin T, et al. Selection of drug-resistant HIV-1 mutants in response to repeated structured treatment interruptions. *AIDS* 2002, 16:895-9.  
<http://amedeo.com/lit.php?id=11919491>
49. Miller V, Sabin C, Hertogs K, et al. Virological and immunological effects of treatment interruptions in HIV-1 infected patients with treatment failure. *AIDS* 2000, 14: 2857-67  
<http://amedeo.com/lit.php?id=11153667>
50. Moreno S, Moreno A, Bernaldo de Quiros JCL, et al. A prospective, randomized trial of treatment discontinuation after immunologic response to HAART. Abstract 601, 2nd IAS 2003, Paris.
51. Mussini C, Bedini A, Borghi V, et al. CD4 cell-monitored treatment interruption in patients with a CD4 cell count > 500 x 10<sup>6</sup> cells/l. *AIDS* 2005, 19:287-94. <http://amedeo.com/lit.php?id=15718839>



52. Mussini C, Pinti M, Bugarini R, et al. Effect of treatment interruption monitored by CD4 cell count on mitochondrial DNA content in HIV-infected patients: a prospective study. *AIDS* 2005, 19:1627-1633. <http://amedeo.com/lit.php?id=16184032>
53. Negro E, Rodriguez-Santiago B, Puig J, et al. Effect of prolonged interruption of ART on mitochondrial toxicity. Abstract 758, 13th CROI 2006, Denver.
54. Neumann AU, Tubiana R, Calvez V, et al. HIV-1 rebound during interruption of HAART has no deleterious effect on reinitiated treatment. *AIDS* 1999, 13: 677-83. <http://amedeo.com/lit.php?id=10397562>
55. Ortiz GM, Nixon DF, Trkola A, et al. HIV-1-specific immune responses in subjects who temporarily contain virus replication after discontinuation of HAART. *J Clin Invest* 1999, 140, R: 13-18. <http://amedeo.com/lit.php?id=10491418>
56. Oxenius A, Price DA, Gunthard HF, et al. Stimulation of HIV-specific cellular immunity by structured treatment interruption fails to enhance viral control in chronic HIV infection. *PNAS* 2002, 99:13747-52. <http://amedeo.com/lit.php?id=12370434>
57. Palmisano L, Giuliano M, Bucciardini R, et al. Final results of a randomized, controlled trial of structured treatment interruptions vs continuous HAART in chronic HIV-infected subjects with persistent suppression of viral replication. Abstract 103, 13th CROI 2006, Denver.
58. Pappasavvas E, Ortiz GM, Gross R, et al. Enhancement of HIV type 1-specific CD4 and CD8 T cell responses in chronically infected persons after temporary treatment interruption. *J Infect Dis* 2000, 182:766-775. <http://amedeo.com/lit.php?id=10950770>
59. Ruiz L, Carcelain G, Martinez-Picado J, et al. HIV dynamics and T-cell immunity after three structured treatment interruptions in chronic HIV-1 infection. *AIDS* 2000, 15: F19-27. <http://amedeo.com/lit.php?id=11416734>
60. Ruiz L, Ribera E, Bonjoch A, et al. Role of structured treatment interruption before a five-drug salvage antiretroviral regimen: the Retrogene Study. *J Infect Dis* 2003, 188:977-985. <http://amedeo.com/lit.php?id=14513417>
61. Ruiz L, Gomez G, Domingo P, et al. A multicenter randomized controlled clinical trial of continuous vs. intermittent HAART guided by CD4+ T cell counts and plasma HIV RNA levels: two-year follow-up. Abstract TuPeB4567, XV Int AIDS Conf 2004, Bangkok.
62. Ruiz L, Romeu J, Martinez-Picado J, et al. Selection of drug-resistance mutations in chronic HIV-infected patients during therapy interruptions guided by CD4+ T-cell counts and viral load levels: The Tibet Study. Abstract 679, 12<sup>th</sup> CROI 2005, Boston.
63. Schweighardt B, Ortiz GM, Grant RM, et al. Emergence of drug-resistant HIV-1 variants in patients undergoing structured treatment interruptions. *AIDS* 2002, 16:2342-2344. <http://amedeo.com/lit.php?id=12441810>
64. Sellier P, Clevenbergh P, Mazon MC, et al. Fatal interruption of a 3TC-containing regimen in a HIV-infected patient due to re-activation of chronic hepatitis B virus infection. *Scand J Infect Dis* 2004, 36:533-5.
65. Skiest D, Havlir D, Coombs R, et al. Predictors of HIV disease progression in patients who stop ART with CD4 counts >350/mm<sup>3</sup>. Abstract 101, 13th CROI 2006, Denver.
66. Skiest DJ, Morrow P, Allen B, et al. It is safe to stop antiretroviral therapy in patients with preantiretroviral CD4 cell counts >250 cells/microL. *J AIDS* 2004, 37:1351-7. <http://amedeo.com/lit.php?id=15483464>
67. Taffe P, Rickenbach M, Hirschel B, et al. Impact of occasional short interruptions of HAART on the progression of HIV infection: results from a cohort study. *AIDS* 2002, 16: 747-55. <http://amedeo.com/lit.php?id=11964531>
68. Tebas P, Henry K, Mondy K, et al. Effect of prolonged discontinuation of successful antiretroviral therapy on CD4+ T cell decline in HIV-infected patients: implications for intermittent therapeutic strategies. *J Infect Dis* 2002, 186:851-4. <http://amedeo.com/lit.php?id=12198623>
69. Toulson AR, Harrigan R, Heath K, et al. Treatment interruption of highly active antiretroviral therapy in patients with nadir CD4 cell counts >200 cells/mm<sup>3</sup>. *J Infect Dis* 2005, 192:1787-93. <http://amedeo.com/lit.php?id=16235178>
70. Tuldra A, Fumaz CR, Ferrer MJ, et al. Psychological impact of structured treatment interruptions in patients with prolonged undetectable HIV-1 viral loads. *AIDS* 2001, 15: 1904-6. <http://amedeo.com/lit.php?id=11579263>
71. Ulmer A, Muller M, Bertisch-Mollenhoff B, Frietsch B. Low dose prednisolone reduces CD4+ T cell loss in therapy-naive HIV-patients without antiretroviral therapy. *Eur J Med Res* 2005, 10:105-9.
72. Walter H, Low P, Harer T, et al. No evidence for persistence of multidrug-resistant viral strains after a 7-month treatment interruption in an HIV-1-Infected Individual. *J AIDS* 2002, 31:137-46. <http://amedeo.com/lit.php?id=12394791>
73. Wit FW, Blanckenberg DH, Brinkman K, et al. Safety of long-term interruption of successful antiretroviral therapy: the ATHENA cohort study. *AIDS* 2005, 19:345-8. <http://amedeo.com/lit.php?id=15718848>

74. Wolf E, Hoffmann C, Procaccianti M, et al. Long-term consequences of treatment interruptions in chronically HIV-1-infected patients. *Eur J Med Res* 2005, 10:56-62. <http://amedeo.com/lit.php?id=15817423>
75. Yerly S, Fagard C, Gunthard HF, et al. Drug resistance mutations during structured treatment interruptions. *Antivir Ther* 2003, 8:411-5.
76. Zeller V, Charlois C, Duvivier C, et al. Pseudo-primary infection syndrome following discontinuation of antiretroviral therapy. *Antivir Ther* 2001, 6: 191-3. <http://amedeo.com/lit.php?id=11808754>

## 11. Monitoring

Christian Hoffmann

Which parameters should be included in routine laboratory monitoring of HIV patients? What can be expected from the results? This section deals with viral load, CD4+ T-cells, routine checks, and plasma levels. Resistance tests are the subject of a separate chapter (“HIV Resistance Testing”). For the tests to be performed on initial presentation see the appropriate chapter.

### Viral load

“Viral load” is the amount of viral copies in the blood. Alongside the CD4+ T-cell count, viral load has become the most important surrogate marker for HIV infection (Hughes 1997, Mellors 1997, Lyles 2000, Ghani 2001, Phillips 2004). It provides both valuable information on the level of risk of disease progression and whether antiretroviral therapy is indicated; it is the critical value in determining the success of therapy. Other surrogate markers used frequently in the past, such as p24, neopterin or  $\beta_2$ -microglobulin, are now superfluous and should be avoided, as they do not provide any additional information.

Viral load assays measure the amount of HIV RNA (viral genetic material), which correlates directly with the number of viruses. The units are viral copies/ml (or genome equivalents). This is reported either as a direct, whole number, or as a logarithmic number. A change of one or more “logs” refers to the change in viral load by one or more decimal powers.

Number of copies	Log <sub>10</sub>
10	1.0
50	1.7
100	2.0
500	2.7
1,000	3.0
10,000	4.0
50,000	4.7
100,000	5.0
1,000,000	6.0

### Assessment

The higher the viral load, the higher the risk of a decrease in CD4+ T-cells, with subsequent disease progression or occurrence of AIDS-related illnesses (Mellors 1997, Lyles 2000, Phillips 2004). A viral load above 100,000 copies/ml, i.e. 5.0 logs (sometimes even above 50,000 copies/ml), is generally considered to be high; a value below 10,000 copies/ml (sometimes less than 5,000 copies/ml), low. However, these thresholds are not absolute and can only provide points of reference.

The effects of plasma viremia on immune status can vary greatly between individuals. There are some patients whose CD4+ T-cells remain stable for relatively long periods despite having a high viral load, while others experience a rapid drop, although the viral load is relatively low. Viral load is probably generally lower in women than in men. In a meta-analysis, the difference was 41 % or 0.23 logs (95 % confidence interval 0.16-0.31 logs) (Napravnik 2002). The reason for this phenomenon remains unclear and whether it should have an impact on the indication for treatment, is still the subject of discussion.

## Methods

Three methods or assays are currently used to measure viral load: Reverse Transcription Polymerase Chain Reaction (RT-PCR); branched-chain DNA (b-DNA); and, occasionally, Nucleic Acid Sequence-Based Amplification (NASBA). These three methods differ both in levels of detection and in the linear range within which measurement is reliable or reproducible (see Table 11.1 below). In all methods, the minute amount of viral RNA must first be amplified to enable measurement. In the case of PCR and NASBA, the viral RNA is transformed in several enzymatic steps and then amplified to measurable amounts. B-DNA does not require this enzymatic step; signal amplification occurs via binding of branched DNA fragments to viral RNA.

Although intra-assay variability is fairly good for all three methods and one can expect reproducible values, methodological variations should be carefully considered. Differences of less than 0.5 logs are not considered significant. A decrease from 4.3 to 3.9 logs, for example (corresponding to a decrease from approximately 20,000 to 8,000 viral copies/ml), does not necessarily signify a drop in viral load. The same holds for increases in viral load. Changes of up to threefold can therefore be irrelevant! Patients who, after hearing mere numbers, frequently worry unnecessarily or become falsely optimistic should be made aware of this.

Considerable differences exist between the three methods (Coste 1996), and to change from one method to another is therefore generally not advisable. The results obtained by b-DNA are usually lower than the PCR by a factor of 2. Different subtypes are also detected with varying success according to the method employed (Parekh 1999); one should be particularly cautious in patients from Africa and Asia with non-B subtypes, for example, in whom the viral load at first presentation can be unexpectedly low. In such cases, use of a different assay may actually be indicated. However, newer versions with improved primers are probably superior in measuring even unusual HIV subtypes with adequate sensitivity. All assays have a linear dynamic range, outside of which precise numbers are not so reliable. There are two tests for PCR, the standard and the ultrasensitive assay. The linear range of the ultrasensitive assay ends at 75,000 copies/ml, and thus this test should only be used if low viral loads are expected.

The following rule applies: one method, one laboratory! The laboratory should be experienced and routinely perform a sufficiently large number of tests. Measurement should take place as soon as possible after blood withdrawal, and correct collection and shipping of centrifuged plasma is also important (contact the laboratory ahead of time on these issues).

Table 11.1: Methods of measurement, including test version, linear range and level of detection should be clearly indicated for the clinician on every test result

Company	Roche/Abbott	Bayer/Chiron	Organon
Method	RT-PCR	b-DNA	NucliSens HIV-1 QT
Linear range of assay	400 – 750,000 ultrasensitive: 50 – 75,000	100 – 500,000	40 – 10,000,000
Comparability	Values ca. 2 x higher than b-DNA (version 2.0 and 3.0)	Values ca. 50 % of PCR (version 2.0 and 3.0)	Values approx. like PCR
Advantages	Less false positive results than b-DNA	Equally good for all subtypes (A-G), technically relatively simple	Equally good for all subtypes (A-G), large linear range

### Influencing factors

Apart from methodological variability, a host of other factors may influence levels of viral load, including vaccinations and concurrent infections. During active opportunistic infections, viral load is often particularly high. One study showed a 5- to 160-fold elevated viral load during active tuberculosis (Goletti 1996). Viral load can also increase significantly during syphilis (Buchacz 2004). In these situations, determining the viral load does not make much sense. Following immunizations, for instance for influenza (O'Brien 1995) or pneumococcus (Farber 1996), the viral load may be transiently elevated (Kolber 2002). As the peak occurs one to three weeks after immunization, routine measurements of viral load should be avoided within four weeks of immunization. It should be noted that not every increase in viral load is indicative of virological treatment failure and resistance. Slight transient increases in viral load, called blips, are usually of no consequence, as numerous studies in the last few years have shown (see chapter on “Goals and Principles of Therapy”). The possibility of mixing up samples always has to be considered. Unusually implausible results should be double-checked with the laboratory in the first instance, and if no cause is found there, then they need to be controlled – people make mistakes.

### Viral kinetics on HAART

The introduction of viral load measurement in 1996-1997 fundamentally changed HIV therapy. The breakthrough studies by David Ho and his group showed that HIV infection has significant *in vivo* dynamics (Ho 1995, Perelson 1996). The changes in viral load on antiretroviral therapy clearly reflect the dynamics of the process of viral production and elimination. The concentration of HIV-1 in plasma is usually reduced by 99 % as early as two weeks after the initiation of HAART (Perelson 1997). In one large cohort, the viral load in 84 % of patients was already below 1,000 copies/ml after four weeks. The decrease in viral load follows biphasic kinetics. In the first phase, i.e. within the first three to six weeks, an extremely rapid drop occurs, followed by a longer phase during which the viral load only gradually decreases further (Wu 1999).

The higher the viral load at initiation of therapy, the longer it takes to drop below the level of detection. In one study, the range was between 15 days with a baseline viral load of 1,000 and 113 days with a baseline of 1 million viral copies/ml (Riz-

zardi 2000). The following figure shows a typical biphasic decrease in viral load after initial high levels.

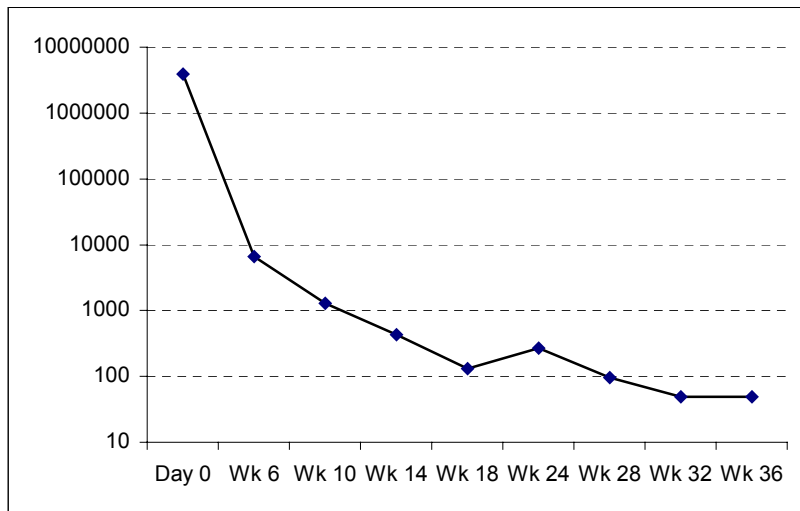


Figure 1: Typical biphasic decrease in viral load on HAART. Viral load was initially very high, and reached a level below 50 copies/ml only at week 32. Note the temporary increase at week 24, which is possibly due to methodological variability. HAART was not changed.

Numerous studies have focused on whether durable treatment success can be predicted early in treatment (Demeter 2001, Kitchen 2001, Lepri 2001, Thiabaut 2000). In a study on 124 patients, a decrease of less than 0.72 logs after one week was predictive of virological treatment failure in more than 99 % of patients (Polis 2001). However, this has little clinical relevance, and in our opinion, it is pointless to start measurement of viral load only one or two weeks after initiation of therapy.

In the first few months, we typically measure viral load every four weeks until it has dropped below the level of detection – the most important goal! After this, viral load can be measured every three months. In case of rebound, closer monitoring becomes necessary. Following initiation of therapy, viral load should be below 5,000 copies/ml after one month. Higher values are predictive of failure to reach levels below detection (Maggiolo 2000).

Viral load can also be measured fairly reliably in body fluids other than blood or plasma (for example cerebrospinal, vaginal or seminal fluid). However, such tests are usually performed for scientific purposes and are not routine.

**Practical tips for dealing with viral load (see also chapter “Goals and Principles of Therapy”)**

- Use only one assay, if possible.
- Use only one experienced laboratory, if possible, no home-brewed assays.
- Watch for assay variability (up to half a log) and explain this to the patient!
- Monitor viral load every four weeks with new HAART, until the viral load is below the level of detection (50 copies/ml).
- Then measure viral load sparingly – on successful HAART every three months may be sufficient.
- Without HAART, measurement every three months is usually sufficient.
- Don't measure shortly after vaccinations or with concurrent infections.
- Implausible results should be rechecked after 2-4 weeks.
- Remember differences between subtypes (in some cases it may be useful to use another method).

## CD4+ T-cells

CD4+ T-cells are T lymphocytes that express the CD4 receptor on their surface. This lymphocyte subpopulation is also referred to as “T helper cells”. Alongside viral load, measurement of the CD4+ T-cell level is the most important parameter or surrogate marker in HIV medicine. It allows for a reliable estimation of the individual risk of developing AIDS. Every HIV patient should have had a CD4+ T-cell measurement within the last six months! Two reference values are generally accepted: above 400-500 CD4+ T-cells/ $\mu$ l, severe AIDS-related diseases are very rare; below 200 CD4+ T-cells/ $\mu$ l, the risk of AIDS-related morbidity increases significantly with increased duration of immunosuppression. However, most AIDS-related illnesses only occur below 100 CD4+ T-cells/ $\mu$ l.

Several points should be considered when measuring CD4+ T-cells (usually by flow cytometry). Blood samples should be processed within 18 hours. The lower normal values are between 400 and 500 cells/ $\mu$ l, depending on the laboratory. Samples should always be sent to only one (experienced) laboratory. The same applies to viral load as to CD4+ T-cells: the higher the level, the greater the variability. Differences of 50-100 cells/ $\mu$ l are not unusual. In one study, the 95 % confidence intervals with a real value of 500 cells/ $\mu$ l were between 297 and 841 cells/ $\mu$ l. At 200 CD4+ T-cells/ $\mu$ l, the 95 % confidence interval was between 118 and 337 cells/ $\mu$ l (Hoover 1993).

Measurement of CD4+ T-cells should only be repeated in the case of highly implausible values. As long as the viral load remains below the level of detection, there is no need to be concerned, even with greater decreases in CD4+ T-cells. In such cases, the relative values (CD4 percentages) and the CD4/CD8 ratio (ratio of CD4+ to CD8+ T-cells) should be referred to; these are usually more robust and less prone to fluctuation. As a general point of reference: with values above 500 CD4+ T-cells/ $\mu$ l, more than 29 % is to be expected, with less than 200 CD4+ T-cells/ $\mu$ l less than 14 %. Individual laboratories may define the normal ranges for

the relative values and the ratio differently. If there are considerable discrepancies between absolute and relative CD4+ T-cells, any decisions involving treatment should be carefully considered – if in doubt, it is better to check the values one more time! The remaining differential blood count should also be scrutinized carefully: is leucopenia or leukocytosis present?

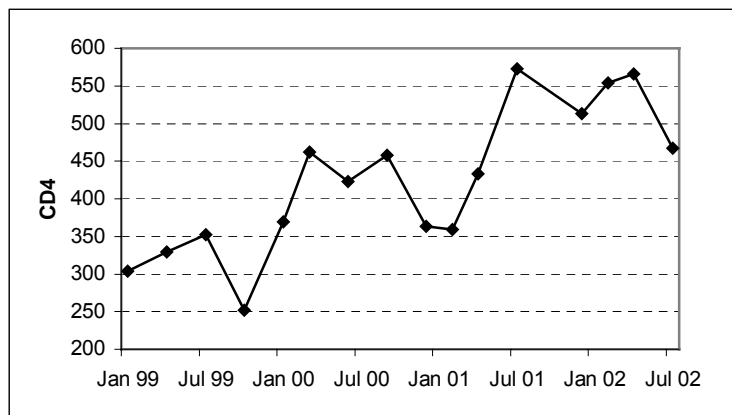


Figure 2. Patient example for variations in absolute CD4+ T-cells/ $\mu$ l over a period of four years. The viral load was continuously below 50 copies/ml; HAART remained unchanged.

Clinicians sometimes forget that the result of the CD4+ T-cell count is of existential importance for the patient. To go to the doctor and discuss the test results involves a great deal of stress for many patients. Insensitively informing the patient of a supposedly bad result can lead to reactive depression. From the start, patients must be informed about the possible physiological and method-related variability of laboratory tests. In the case of unexpectedly good results, every effort should be made to contain premature euphoria. In the long run, this saves time and discussions, and the patient is spared unnecessary ups and downs. We do not consider it advisable for non-physician personnel (without extensive HIV experience) to inform patients of results.

Once CD4+ T-cell counts within the normal range are reached in addition to adequate viral suppression, half-yearly measurements suffice, in our opinion. The probability of CD4+ T-cells dropping to values below 350/ $\mu$ l is extremely low in such cases (Phillips 2003). Patients, who might sometimes insist on more frequent monitoring of immune status, can be assured that there are usually no detrimental changes in the CD4+ T-cell count as long as HIV remains suppressed.

### Influencing factors

Several other factors influence CD4+ T-cell counts apart from laboratory-related variables. These include concurrent infections, leucopenia of varying etiology, and steroids or other immunosuppressive therapies. Extreme exertion, surgical procedures or pregnancy can also lead to lower values. Even diurnal variation occurs; CD4+ T-cells are lower at noon, and highest in the evening around 8 p.m. (Malone



1990). Psychological stress seems to play a negligible role, even though patients often assume the contrary.

### **Kinetics of CD4+ T-cells on HAART**

Similarly to viral load, a biphasic increase in CD4+ T-cells occurs following the initiation of HAART (Renaud 1999, Le Moing 2002), with a rapid increase within the first three to four months and a much slower rise thereafter. In a study of almost 1,000 patients, the CD4+ T-cell count increased by 21/ $\mu$ l per month during the first three months. In the following 21 months, this rate was only 5.5 CD4+ T-cells/ $\mu$ l per month (Le Moing 2002). The initial rapid increase in CD4+ T-cells is probably due to redistribution, which is followed by the new production of naïve T-cells (Pakker 1998). Diminished apoptosis may also play a role (Roger 2002).

It is still being debated whether the immune system steadily continues its recovery even after a long period of viral load suppression, or whether a plateau is reached after three to four years, beyond which there is no further improvement (Smith 2004, Viard 2004).

Several factors can influence the extent of immune reconstitution during HAART. The degree of viral suppression is crucial – the lower the viral load, the more pronounced the effect (Le Moing 2002). The absolute increase is higher if CD4+ T-cell counts were high at the start of HAART (Kaufmann 2000). Naïve T cells still present at initiation of therapy are a particularly important factor for long-term immune reconstitution (Notermans 1999). Age is also important (Grabar 2004). The larger the thymus and the more active the process of thymopoiesis, the more significant the rise in CD4+ T-cells is likely to be (Kolte 2002); due to age-related degeneration of the thymus, CD4+ T-cells in older patients do not increase as much as those in younger ones (Viard 2001). However, we have seen both 20 year-old patients with very poor CD4+ T-cell count recovery and 60 year-old patients with very good, above average increases in CD4+ T-cells. The regenerative capacity of the human immune system seems to vary considerably, and no method to date has been capable of reliably predicting this capacity.

It is possible that some antiretroviral therapies such as the ddI+tenofovir combination are associated with less immune reconstitution than others. Immunosuppressive concurrent medications should also be considered (see chapter “Goals and Principles of Therapy”).

Beyond the measurement of the CD4+ T-cell count and lymphocyte subpopulations, a number of other assays allow detailed testing of the qualitative or functional capacity of the immune system, for example in response to specific antigens (Gorochov 1998, Lederman 2001, Lange 2002, review in Telenti 2002). These, often cumbersome, methods are not currently necessary for routine diagnostics, and their use remains questionable. However, they could one day help to better describe individual immune status and, for example, identify those (few) patients, who are at risk of developing opportunistic infections despite good CD4+ T-cell counts.

### Practical tips for dealing with CD4+ T-cell counts

- As with viral load: use only one (experienced) laboratory.
- The higher the values, the greater the variability (consider numerous factors) – compare the relative (percentage) values and CD4/CD8 ratio with previous results!
- Do not disconcert the patient when there are apparent decreases – if viral suppression is sufficient, the drop is usually not HIV-related! Only highly implausible results should be repeated.
- If the viral load is below the level of detection, three-monthly measurements of CD4 cells are sufficient.
- In the presence of good viral suppression, CD4+ T-cells (not viral load!) may also be checked less frequently.
- CD4+ T-cell count and viral load should be discussed with the physician. Do not leave patients alone with their results.

### Other routine checks – what else should be monitored?

Besides the CD4+ T-cell count and viral load, several other parameters should be monitored in the HIV patient. The following recommendations apply to clinically asymptomatic patients with normal results on routine laboratory evaluation, who have been on stable treatment for several months, or who are not taking antiretroviral therapy. Of course, if treatment is started or changed, or if the patient develops complaints, more frequent monitoring is required. Depending on the problem, additional tests may be necessary. A complete physical examination should be performed regularly, and this often leads to the discovery of important findings such as Kaposi lesions or mycoses (thrush!). The lower the CD4+ T-cells, the more frequently patients should be examined.

Table 11.2: Minimal evaluations per year in stable asymptomatic patients

	Patient on ART per year	Untreated per year
Blood count, LDH, ALT, AST, creatinine, bilirubin, AP, lipase, $\gamma$ GT, glucose	4-6 x	2-4 x
Viral load	4 x	2-4 x
CD4+ T-cells	2-4 x	2-4 x
Lipids	1-2 x	1 x
Physical examination	2-4 x	1-2 x
Gynecological examination	1 x	1 x
Fundoscopy if CD4+ T-cells < 200/ $\mu$ l	2-4 x	4 x

In patients with less than 200 CD4+ T-cells/ $\mu$ l, we usually perform fundoscopies every three to six months to exclude CMV retinitis. Close cooperation with an HIV-experienced ophthalmologist is important. The better the CD4 cells, the less often fundoscopies are necessary – in our opinion, when CD4+ T-cell counts have nor-

malized, these can be stopped completely. In contrast, regular gynecological examinations with PAP smears are recommended, regardless of CD4 count (see also the European guidelines: <http://hiv.net/link.php?id=185>). Many experts now also recommend rectal examination (including proctoscopy) for the early detection of precancerous lesions and anal cancer.

However, such guidelines or recommendations are interpreted very differently. In our experience, in cases of good immune status, unless there is a specific suspicion, routine X-rays, ultrasound examinations (exception: patients with chronic hepatitis, as hepatocellular carcinoma is not rare in such cases!), multiple serologies or lactate measurements are not necessary.

An annual ECG is only indicated in our view in patients with a specific risk profile (see also the chapter “HIV and Cardiac Disease”). The tuberculin test (the Mendel-Mantoux skin test with 5 IE once a year) should only be repeated if it is negative initially.

### **Therapeutic drug monitoring (TDM) – when should plasma levels be measured?**

Individual plasma levels of many antiretroviral drugs may vary considerably for differing reasons (e.g. compliance, metabolism, absorption). But, sufficient plasma levels are essential for success of virological treatment (Acosta 2000). In the VIRADAPT Study, adequate PI-concentrations were even more crucial than knowledge of resistance mutations (Durant 2000). The importance of sufficient plasma levels has also been shown for NNRTIs (Marzolini 2001, Veldkamp 2001).

On the other hand, very high plasma levels correlate with a higher rate of side effects. Reported renal problems with indinavir (Dielemann 1999), gastrointestinal disturbances with ritonavir (Gatti 1999), hepatotoxicity with nevirapine (Gonzalez 2002), or CNS problems with efavirenz (Marzolini 2001) were all associated with high plasma levels.

The measurement of drug concentrations in serum or plasma (therapeutic drug monitoring, TDM) has therefore become an important tool for monitoring therapy. The best reviews are to be found in Back 2002, Burger 2002, and Clevenbergh 2004. Due to the increasing complexities of antiretroviral combinations, TDM of protease inhibitors and NNRTIs will probably become more important in the future.

Several problems associated with TDM are limiting its broader use. The measurement of nucleoside analogs, for example, is senseless since they are converted to the active metabolites only intracellularly. Intracellular measurements are difficult and will not be available in routine clinical practice.

Measuring NNRTIs or PIs may therefore currently determine levels of only one component of a (failing) combination. Further problems include not only viral strains with different levels of resistance, different inhibitory concentrations, variable protein binding, and time-dependent variability of plasma levels, but also methodological problems with the assays, as well as the lack of clearly defined limits. Many uncertainties thus remain in the assessment of therapeutic drug plasma levels. Until data from randomized studies is available, proving the clinical value of TDM, both the measurement and interpretation of the results should be left to specialized centers.

Measurement of plasma levels is currently recommended (German-Austrian guidelines from May 2004) in the following situations:

- Complex drug combinations
- Concomitant medications that could lead to interactions or reduced efficacy
- Suspected absorption problems
- Pregnancy

## References

1. Acosta EP, Kakuda TN, Brundage RC, Anderson PL, Fletcher CV. Pharmacodynamics of HIV type 1 protease inhibitors. *Clin Infect Dis* 2000, Suppl 2:S151-9. <http://amedeo.com/lit.php?id=10860900>
2. Back D, Gatti G, Fletcher C, et al. Therapeutic drug monitoring in HIV infection: current status and future directions. *AIDS* 2002, Suppl 1:S5-37. Review. <http://amedeo.com/lit.php?id=12035820>
3. Buchacz K, Patel P, Taylor M, et al. Syphilis increases HIV viral load and decreases CD4 cell counts in HIV-infected patients with new syphilis infections. *AIDS* 2004, 18:2075-2079. <http://amedeo.com/lit.php?id=15577629>
4. Burger DM, Aarnoutse RE, Hugen PW. Pros and cons of therapeutic drug monitoring of antiretroviral agents. *Curr Opin Infect Dis* 2002, 15:17-22. <http://amedeo.com/lit.php?id=11964901>
5. Clevenbergh P, Mouly S, Sellier P, et al. Improving HIV infection management using antiretroviral plasma drug levels monitoring: a clinician's point of view. *Curr HIV Res* 2004, 2:309-21. <http://amedeo.com/lit.php?id=15544452>
6. Coste J, Montes B, Reynes J, et al. Comparative evaluation of three assays for the quantitation of HIV type 1 RNA in plasma. *J Med Virol* 1996, 50:293-302. <http://amedeo.com/lit.php?id=8950685>
7. Demeter LM, Hughes MD, Coombs RW, et al. Predictors of virologic and clinical outcomes in HIV-1-infected patients receiving concurrent treatment with indinavir, zidovudine, and lamivudine. *ACTG Protocol 320. Ann Intern Med* 2001, 135: 954-64. <http://amedeo.com/lit.php?id=11730396>
8. Dieleman JP, Gyssens IC, van der Ende ME, de Marie S, Burger DM. Urological complaints in relation to indinavir plasma concentrations in HIV-infected patients. *AIDS* 1999, 13:473-8. <http://amedeo.com/lit.php?id=10197375>
9. Durant J, Clevenbergh P, Garraffo R, et al. Importance of protease inhibitor plasma levels in HIV-infected patients treated with genotypic-guided therapy: pharmacological data from the Viradapt Study. *AIDS* 2000, 14:1333-9. <http://amedeo.com/lit.php?id=10930147>
10. Farber CM, Barath AA, Dieye T. The effects of immunization in HIV type 1 infection. *N Engl J Med* 1996, 335:817; discussion 818-9.
11. Gatti G, Di Biagio A, Casazza R, et al. The relationship between ritonavir plasma levels and side-effects: implications for therapeutic drug monitoring. *AIDS* 1999, 13:2083-9. <http://amedeo.com/lit.php?id=10546861>
12. Ghani AC, de Wolf F, Ferguson NM, et al. Surrogate markers for disease progression in treated HIV infection. *J Acquir Immune Defic Syndr* 2001; 28: 226-31.. Abstract: <http://amedeo.com/lit.php?id=11694828>
13. Goletti D, Weissman D, Jackson RW, et al. Effect of Mycobacterium tuberculosis on HIV replication. Role of immune activation. *J Immunol* 1996, 157:1271-8. <http://amedeo.com/lit.php?id=8757635>
14. Gonzalez de Requena D, Nunez M, Jimenez-Nacher I, Soriano V. Liver toxicity caused by nevirapine. *AIDS* 2002, 16:290-1. <http://amedeo.com/lit.php?id=11807315>
15. Gorochov G, Neumann AU, Kereveur A, et al. Perturbation of CD4+ and CD8+ T-cell repertoires during progression to AIDS and regulation of the CD4+ repertoire during antiviral therapy. *Nat Med* 1998, 4: 215-21. <http://amedeo.com/lit.php?id=9461196>
16. Grabar S, Kousignian I, Sobel A, et al. Immunologic and clinical responses to highly active antiretroviral therapy over 50 years of age. Results from the French Hospital Database on HIV. *AIDS* 2004, 18:2029-2038. <http://amedeo.com/lit.php?id=1557762>
17. Ho DD, Neumann AU, Perelson AS, et al. Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. *Nature* 1995, 373:123-6. <http://amedeo.com/lit.php?id=7816094>
18. Hoover DR. Would confirmatory retesting of CD4+ cells to verify AIDS status be too expensive? *J Acquir Immune Defic Syndr* 1993, 6:537-9.
19. Hughes MD, Johnson VA, Hirsch MS, et al. Monitoring plasma HIV-1 RNA levels in addition to CD4+ lymphocyte count improves assessment of antiretroviral therapeutic response. *ACTG 241 Protocol Virology Substudy Team. Ann Intern Med* 1997; 126: 929-38. <http://amedeo.com/lit.php?id=9182469>

20. Kaufmann GR, Bloch M, Zaunders JJ, Smith D, Cooper DA. Long-term immunological response in HIV-1-infected subjects receiving potent antiretroviral therapy. *AIDS* 2000, 14: 959-69. <http://amedeo.com/lit.php?id=10853977>
21. Kitchen CM, Kitchen SG, Dubin JA, Gottlieb MS. Initial virological and immunologic response to HAART predicts long-term clinical outcome. *Clin Infect Dis* 2001; 33: 466-72. <http://amedeo.com/lit.php?id=11462181>
22. Kolber MA, Gabr AH, De La Rosa A, et al. Genotypic analysis of plasma HIV-1 RNA after influenza vaccination of patients with previously undetectable viral loads. *AIDS* 2002, 16: 537-42. <http://amedeo.com/lit.php?id=11872996>
23. Kolte L, Dreves AM, Ersboll AK, et al. Association between larger thymic size and higher thymic output in HIV-infected patients receiving HAART. *J Infect Dis* 2002, 185:1578-85. <http://amedeo.com/lit.php?id=12023763>
24. Lange CG, Valdez H, Medvik K, Asaad R, Lederman MM. CD4+ T-lymphocyte nadir and the effect of HAART on phenotypic and functional immune restoration in HIV-1 infection. *Clin Immunol* 2002, 102:154-61. <http://amedeo.com/lit.php?id=11846457>
25. Le Moing V, Thiebaut R, Chene G, et al. Predictors of long-term increase in CD4(+) cell counts in HIV-infected patients receiving a protease inhibitor-containing antiretroviral regimen. *J Infect Dis* 2002, 185: 471-80. <http://amedeo.com/lit.php?id=11865399>
26. Lederman MM. Immune restoration and CD4+ T-cell function with antiretroviral therapies. *AIDS* 2001, Suppl 2:S11-5. <http://amedeo.com/lit.php?id=11424971>
27. Lepri AC, Miller V, Phillips AN, et al. The virological response to HAART over the first 24 weeks of therapy according to the pre-therapy viral load and the weeks 4-8 viral load. *AIDS* 2001, 15: 47-54. <http://amedeo.com/lit.php?id=11192867>
28. Lyles RH, Munoz A, Yamashita TE, et al. Natural history of HIV type 1 viremia after seroconversion and proximal to AIDS in a large cohort of homosexual men. *J Infect Dis* 2000, 181:872-880. <http://amedeo.com/lit.php?id=10720507>
29. Maggiolo F, Migliorino M, Pirali A. Duration of viral suppression in patients on stable therapy for HIV-1 infection is predicted by plasma HIV RNA level after 1 month of treatment. *J Acquir Immune Defic Syndr* 2000, 25:36-43. <http://amedeo.com/lit.php?id=11064502>
30. Malone JL, Simms TE, Gray GC, et al. Sources of variability in repeated T-helper lymphocyte counts from HIV type 1-infected patients: total lymphocyte count fluctuations and diurnal cycle are important. *J Acquir Immune Defic Syndr* 1990, 3:144-51. <http://amedeo.com/lit.php?id=1967309>
31. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001, 15: 71-5. <http://amedeo.com/lit.php?id=11192870>
32. Mellors JW, Munoz AM, Giorgi JV, et al. Plasma viral load and CD4+ lymphocytes as prognostic markers of HIV-1 infection. *Ann Intern Med* 1997, 126:946-954. <http://amedeo.com/lit.php?id=918247>
33. Napravnik S, Poole C, Thomas JC, Eron JJ Jr. Gender difference in HIV RNA levels: a meta-analysis of published studies. *J Acquir Immune Defic Syndr* 2002, 31:11-9. <http://amedeo.com/lit.php?id=12352145>
34. Notermans DW, Pakker NG, Hamann D, et al. Immune reconstitution after 2 years of successful potent ART in previously untreated HIV type 1-infected adults. *J Infect Dis* 1999, 180: 1050-6. <http://amedeo.com/lit.php?id=10479130>
35. O'Brien WA, Grovit-Ferbas K, Namazi A, et al. HIV-type 1 replication can be increased in peripheral blood of seropositive patients after influenza vaccination. *Blood* 1995, 86:1082-9. <http://amedeo.com/lit.php?id=7620162>
36. Pakker NG, Notermans DW, de Boer RJ, et al. Biphasic kinetics of peripheral blood T cells after triple combination therapy in HIV-1 infection: a composite of redistribution and proliferation. *Nat Med* 1998, 4: 208-14. <http://amedeo.com/lit.php?id=9461195>
37. Parekh B, Phillips S, Granade TC, et al. Impact of HIV type 1 subtype variation on viral RNA quantitation. *AIDS Res Hum Retroviruses* 1999, 15:133-42. <http://amedeo.com/lit.php?id=10029245>
38. Perelson AS, Essunger P, Cao Y, et al. Decay characteristics of HIV-1-infected compartments during combination therapy. *Nature* 1997, 387:188-91. <http://amedeo.com/lit.php?id=9144290>
39. Perelson AS, Neumann AU, Markowitz M, Leonard JM, Ho DD. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996, 271:1582-6. <http://amedeo.com/lit.php?id=8599114>
40. Phillips AN, Youle M, Lampe F, et al. CD4 cell count changes in individuals with counts above 500 cells/mm and viral loads below 50 copies/ml on antiretroviral therapy. *AIDS* 2002; 16: 1073-5.
41. Phillips A, CASCADE Collaboration. Short-term risk of AIDS according to current CD4 cell count and viral load in antiretroviral drug-naïve individuals and those treated in the monotherapy era. *AIDS* 2004, 18:51-8. <http://amedeo.com/lit.php?id=15090829>

42. Polis MA, Sidorov IA, Yoder C, et al. Correlation between reduction in plasma HIV-1 RNA concentration 1 week after start of antiretroviral treatment and longer-term efficacy. *Lancet* 2001, 358: 1760-5 <http://amedeo.com/lit.php?id=11734232>
43. Renaud M, Katlama C, Mallet A, et al. Determinants of paradoxical CD4 cell reconstitution after protease inhibitor-containing antiretroviral regimen. *AIDS* 1999, 13:669-76. <http://amedeo.com/lit.php?id=10397561>
44. Rizzardì GP, DeBoer RJ, Hoover S, et al. Predicting the duration of antiretroviral treatment needed to suppress plasma HIV-1 RNA. *J Clin Invest* 2000, 105:777-782. <http://amedeo.com/lit.php?id=10727446>
45. Roger PM, Breittmayer JP, Durant J, et al. Early CD4(+) T cell recovery in HIV-infected patients receiving effective therapy is related to a down-regulation of apoptosis and not to proliferation. *J Infect Dis* 2002, 185: 463-70. <http://amedeo.com/lit.php?id=11865398>
46. Smith CJ, Sabin CA, Youle MS, et al. Factors influencing increases in CD4 cell counts of HIV-positive persons receiving long-term highly active antiretroviral therapy. *J Infect Dis* 2004, 190:1860-8. <http://amedeo.com/lit.php?id=15499544>
47. Smith CJ, Staszewski S, Sabin CA, et al. Use of viral load measured after 4 weeks of highly active antiretroviral therapy to predict virologic outcome at 24 weeks for HIV-1-positive individuals. *J AIDS* 2004, 37:1155-1159. <http://amedeo.com/lit.php?id=15319675>
48. Telenti A. New developments in laboratory monitoring of HIV-1 infection. *Clin Microbiol Infect* 2002, 8:137-43. <http://amedeo.com/lit.php?id=12010168>
49. Thiebaut R, Morlat P, Jacqmin-Gadda H, et al. Clinical progression of HIV-1 infection according to the viral response during the first year of antiretroviral treatment. *AIDS* 2000, 14: 971-8. <http://amedeo.com/lit.php?id=10853978>
50. Veldkamp AI, Weverling GJ, Lange JM, et al. High exposure to nevirapine in plasma is associated with an improved virological response in HIV-1-infected individuals. *AIDS* 2001; 15: 1089-95. <http://amedeo.com/lit.php?id=11416710>
51. Viard JP, Mocroft A, Chiesi A, et al. Influence of age on CD4 cell recovery in HIV-infected patients receiving HAART: evidence from the EuroSIDA study. *J Infect Dis* 2001, 183: 1290-4. <http://amedeo.com/lit.php?id=11262215>
52. Viard JP, Burgard M, Hubert JB, et al. Impact of 5 years of maximally successful highly active antiretroviral therapy on CD4 cell count and HIV-1 DNA level. *AIDS* 2004, 18:45-9. <http://amedeo.com/lit.php?id=15090828>
53. Walter EA, Gilliam B, Delmar JA, et al. Clinical implications of identifying non-B subtypes of HIV type 1 infection. *Clin Infect Dis* 2000, 31:798-802. <http://amedeo.com/lit.php?id=11017832>
54. Wu H, Kuritzkes DR, McClernon DR, et al. Characterization of viral dynamics in HIV type 1-infected patients treated with combination antiretroviral therapy: relationships to host factors, cellular restoration, and virologic end points. *J Infect Dis* 1999, 179: 799-807. <http://amedeo.com/lit.php?id=10068574>

## 6. Management of Side Effects

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Patients on HAART commonly suffer from side effects. As a result, treatment of HIV infection has become a complicated balancing act between the benefits of durable HIV suppression and the risks of drug toxicity. About 25 % of patients stop therapy within the first year on HAART because of side effects (d'Arminio Monforte 2000). About the same number of patients do not take the recommended dosages of their medication due to concerns regarding the side effects (Eron 2000, Chesney 2000). Patients, who report significant side effects, are more often non-adherent to therapy (Ammassari 2001).

The patient should be counseled in detail on the potential side effects, so that he or she is in a position to recognize them and to consult his physician in time. This can save lives, for example in the case of the abacavir hypersensitivity reaction, and the irreversible damage of side effects, such as polyneuropathy, can be prevented through early diagnosis. Being prepared for the occurrence of possible problems and providing potential solutions improves both the acceptance of treatment and the adherence. However, patients should not be frightened by all this information – the extensive package inserts are often ominous enough. It may be difficult to distinguish between symptoms related to HIV infection and those caused by antiretroviral therapy. An accurate history, including any co-medication (not forgetting over-the-counter products!) is paramount. It is important to consider the intensity, variation and reproducibility of complaints, as other possible causes should be excluded before symptoms are judged as being side effects of treatment.

It must be stressed that the majority of patients are able to tolerate HAART well, even over years. Nevertheless, the monitoring of treatment by an HIV clinician, even in asymptomatic patients, is recommended in at least three-monthly intervals, and even more often at the beginning of a new HAART, when it should be weekly or fortnightly. Standard evaluations include a thorough history (allergies?, other side effects?), physical examination and measurement of vital signs and body weight. Routine investigations include a full blood count, liver, pancreas and renal function tests, electrolytes (plus phosphate in patients on tenofovir) as well as fasting cholesterol, triglycerides and glucose levels.

For lipodystrophy see chapter on “Lipodystrophy Syndrome”.

### **Gastrointestinal side effects**

Gastrointestinal problems are the most common side effects of almost all antiretroviral drugs - nucleoside analogs, NNRTIs and particularly protease inhibitors - and occur especially during the early stages of therapy. Typical symptoms include abdominal discomfort, loss of appetite, diarrhea, nausea and vomiting. Heartburn, abdominal pain, meteorism and constipation may also occur. Nausea is a common symptom with zidovudine-containing regimens; diarrhea occurs frequently with zidovudine, didanosine and all PIs, particularly with ritonavir and nelfinavir, as well as with saquinavir, lopinavir/r, atazanavir and tipranavir. Treatment with zi-

dovudine rarely leads to a severe form of gastritic pain, nausea and vomiting in the early phase of therapy, in which case it should be discontinued.

In addition to the often considerable impact on everyday life, gastrointestinal side effects can lead to dehydration, malnutrition with weight loss, and low plasma drug levels with the risk of development of resistant viral strains.

In most cases, symptoms occur at the beginning of therapy. Patients should be informed that these side effects usually resolve after four to six weeks of treatment. If gastrointestinal side effects occur for the first time after longer periods on HAART, other causes such as gastritis and infectious diarrhea are likely.

## Nausea and vomiting

If administration on an empty stomach leads to nausea and vomiting, most drugs can also be taken together with meals. When a drug (e.g. didanosine, indinavir, rifampin) has to be administered on an empty stomach, small quantities of low-fat salty crackers may lessen the nausea. Ginger, peppermint or chamomile teas or sweets may also be helpful, as well as frequent small meals. Care should be taken with fatty foods and dairy products. Coffee, smoking, alcohol, aspirin and very spicy foods should be avoided if possible.

If symptomatic treatment is necessary, metoclopramide has been proven to be useful. Dimenhydrinate, cimetidine, ranitidine or ondansetron can also be taken. Antiemetic drugs should not only be administered if the patient is already feeling sick, but rather taken regularly, ideally 30 to 45 minutes before HAART. If taken on a regular basis, attention should be paid to side effects such as dyskinesia. After a few weeks, doses can generally be slowly reduced. If nausea persists for more than two months, a change of treatment should be considered – otherwise adherence problems will certainly occur.

Emend™ (aprepitant) is a substance P/neurokinin 1 (NK1) receptor antagonist. It is used since 2004 to prevent and control nausea and vomiting caused by cancer chemotherapy. Hitherto, no data exist regarding the use in HIV drug-associated nausea. However, due to the potential interaction with many HIV drugs (cytochrome P450 3A4 system) it should not be used.

## Diarrhea

In patients with massive diarrhea, the priority is to treat dehydration and loss of electrolytes. Other causes such as gastrointestinal infections or lactose intolerance should be excluded. Difficult to digest foodstuffs (particularly those rich in fats or glucose) should be avoided and those that are easy to digest (e.g. potatoes, rice, noodles), eaten instead. It makes sense to remember approved homespun remedies (see table 1).

If significant dehydration and loss of electrolytes occur, coke and salty crackers, sports drinks, herbal teas or electrolyte solutions may be taken (reviews in: Highleyman 2002, Schwarze 2002, Sherman 2000). Oral rehydration solution can be easily made from the juice of 5 oranges, 800 ml of boiled water or tea (cooled to room temperature), one teaspoon of iodized salt and two tablespoons of sugar.

Oat bran tablets have been proven to be useful and cheap for PI-associated diarrhea. They are taken together with antiretroviral therapy (daily dose 1500 mg). Pancreli-



pase, a synthetic pancreatic enzyme, has also been shown to be effective for PI-associated diarrhea.

PI-associated diarrhea is alleviated by calcium (Turner 2004), taken as calcium carbonate, at a dosage of 500 mg bid. However, as calcium binds many other substances, it should be taken 2 hours apart from HIV medication.

Oral supplements of glutamine (10 – 30 g/day) or alanyl–glutamine (up to 44 g/day) alleviate diarrhea and can also boost the levels of antiretroviral drugs in the blood (Bushen 2004, Heiser 2002, Heiser 2004). Glutamine can be purchased in drugstores or ordered via the Internet. The probiotics, *Saccharomyces boulardii* and *Lactobacillus acidophilus* are used in infectious diarrhea and for the prevention of antibiotic-associated diarrhea. They can sometimes ameliorate medication-associated diarrhea. Case reports implicated *S. boulardii* as an etiologic agent of possibly fatal invasive fungal infection. Particularly at risk were patients with an intravascular catheter or on antibiotic therapy (see review in: Enanche-Angoulvant 2005).

Alternatively, psyllium may be effective. It should not be taken together with loperamide or opium tincture, or at the same time as HIV medication.

The cornerstone of symptomatic treatment is loperamide which inhibits bowel movement (initially 2 – 4 mg, followed by 2 mg, up to a maximum of 16 mg daily). If loperamide is not effective, opium tincture is an alternative (initially 5 drops, maximum 15 to 20 drops), attention should be paid to the risk of intestinal obstruction, especially if overdosed. In some cases, a combination of different antidiarrheal drugs may be appropriate.

Table 1: “Approved” homespun remedies

**Pectin**

in apples (raw with paring), bananas (purée), carrots (purée, cooked, soup), St. John’s bread (oatmeal gruel or rice gruel with St. John’s flour). Pectin is a dietary fiber, which is not digested, it binds water and toxic substances and lessens the diarrhea.

**Gruel**

Soups made of oatmeal or rice gruel

**Tanning agents**

Black or green tea, dried blueberries (tea, powder), dark chocolate

## Hepatotoxicity

Elevated liver function tests are common with HAART, and severe hepatotoxicity occurs in up to 6 % of patients (Becker 2004). Their occurrence depends on the drug classes or agents used as well as on pre-existing liver dysfunction. The level of liver toxicity ranges from mild and fully reversible liver enzyme elevation to rare but rapidly occurring, occasionally fatal, liver failure.

Nevirapine and ritonavir have been associated with severe hepatotoxicity and hepatic failure with several fatalities linked to nevirapine (Bjornson 2006, De Maat 2003). Case reports also exist about liver failure occurring on indinavir, atazanavir, efavirenz, nelfinavir and different nucleoside analogs (Carr 2001, Clark 2002). Pa-

tients with pre-existing liver disease should receive these drugs only under strict monitoring (Sulkowski 2002+2004).

Hepatotoxic reactions occur at different time points for different drug classes: nucleoside analogs lead to hepatic steatosis, which is probably caused by mitochondrial toxicity and usually occurs after more than 6 months on treatment (Montessori 2003). NNRTIs often cause a hypersensitivity reaction within the first 12 weeks. In one study, severe hepatotoxicity was observed in 15.6 % of patients on nevirapine and in 8 % of those on efavirenz. Those patients who were concurrently taking PIs and were co-infected with hepatitis B virus and/or hepatitis C virus had the highest risk (Sulkowski 2002). The exact cause remains unclear, but higher PI drug levels due to decreased metabolism may play a crucial role. PIs can lead to hepatotoxicity at any stage during the course of treatment – once again, patients with chronic viral hepatitis are particularly at risk. One possible cause is an immune reconstitution syndrome on HAART, with increased cytolytic activity against the hepatitis viruses. Among the PIs, toxic hepatitis is seen most frequently in patients on boosted atazanavir, indinavir and tipranavir, a novel non-peptidic protease inhibitor (Hicks 2006, Sulkowski 2004).

## Nevirapine

Liver toxicity occurs more commonly on nevirapine than on other antiretroviral drugs. Clinically asymptomatic and symptomatic liver toxicity, including rapidly occurring fatal liver failure have been observed (Bjornsson 2006). Serious and fatal liver toxicity has been reported even during post-exposure prophylaxis, but not after single doses of nevirapine (Jackson 2003, Wood 2005). Females, especially those patients with low Body Mass Index (BMI) and higher CD4 cell counts are at increased risk of liver toxicity on nevirapine. The risk of symptomatic hepatotoxicity for females is more than three-fold that of males, and in females with CD4+ T-cell counts > 250/ $\mu$ l, the risk is 12-fold in comparison to females with < 250/ $\mu$ l (11 vs. 0.9 %). Males with CD4+ T-cell counts > 400/ $\mu$ l have a five-fold increased risk of symptomatic liver toxicity than males with < 400/ $\mu$ l (6.3 vs. 1.2 %) (Stern 2003). Females with a BMI lower than 18.5 kg/m<sup>2</sup> have also an increased risk of liver toxicity on nevirapine (Sanne 2005). The Indications and Usage section of the Viramune label advises against starting nevirapine treatment in women with CD4+ T-cell counts greater than 250/ $\mu$ l unless benefits clearly outweigh risks (<http://www.fda.gov/cder/drug/advisory/nevirapine.htm>).

Liver toxicity occurs usually early during therapy (within 18 weeks of starting). If liver enzymes increase to > 5 times upper limit of normal (ULN) during treatment, nevirapine should be stopped immediately. If liver enzymes return to baseline values and if the patient has had no clinical signs or symptoms of hepatitis, rash, constitutional symptoms or other findings suggestive of organ dysfunction, it may, on a case-by-case basis, be possible to reintroduce nevirapine. However, frequent monitoring is mandatory in such cases. If liver function abnormalities recur, nevirapine should be permanently discontinued. If clinical hepatitis (anorexia, nausea, jaundice, etc.) occurs, nevirapine must be stopped immediately and never readministered.

## Protease inhibitors

Atazanavir and indinavir inhibit the hepatic enzyme UDP-glucuronosyltransferase, increasing the level of bilirubin in up to 47 % of the patients. Hyperbilirubinemia is not usually associated with signs or symptoms of hepatocellular injury, and clinically resembles Gilbert's syndrome. Fewer than 2 % of patients discontinue atazanavir therapy because of this adverse effect (Busti 2004). Hyperbilirubinemia is associated with higher ATV plasma levels (Barrios 2004). Individuals who are homozygous for UGT1A1\*28 are at particular risk of atazanavir or indinavir associated hyperbilirubinemia (Rotger 2005). Genotyping for UGT1A1\*28 before initiation of therapy would identify individuals at risk, but might not be cost-effective.

The levels of bilirubin return to normal following discontinuation of the drugs. If bilirubin is only mildly elevated (< 3 times ULN) and the serum liver enzyme levels are normal, treatment change is not mandatory. If the bilirubin is constantly markedly elevated, medication should be discontinued: nobody knows about the long-term consequences of hyperbilirubinemia (Sulkowsky 2004). The tipranavir-ritonavir intake is associated with a risk of elevation of alanine and aspartate transaminases (Hicks 2006).

Besides serological tests for viral hepatitis, an abdominal ultrasound should be performed to recognize structural liver dysfunction early, e.g. non-alcoholic steatohepatitis or liver cirrhosis, before initiating HAART. Liver function should be monitored biweekly at the start of treatment with nevirapine and PIs and even more frequently in patients with pre-existing liver disease. Monthly tests are generally sufficient for all other drugs. If liver enzymes (ALT, AST) are moderately elevated (< 3.5 times ULN) in the absence of clinical symptoms, treatment can be continued under close monitoring. If liver enzymes are elevated to more than 3.5 times ULN, additional diagnostic tests should be performed, including an abdominal ultrasound. In cases of co-infection with hepatitis B or C, treatment of these conditions should be considered. With other pre-existing liver conditions, it may be useful to determine drug plasma levels. Discontinuation of treatment may not be necessary (exception: nevirapine).

If liver enzymes are elevated in a later phase of therapy (after more than 6 months), a thorough investigation including serology for viral hepatitis, CMV, and EBV, as well as an abdominal ultrasound, should be performed. Lactic acidosis, hypersensitivity reactions to abacavir and other hepatotoxic drugs should also be considered. Furthermore, analysis of blood gases including pH, base excess and bicarbonate concentration, lactate levels and a thorough drug history can help. Liver biopsy reveals macro- and microvesicular steatosis and mitochondrial alterations in NRTI-induced steatosis and is therefore helpful to identify a nucleoside-induced hepatopathy and to distinguish it from other causes of liver injury.

In patients with HCV co-infection, hepatitis C should, if possible, be treated before the initiation of HAART, to reduce the frequency of severe hepatotoxicity (see Chapter "Hepatitis C"). In HBV co-infection, the HAART regimen should include lamivudine and/or tenofovir. Patients with pre-existing liver dysfunction should undergo drug plasma level monitoring, especially during treatment with PIs. Doses can be adjusted according to the plasma levels so that a precocious discontinuation

of therapy can be avoided. However, no relationship has been found between hepatic injury and plasma levels of nevirapine (Daily 2004).

Finally, drug interactions and hepatotoxicity related to other drugs (e.g. ACE inhibitors), taken concomitantly, should not be overlooked.

## Pancreatitis

Up to 7 % of patients treated with didanosine suffer from pancreatitis. Occasionally, stavudine, lamivudine and zalcitabine cause pancreatitis too. The development of the NRTI dextelvucitabine was halted due to significantly elevated lipase levels. The combinations of didanosine plus stavudine or didanosine plus tenofovir carry a particularly high risk for pancreatitis. Alcohol consumption and treatment with intravenous pentamidine are further risk factors.

The mechanism by which didanosine triggers pancreatitis is not known but may be influenced by its metabolism through the purine pathway (Moyle 2004). A significant interaction between didanosine and tenofovir leads to a 40 % rise in didanosine plasma concentration. Cases of severe, sometimes fatal, pancreatitis on concurrent didanosine and tenofovir therapy, have been reported. Didanosine and tenofovir should therefore not be co-administered in patients weighing less than 60 kg, who have renal dysfunction or who take lopinavir/r (see Lopinavir) (Blanchard 2003, Martinez 2004).

Antiretroviral drug-induced pancreatitis is not distinguishable from pancreatitis of any other etiology, either clinically or in laboratory tests. Antiretroviral therapy should be stopped immediately. Treatment is the same as for pancreatitis of other etiologies. The symptoms and laboratory changes usually resolve rapidly (Carr 2001). Drugs that have induced pancreatitis once, must never be given again. If patients have a history of pancreatitis of any origin, didanosine is contraindicated.

## Renal problems

### Indinavir

Renal problems occur particularly on indinavir treatment, and are caused by indinavir crystals, which may be found in the urine of up to 20 % of patients. Approximately 10 % of patients develop nephrolithiasis, which is not visible on X-ray, accompanied by renal colic. Nephrolithiasis is primarily caused by high indinavir levels in relation to a low body mass index (Meraviglia 2002), drug interactions and individual fluctuations of the drug plasma level. In one study, the intake of indinavir/ritonavir 800/100 mg with a light meal reduced the indinavir nephrotoxic maximum plasma concentration, probably reflecting a food-induced delay in the absorption of indinavir (Aarnoutse 2003). More than 20 % of patients have persistent asymptomatic leukocyturia associated with a gradual loss of renal function without urological symptoms (Dielemann 2003). However, renal failure is rare (Kopp 2002). In case of suspected high indinavir levels, therapeutic drug monitoring should be performed and the dose adjusted.

Symptoms of acute colic include back pain and flank pain as well as lower abdominal pain, which may radiate to the groin or testes. Hematuria may also occur.

Evaluations should include a physical examination, urine and renal function tests. Ultrasound evaluation can exclude urinary obstruction but does not detect small indinavir stones.

For acute therapy, intravenous analgesia (e.g. metamizole, 1 to 2.5 g) or diclofenac (e.g. 100-150 mg) may be given in combination with spasmolytic drugs (e.g. butylscopolamine, 20 mg). This usually relieves the symptoms quite rapidly, and may be repeated after a few minutes if symptoms persist. If this is unsuccessful, pethidine 50-100 mg by i.v. or i.m. injection can be administered. Fluids should be given in moderation during colics.

As prophylaxis, a daily intake of 1.5 l of fluids is recommended, which should be increased during hot weather and on consumption of alcohol. Interruption of therapy, following a single incidence of colic, is not usually necessary. Indinavir plasma levels should be measured and, if high, the dose adjusted. Renal function and urine should be monitored in all patients, at least every 3 months during indinavir treatment, even in the absence of urological symptoms. With recurring colics, however, indinavir should be discontinued. Non-steroidal anti-inflammatory drugs, quinolones, ampicillin, foscarnet, acyclovir, sulfonamides (cotrimoxazole, sulfadiazine) and allopurinol can also cause nephrolithiasis, and should therefore be used with caution in combination with indinavir (Boubaker 1998).

## Tenofovir

Tenofovir has been approved since 2001 and is, like the two nephrotoxic drugs, adefovir and cidofovir, a nucleotide analog. Animal studies showed a dose-related nephrotoxicity, but although several case reports have suggested its occurrence, severe renal toxicity occurs rarely and was not observed in the major clinical trials with tenofovir (Gallant 2004, Schooley 2002, Scott 2006). Acute renal failure and proximal tubulopathy with Fanconi's syndrome and nephrogenic diabetes insipidus and rarely hypophosphatemic osteomalacia have been reported (Callens 2003, Creput 2003, Earle 2004, Parsonage 2005, Rollet 2003, Saumoy 2004, ). Two studies showed that the use of tenofovir is also associated with a modest decline in creatinine clearance in comparison to patients never treated with tenofovir (Gallant 2005, Mauss 2005).

Proximal tubular damage manifests as proximal tubular acidosis, normoglycemic glycosuria, hypophosphatemia, hypouricemia, hypokalemia, generalized aminoaciduria, and proteinuria. Renal toxicity occurs after some months, rarely at the beginning of therapy (Hansen 2004, Izzedine 2004, Rifkin 2004). Risk factors include a relatively high tenofovir exposure, pre-existing renal impairment, low body weight, co-administration of nephrotoxic drugs, or lopinavir/ritonavir, and atazanavir/didanosine treatment. Protease inhibitors can interact with the renal transport of organic anions, leading to proximal tubular intracellular accumulation of tenofovir. This may lead to Fanconi's syndrome-type tubulopathy and systemic accumulation of didanosine (Izzedine 2004, Rollet 2003, Zimmermann 2006). Furthermore, extensive pre-treatment with nucleoside reverse transcriptase inhibitors seems to be another risk factor (Peyrière 2004, Saumoy 2004). However, even in patients without any predisposing factors, nephrotoxicity may occur (Barrios 2004).

In case of renal dysfunction, especially in patients with low body weight and on lopinavir treatment, tenofovir should be avoided if possible, or the dosing interval

should be adjusted. The manufacturer recommends administering tenofovir every 48 hours in patients with a creatinine clearance between 30 and 49 ml/min and twice a week between 10 and 29 ml/min. Normal creatinine levels may be misleading especially in subjects with low body weight, which is why creatinine clearance should be measured before initiating tenofovir treatment. Renal function tests including creatinine, urea, creatinine clearance, proteinuria, glycosuria, blood and urine phosphate should be monitored every other week.

Tenofovir is not recommended for use in patients with pre-existing renal insufficiency. It should also be avoided with concomitant or recent use of nephrotoxic agents such as aminoglycosides, amphotericin B, foscarnet, ganciclovir, pentamidine, vancomycin, cidofovir or interleukin-2. Usually the abnormalities resolve after discontinuation of the drug (Izzedine 2004, Rifkin 2004, Roling 2006).

An increase in creatine kinase (CK, CK-MB) is common with tenofovir (Shere-Wolfe 2002). Analysis of CK-MB isoenzyme activity and mass concentration revealed evidence for Macro CK 2 (Schmid 2005). Therefore, the elevated CK might not be an indicator of ischemic heart disease but Macro CK-2 appearance on tenofovir treatment. The CK elevation resolves after discontinuation of tenofovir.

## **CNS disorders**

### **Efavirenz**

In up to 40 % of patients, treatment with efavirenz leads to CNS side effects such as dizziness, insomnia, nightmares; even mood fluctuations, depression, depersonalization, paranoid delusions, confusion and suicidal ideation may occur (Lochet 2003). These side effects are observed mainly during the first days and weeks of treatment. Discontinuation of therapy becomes necessary in only 3 % of patients. There is an association between high plasma levels of efavirenz and the occurrence of CNS symptoms (Marzolini 2001).

On the one hand, high efavirenz plasma levels can be caused by medication interactions, so a thorough drug history should be taken; on the other hand the different perception of drug tolerance of the patients can play an important role. Patients should be informed about the nature of these symptoms, and that they are usually expected to resolve after a short period of time. Driving cars or bicycles or operating machinery can be impaired in the first weeks. If dizziness or drowsiness is experienced, these activities should be avoided. Treatment with efavirenz should not be started before exams or other important events.

If the CNS side effects persist for more than two to four weeks, it is reasonable to prescribe 200 mg pills, so that the dose can be divided into a 400 mg night dose and a 200 mg morning dose. We experienced a reduction in unpleasant CNS side effects in 50 % of our patients. The daily dose should not be reduced from 600 mg to 400 mg because of the higher risk of therapy failure and development of drug resistance.

Measurement of drug levels makes sense from the second week of therapy to verify overdosage, but the only consequence is the splitting of the 600 mg dosage (by no means should the dose be reduced to 400 mg). Taking 400 mg/200 mg can reduce the C<sub>max</sub> levels and therefore the toxic potential becomes milder.

Lorazepam can diminish the CNS side effects, and haloperidol can be given for panic attacks and nightmares, but both drugs should be restricted to severe cases, because of their side effects and addictive potency (lorazepam).

Efavirenz is metabolized by cytochrome P4502B6 (CYP2B6). An American study showed that an allelic variant CYP2B6, which is more common in African-Americans than in Europeans-Americans, was associated with significantly greater efavirenz plasma exposure during HIV therapy (Haas 2004). CNS side effects are rarely seen with other NNRTIs. If they persist even after splitting the dosage for more than six weeks, efavirenz should be replaced, for example by nevirapine.

### **Lamivudine/abacavir**

Depression, insomnia and even psychosis rarely occur or get worse on lamivudine or abacavir therapy. If the patient complains of CNS-related side effects, lamivudine or abacavir should be considered as a possible cause (Foster 2004).

## **Peripheral polyneuropathy**

Peripheral polyneuropathy is mainly caused by the NRTIs, zalcitabine, didanosine and stavudine. It usually presents with a distal symmetrical distribution and sensorimotor paralysis. Patients complain of paresthesia and pain in their hands and feet, and often, with zalcitabine, about perioral dysesthesia. The symptoms often begin gradually after several months of therapy. HIV infection itself can lead to peripheral polyneuropathy, but the drug-induced form becomes apparent much earlier and may develop within a shorter period of time. Patients must be informed that they should consult their treating physician as soon as possible if the typical complaints develop. Additional risk factors for polyneuropathy, such as vitamin B12 deficiency, alcohol abuse, diabetes mellitus, malnutrition, or treatment with other neurotoxic drugs, e.g. INH, should be addressed in the appropriate manner. In any case, the nucleoside analogs, zalcitabine, didanosine and stavudine have been dropped from first-line therapy. If possible they should be avoided for salvage therapy, too. Symptoms frequently improve within the first two months following discontinuation of the drugs responsible, but may initially increase in intensity and are not always fully reversible. Because treatment is difficult, and there is no specific therapy, it is extremely important that peripheral polyneuropathy is recognized early by the doctor, resulting in an early change of treatment. The causative agent has to be abandoned.

An easy test, in practice, is to test vibration with a tuning fork. A 64-Hz tuning fork (Rydel-Seiffer) is applied to the appropriate bony surface (e.g., distal hallux, medial malleolus or lateral malleolus) bilaterally. The patient is asked to report the perception of both the start of the vibration sensation and the cessation of vibration on dampening. As the intensity of the vibration starts to diminish the two triangles move closer together again. The intensity at which the patient no longer detects the vibration is read as the number adjacent to the intersection. It can thus be quantified and compared to the results of other tests. Through this simple method first signs of polyneuropathy can be recognized easily and early.

Apart from symptomatic treatment with metamizole, acetaminophen (paracetamol), carbamazepine, amitriptyline, gabapentine and opioids, methods such as acupunc-

ture or transcutaneous nerve stimulation have been tried with variable success. Vitamin B supplementation can help to improve peripheral polyneuropathy faster. Tight shoes or long periods of standing or walking should be avoided; cold showers may relieve pain before going to bed. Uridintriphosphate (Keltican™) is approved for diabetic polyneuropathy, but data about its effectiveness are scant. Indeed, no data or evidence is available to date on its use in HIV neuropathy.

For Uridine see also chapter on “Mitochondrial Toxicity”.

## Haematological changes

### Anemia

Some of the antiretroviral drugs (especially zidovudine) are myelosuppressive, especially with respect to the red cells, and therefore lead to anemia (de Jesus 2004). Most commonly affected are patients with advanced HIV infection and pre-existing myelosuppression, on chemotherapy or co-medication with other myelotoxic drugs such as cotrimoxazole, pyrimethamine, amphotericin B, ribavirin, and interferon, or with other antiretroviral drugs.

5 to 10 % of patients taking zidovudine develop anemia – usually during the first 3 months of therapy, but sometimes even after years on treatment (Carr 2001). Zidovudine should be discontinued in severe cases, and a blood transfusion may be necessary. MCV is always elevated, even in patients on zidovudine without anemia, and is therefore a good proof of adherence. It sometimes makes sense to change from Combivir™ to the single drugs Retrovir™ and Epivir™ in anemic patients, because of the lower zidovudine dose in Retrovir™ (250 mg) compared to Combivir™ (300 mg). In patients with advanced HIV infection and multiple viral resistance, and therefore no options to change to less myelotoxic drugs, erythropoietin is an option, but should be avoided as a long-term option if possible, due to the associated high costs (Henry 2004).

### Leukopenia

HIV infection itself may cause pancytopenia. A very low CD4+ T-cell count may therefore be rarely due to a severe leukopenia. In this case, the percentage of the CD4+ T-cells and the CD4/CD8 ratio is normal.

Due to drug-induced neutropenia, it is possible that besides viral suppression the CD4+ T-cells remain low after an initial rise. In these cases treatment should be changed to less myelotoxic antiretroviral drugs such as stavudine, lamivudine, most of the PI and all NNRTIs. Zidovudine should be avoided. Leukopenia may also occur on indinavir, abacavir or tenofovir.

Negredo (2004) showed that in patients with good virological control, on tenofovir and didanosine as the nuke backbone, the CD4+ T-cell count rose as expected until around 6 months, when it gradually decreased again. It was seen especially in patients with a daily dose of 400 mg didanosine, but also in patients on the lower dose (250 mg/day). The probable cause is the synergistic myelotoxic potential and an increased mitochondrial toxicity of the two drugs, which has a negative effect on the T-cells in particular.



## Allergic reactions

Allergic reactions are frequent during HIV therapy (Pirmohamed 2001). They occur with all NNRTIs, as well as with the nucleoside analog, abacavir (see below) and the PIs, amprenavir, and atazanavir. Because amprenavir is a sulfonamide, it should be given with caution to patients with sulfonamide allergies. When there are limited alternative treatment options, desensitization may permit continued use of amprenavir in patients with a history of amprenavir-induced maculopapular eruptions (Kohli-Pamnani 2005). Atazanavir-associated macular or maculopapular rash is reported in about 6 % of patients and is usually mild, so that treatment withdrawal is not necessary (Ouagari 2006).

### NNRTIs

Nevirapine and delavirdine may cause a slight rash in 15 to 20 % of patients, 5 to 10 % of which discontinue treatment. The rash is seen less frequently on efavirenz therapy, where only 2 % of the patients discontinue the drug (Carr 2001).

The NNRTI allergy is a reversible, systemic reaction and typically presents as an erythematous, maculopapular, pruritic and confluent rash, distributed mainly over the trunk and arms. Fever may precede the rash. Further symptoms include myalgia (sometimes severe), fatigue and mucosal ulceration. The allergy usually begins in the second or third week of treatment. Women are more often and more severely affected (Bersoff-Matcha 2001). If symptoms occur later than 8 weeks after initiation of therapy, other drugs should be suspected. Severe reactions such as the Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome) or anicteric hepatitis are rare (Rotunda 2003).

Treatment should be discontinued immediately in cases with mucous membrane involvement, blisters, exfoliation, hepatic dysfunction (transaminases > 5 times the upper limit of normal) or fever > 39°C.

If patients present with a suspected nevirapine-associated rash, additional hepatotoxicity and liver failure should be considered and liver function tests should be performed. Patients with rash-associated AST or ALT elevations should be permanently discontinued from nevirapine.

Approximately 50 % of NNRTI allergies resolve despite continuation of therapy. Antihistamines may be helpful. Prophylactic treatment with glucocorticosteroids or antihistamines has been shown to be of no benefit for the prevention of nevirapine allergy; in fact, rashes were even more common in some studies (Knobel 2001, Montaner 2003, The Grupo Estudio 2004). Following a severe allergic reaction, the drug responsible for the reaction should never be given again.

### Abacavir hypersensitivity

Abacavir causes a hypersensitivity reaction (HSR), which may be life threatening if not recognized in time. It occurs in approximately 4-8 % of patients (reviews: Hewitt 2002, Clay 2002). A higher rate is noted in patients on a once-daily regime, in art-naïve patients, in patients with a nevirapine allergy, and in acute HIV infection (James 2005, Chirouze 2005). In 93 % of cases, the HSR occurs after a median of 8 days, and within the first 6 weeks.

Different studies have found a strong predictive association between HLA-B\*57:01 and the occurrence of HSR (Hetherington 2002, Mallal 2002, Martin 2004), indicating that exclusion of HLA-B\*57:01 individuals from abacavir treatment could largely prevent HSR (Rauch 2006). Possibly pre-prescription routine HLA typing or flow cytometry for HLA-B57 (Martin 2006) may be reasonable and cost-effective in the future. A large randomized trial is planned with sites in Australia and Europe.

The rash associated with the abacavir hypersensitivity reaction is often discrete, in contrast to the skin reactions caused by nevirapine and efavirenz; in 30 % of patients it may not occur at all. 80 % of patients have fever. In addition to general malaise (which gets worse from day to day!), other frequent symptoms include gastrointestinal side effects such as nausea, vomiting, diarrhea and abdominal pain. Respiratory symptoms, such as dyspnea, cough and sore throat, are rare. Changes in the blood count, elevation of liver transaminases, alkaline phosphatase, creatinine and LDH may accompany the HSR. There is usually no eosinophilia. One case of Stevens-Johnson syndrome has been described (Bossi 2002).

The synchronous start of therapy with abacavir and NNRTIs is unfavorable because of the difficulties of differentiating between allergic reactions to NNRTIs and HSR. If abacavir is part of the initial therapy and flu-like symptoms occur, it is difficult to distinguish between immune reconstitution inflammatory syndrome (IRIS) and HSR; hence HIV therapy should be carried out by HIV-experienced doctors. The HSR is diagnosed clinically. The differential diagnosis from an intercurrent infection is often difficult. Criteria in favor of HSR include the development of symptoms within the first six weeks of treatment, deterioration with each dose taken and the presence of gastrointestinal side effects. If abacavir is discontinued in time, the HSR is completely reversible within a few days. HSR may be fatal if not diagnosed. Following discontinuation of abacavir, further supportive treatment includes intravenous hydration and possibly steroids.

If the suspicion of HSR is only vague, and abacavir is not stopped, the patient should be seen or spoken to (by telephone) daily, to be able to react immediately in case of clinical worsening. Once the diagnosis of HSR has been established, rechallenge with abacavir can be fatal and is strictly contraindicated. If there was only a vague suspicion of HSR, rechallenge under in-patient conditions is possible. Whenever treatment has been interrupted, it should be noted that the HSR can occur for the first time after restarting treatment, even without a prior HSR.

Treatment with abacavir requires detailed counseling (and documentation!) on the possible occurrence and symptoms of the HSR. Patients should know whom to contact in cases of suspected HSR, preferably also at night and at weekends. It is important, however, not to frighten patients to the extent that they themselves discontinue treatment too early.

## Lactic acidosis

In comparison to asymptomatic hyperlactacidemia, which occurs in approximately 15-35 % of NRTI-treated patients (Carr 2001, Hocqueloux 2003), lactic acidosis is a rare but life-threatening complication. NRTIs are thought to cause mitochondrial toxicity via inhibition of the mitochondrial DNA polymerase. The incidence is ap-

proximately 3.9/1000 NRTI patient years (John 2001) (see also chapter on Mitochondrial Toxicity).

It occurs most frequently on treatment with stavudine and didanosine, less in patients on zidovudine, abacavir and lamivudine. Risk factors are obesity, female sex, pregnancy and therapy with ribavirin or hydroxyurea, a diminished creatinine clearance and a low CD4+ T-cell nadir (Bonnet 2003, Butt 2003, Carr 2003 Wohl 2006). In case treatment with ribavirin is necessary, didanosine has to be replaced.

The clinical symptoms, including fatigue, nausea and vomiting, abdominal pain, weight loss and dyspnea, are non-specific and may develop acutely or more gradually. Blood results show elevated lactate levels with or without metabolic acidosis (blood should be taken without using a tourniquet in a cooled fluoride oxalate tube, with transport on ice and the lactate measured within 4 hours). CPK, LDH, lipase, amylase,  $\gamma$ GT and the anion gap may be increased; serum bicarbonate may be decreased. Hepatic steatosis can be seen on ultrasound or CT.

One study showed that serum lactate levels rise significantly after initiation of NRTI therapy, and then remain stable between 1.5 and 3 mmol/l (John 2001). 8 to 21 % of the patients with at least one NRTI have elevated serum lactate levels (< 4 mmol/l), with no or only mild symptoms. Cases of severe lactic acidosis can occur without prior symptomatic hyperlactacidemia. Lactate levels should therefore not be monitored routinely, as increases are not predictive and may lead to unnecessary changes in treatment (Brinkman 2000, Tan 2006, Vroenenraets 2002). In contrast, lactate levels should be tested immediately in symptomatic patients complaining of fatigue, sudden weight loss, abdominal disturbances, nausea, vomiting or sudden dyspnea, in pregnant women on NRTI treatment and in patients, who receive NRTIs again after having suffered a lactic acidosis (Carr 2003).

For lactate levels between 2 and 5 mmol/l, "watchful waiting" with regular monitoring is recommended (see Brinkman 2001). If the resistance profile allows, NRTI treatment may be modified, e.g. switch from stavudine/didanosine to abacavir, zidovudine or tenofovir. At levels above 5 mmol/l, NRTI treatment should be stopped immediately and supportive treatment initiated; for example, correction of the acidosis. The mortality of patients with lactate levels above 10 mmol/l is approximately 80 % (Falco 2002).

Different drugs have been used to treat lactic acidosis with limited success, including vitamin B complex, coenzyme Q10, vitamin C and L-carnitine. These treatment approaches are based on case reports, not studies. In one small study, 6 patients were successfully treated with intravenous vitamin B-complex (100 mg thiamine, 20 mg riboflavin, 200 mg nicotinamide, 20 mg pyridoxine, 20 mg dexpanthenol) plus L-carnitine (1000 mg) twice daily (Brinkman 2000). The AIDS Clinical Trials Group recommends a higher riboflavin dose (50 – 200 mg per day), the dosage of coenzyme Q 10 should be more than 50 mg per day (AIDS Clinical Trials Group 2002). This treatment is given intravenously until lactate levels fall below 3 mmol/l, and is then continued orally. Normalization of lactate takes an average of 8 weeks following the discontinuation of therapy. The supplementation of uridine is a new, but promising treatment approach (Walker 2003, Walker 2004) (see chapter on Mitochondrial Toxicity).

## Avascular necrosis

The incidence of asymptomatic avascular necrosis is approximately 0.4 % of HIV patients, significantly more frequent than in the general population (Cheonis 2002, Lawson-Ayayin 2005). The postulated association with PIs could not be confirmed (Miller 2002, Loiseau-Peres 2002). Risk factors for avascular necrosis are alcohol abuse, hyperlipidemia, steroid treatment, hypercoagulability, hemoglobinopathy, trauma, nicotine abuse and chronic pancreatitis. Virological (viral load) or immunological parameters are not associated with a risk of developing avascular necrosis (Miller 2002, Mondy 2003, Lawson-Ayayin 2005).

The most common site of the necrosis is the femoral head and, less frequently, the head of the humerus. Initially, patients complain of pain when bearing weight on the affected joint, with symptoms worsening over days and weeks. The initial stages may be asymptomatic, but are followed by severe bone pain and reduced mobility. Necrosis of the femoral head produces pain in the hip or groin, which may radiate to the knee.

All patients on HAART, especially those with additional risk factors (steroids!) should be monitored closely if hip pain occurs for the first time. Even in subjects with moderate bone or joint pain, an MRI should be performed early on, as this is more sensitive than conventional radiography. Early diagnosis and treatment can spare patients pain, loss of mobility and surgical intervention.

If the diagnosis is confirmed, patients should be referred to an orthopedic surgeon as soon as possible. Different treatment strategies are available for reducing bone and joint damage as well as pain, depending on the stage of disease, localization and grade of severity. In the early stages, reduced weight bearing with crutches is often sufficient. Surgical core decompression is an option: several holes are drilled in the femoral neck or head, causing new blood vessels to develop and thereby reducing the pressure within the bone. In the more advanced stages, the chances of success decrease with the size of the necrosis. The alternative – osteotomy – has the disadvantage of reducing the mobility of patients over long periods of time. In severe cases, a total endoprosthesis (TEP) is usually necessary.

Further risk factors need to be identified and eliminated. If possible, steroids should be discontinued. Sufficient data are missing as to whether treatment modification on non-PI therapy is successful (Mondy 2003). Physiotherapy is recommended. Non-steroidal anti-inflammatory drugs (e.g. ibuprofen) are the treatment of choice for analgesia (Cheonis 2002).

## Osteopenia/osteoporosis

HIV-infected individuals have a lower bone density than uninfected individuals (Loiseau-Peres 2002). Bone density is determined by the measurement of X-ray absorption (e.g. DEXA scan). Results are given as the number of standard deviations (the T-score) from the mean value in young, healthy individuals. Values between -1 and -2.5 standard deviations (SD) are referred to as osteopenia, values above -2.5 SD as osteoporosis.

In addition to HIV infection, other factors such as malnutrition, diminished fat tissues, steroid treatment, hypogonadism, immobilization and treatment with PIs and

NRTIs, seem to play a role in the pathogenesis of this disorder. Osteopenia and osteoporosis are often asymptomatic. Osteoporosis occurs mainly in the vertebrae, lower arms and hips.

The following tests should be performed on all patients with AIDS: a lumbar spine X-ray in the standard anteroposterior and lateral views, bone density measurement (DEXA scan) of the lumbar spine and hip; and laboratory blood tests, including calcium, phosphate and alkaline phosphatase. Osteopenia should be treated with 1000 I.E. vitamin D daily and a calcium-rich diet or calcium tablets with a dose of 1200 mg/day. Patients should be advised to exercise and give up alcohol and nicotine. In cases with osteoporosis, bisphosphonates (e.g. alendronat 70 mg once a week) should be added. The tablets should be taken on an empty stomach 30 min before breakfast, and an upright position should be maintained for at least 30 min. No calcium should be taken on this day. Antiretroviral therapy should not be taken together with calcium. Because testosterone suppresses osteoclasts, hypogonadism should be treated. Alcohol and smoking should be avoided; regular exercise is an essential part of the therapy (Cheonis 2002, Cheonis 2000, Mondy 2003, Tebas 2000).

## Increased bleeding episodes in hemophiliacs

HIV patients with hemophilia A or B, after some weeks of treatment with protease inhibitors, may have increased episodes of spontaneous bleeding into joints and soft tissues. Rarely, intracranial and gastrointestinal bleeding has occurred. The etiology is unclear (Review: Wilde 2000).

## Specific side effects

### Enfuvirtide (T-20)

The typical side effect of enfuvirtide is an injection site reaction (ISR) with erythema, induration, nodules, pruritus, ecchymosis, pain and discomfort. Almost every patient is affected, most of them, however, only mildly. ISR, therefore, rarely limits treatment, and only 3 to 7 % of patients discontinue therapy (Arasteh 2004, Lazzarin 2003). The practitioner and the patient have to get used to the injection technique and the management of ISR. Good injection technique (including aseptic conditions) in conjunction with rotating injection sites (see Table 1), may be most effective in minimizing the incidence and severity, as well as the incidence of associated events, including infections. The appropriate management of ISR can lessen the reaction (see Table 1, Clotet 2004, Buhk 2004).

Desensitization therapy is available for the skin rash that occurs rarely with enfuvirtide (Shahar 2005). Another side effect, observed after 48 weeks in the TORO study, was a higher rate of bacterial pneumonia (gram+/ gram-) in patients taking enfuvirtide. The cause is unclear. Thus, patients undergoing enfuvirtide therapy should be monitored for pneumonia (Clotet 2004, Tashima 2003).

Patients taking enfuvirtide and traveling to foreign countries should be prepared for questions about the injection material. Taking along a medical certificate stating

that the patient is on subcutaneous injection therapy can help to avoid unpleasant situations.

Table 1: Suggestions for prevention and management of injection site reactions (ISR) and other injection-related adverse events (Clotet 2004)

#### Good injection technique

- Ensure solution is at room temperature
- Avoid muscle by beveling needle at 45–90 degrees, depending on body habitus
- Inject slowly
- Maintain sterile technique (wash hands, use gloves, clean injection area and vial caps with alcohol swabs, never touch needle)
- Feel for hard, subcutaneous bumps, avoid injecting into sites of previous ISR
- Avoid indurated or erythematous areas
- Avoid injections on the belt line
- Rotate sites (abdomen, thighs, arms) and never inject two consecutive doses into the same place
- Gentle manual massage after every injection

#### Interventions for ISR

##### 1. Injection pain

- Topical anesthetic (e.g. lidocaine gel)
- Oral analgesics pre-injection (e.g. ibuprofen or metamizole)
- Numb area with ice or a cool pack before injecting

##### 2. Management of pruritus

- Oral antihistamines
- Emollient creams or lotions (non-alcohol based and fragrance-free)

## Indinavir

Paronychia of the toes or fingers and ingrown toenails are typical side effects of indinavir, occurring in 4 to 9 % of patients. Furthermore, approximately 30 % of patients receiving indinavir show two or more mucocutaneous changes, such as cutaneous xerosis, cheilitis, hair loss or alopecia, resembling retinoid-like side effects. Indinavir is the only antiretroviral drug that induces retinoid-like effects, as it probably interferes with the retinoid metabolism. There is no relation to sex, age or immune status, but to indinavir plasma levels. In these patients, measurement of the plasma level makes sense, adjusting the dose if necessary.

These adverse effects are usually mild, so that there is often no need to discontinue therapy. Paronychia, however, can cause massive pain; in which case, stopping indinavir can save the patient from surgical intervention, because it then resolves without recurrence (Garcia-Silva 2002).

## References

1. Aarnoutse RE, Wasmuth JC, Faetkenheuer G, et al. Administration of indinavir and low-dose ritonavir (800/100 mg twice daily) with food reduces nephrotoxic peak plasma levels of indinavir. *Antivir Ther.* 2003; 8:309-14. <http://amedeo.com/lit.php?id=14518700>

2. AIDS Clinical Trials Group (ACTG) metabolic complication guides. <http://aactg.s-3.com/metabolic/default.htm>
3. Ammassari A, Murri R, Pezzotti P, et al. Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection. *J Acquir Immune Defic Syndr* 2001; 28:445-9. <http://amedeo.com/lit.php?id=11744832>
4. Arasteh K, Lazzarin A, Clotet B, et al. TORO: 96 week virological and immunological response and safety evaluation of enfuvirtide with an optimized background regimen. The 15th Int. AIDS Conf., Bangkok 2004, abstract no. MoOrB1058.
5. Barrios A, Garcia-Benayas T, Gonzalez-Lahoz J, et al. Tenofovir-related nephrotoxicity in HIV-infected patients. *AIDS* 2004; 18:960-3. <http://amedeo.com/lit.php?id=15060449>
6. Barrios A, Rendon AL, Gallego O, et al. Predictors of virological response to atazanavir in protease inhibitor-experienced patients. *HIV Clin Trials* 2004; 5:201-5. <http://amedeo.com/lit.php?id=15472794>
7. Becker S. Liver toxicity in epidemiological cohorts. *Clin Infect Dis* 2004; 38:S49-55. <http://amedeo.com/lit.php?id=14986275>
8. Bersoff-Matcha SJ, Miller WC, Aberg JA, et al. Sex differences in nevirapine rash. *Clin Infect Dis* 2001; 32:124-9. <http://amedeo.com/lit.php?id=11118391>
9. Bjornsson E, Olsson R. Suspected drug-induced liver fatalities reported to the WHO database. *Dig Liver Dis* 2006; 38:33-8. <http://amedeo.com/lit.php?id=16054882>
10. Blanchard JN, Wohlfeiler M, Canas A, et al. Pancreatitis with didanosine and tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; 37:e57-62. <http://amedeo.com/lit.php?id=12942419>
11. Bonnet F, Bonarek M, Morlat P, et al. Risk factors for lactic acidosis in HIV-infected patients treated with nucleoside reverse-transcriptase inhibitors: a case-control study. *Clin Infect Dis* 2003; 36:1324-8. <http://amedeo.com/lit.php?id=12746780>
12. Bossi P, Roujeau JC, Bricaire F, et al. Stevens-Johnson syndrome associated with abacavir therapy. *Clin Infect Dis* 2002; 35:902. <http://amedeo.com/lit.php?id=12228837>
13. Boubaker K, Sudre P, Bally F, et al. Changes in renal function associated with indinavir. *AIDS* 1998; 12:F249-54. <http://amedeo.com/lit.php?id=9875572>
14. Brinkman K, Vrouenraets S, Kauffmann R, et al. Treatment of nucleoside reverse transcriptase inhibitor-induced lactic acidosis. *AIDS* 2000; 14:2801-2. <http://amedeo.com/lit.php?id=11125906>
15. Brinkman K. Management of hyperlactatemia: no need for routine lactate measurements. *AIDS* 2001; 15:795-7. <http://amedeo.com/lit.php?id=11371695>
16. Buhk T. Einsatz von Fusionsinhibitoren. In: Hoffmann C, Jäger H (Hrsg.): *AIDS Kongressband der Münchner AIDS-Tage 2004*. Landsberg/ Lech: Verlag Moderne Industrie, 2004.
17. Bushen OY, Davenport JA, Lima AB, et al. Diarrhea and reduced levels of antiretroviral drugs: improvement with glutamine or alanyl-glutamine in a randomized controlled trial in northeast Brazil. *Clin Infect Dis* 2004; 38:1764-70. <http://amedeo.com/lit.php?id=15227625>
18. Busti AJ, Hall RG, Margolis DM. Atazanavir for the treatment of human immunodeficiency virus infection. *Pharmacotherapy*. 2004; 24:1732-47. <http://amedeo.com/lit.php?id=15585441>
19. Butt AA. Fatal lactic acidosis and pancreatitis associated with ribavirin and didanosine therapy. *AIDS Read* 2003; 13:344-8. <http://amedeo.com/lit.php?id=12889452>
20. Callens S, De Roo A, Colebunders R. Fanconi-like syndrome and rhabdomyolysis in a person with HIV infection on highly active antiretroviral treatment including tenofovir. *J Infect* 2003; 47:262-3. <http://amedeo.com/lit.php?id=12963392>
21. Carr A, Cooper DA. Adverse effects of antiretroviral therapy. *Lancet* 2001; 356:1423-30. <http://amedeo.com/lit.php?id=11052597>
22. Carr A, Morey A, Mallon P, et al. Fatal portal hypertension, liver failure, and mitochondrial dysfunction after HIV-1 nucleoside analogue-induced hepatitis and lactic acidemia. *Lancet* 2001; 357:1412-4. <http://amedeo.com/lit.php?id=11356442>
23. Carr A. Lactic acidemia in infection with human immunodeficiency virus. *Clin Infect Dis* 2003; 36:S96-S100. <http://amedeo.com/lit.php?id=12652378>
24. Carr A. Toxicity of antiretroviral therapy and implications for drug development. *Nat Rev Drug Discov* 2003; 2:624-34. <http://amedeo.com/lit.php?id=12904812>
25. Chesney MA, Ickovics JR, Chambers DB, et al. Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments. Patient Care Committee & Adherence Working Group of the Outcomes Committee of the Adult AIDS Clinical Trials Group (AACTG). *AIDS Care* 2000; 12:255-66. <http://amedeo.com/lit.php?id=10928201>
26. Cheonis N. Osteonecrosis and HIV Disease. *BETA* 2002; 15:22-9. <http://www.sfaf.org/treatment/beta/b49/b49osteonecrosis.html>
27. Cheonis N. Osteoporosis and HIV Disease. *BETA* 2001; 14:26-34. <http://hiv.net/link.php?id=17 + http://amedeo.com/lit.php?id=11785482>

## 296 Management of Side Effects

28. Chirouze C, Hustache-Mathieu L, Rougeot C, et al. Risk factors for Abacavir-induced hypersensitivity syndrome in the "real world". *Pathol Biol (Paris)*. 2004;52:529-33. <http://amedeo.com/lit.php?id=15531117>
29. Clark SJ, Creighton S, Portmann B, et al. Acute liver failure associated with antiretroviral treatment for HIV: a report of six cases. *J Hepatol* 2002; 36:295-301. <http://amedeo.com/lit.php?id=11830344>
30. Clay PG. The abacavir hypersensitivity reaction: a review. *Clin Ther* 2002; 24:1502-14. <http://amedeo.com/lit.php?id=12462283>
31. Clotet B, Raffi F, Cooper D, et al. Clinical management of treatment-experienced, HIV infected patients with the fusion inhibitor enfuvirtide: consensus recommendations. *AIDS* 2004; 18:1137-1146. <http://amedeo.com/lit.php?id=15166529>
32. Creput C, Gonzalez-Canali G, Hill G, et al. Renal lesions in HIV-1-positive patient treated with tenofovir. *AIDS* 2003;17:935-7. <http://amedeo.com/lit.php?id=12660548>
33. Dailly E, Billaud E, Reliquet V, et al. No relationship between high nevirapine plasma concentration and hepatotoxicity in HIV-1-infected patients naive of antiretroviral treatment or switched from protease inhibitors. *Eur J Clin Pharmacol* 2004 ; 60:343-8. <http://amedeo.com/lit.php?id=15156302>
34. d'Arminio Monforte A, Lepri AC, Rezza G, et al. Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naïve patients. I.CO.N.A. Study Group. Italian Cohort of Antiretroviral-Naïve Patients. *AIDS* 2000; 14:499-507. <http://amedeo.com/lit.php?id=10780712>
35. De Jesus E, Herrera G, Teofilo E et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naïve HIV-infected adults. *Clin Infect Dis* 2004, 39:1038-46. <http://amedeo.com/lit.php?id=15472858>
36. De Maat MM, ter Heine R, van Gorp EC et al. Case series of acute hepatitis in a non-selected group of HIV-infected patients on nevirapine-containing antiretroviral treatment. *AIDS* 2003; 17:2209-14. <http://amedeo.com/lit.php?id=14523278>
37. Dieleman JP, van Rossum AM, Stricker BC, et al. Persistent leukocyturia and loss of renal function in a prospectively monitored cohort of HIV-infected patients treated with indinavir. *J Acquir Immune Defic Syndr* 2003; 32:135-142. <http://amedeo.com/lit.php?id=12571522>
38. Earle KE, Seneviratne T, Shaker J, et al. Fanconi's syndrome in HIV+ adults: report of three cases and literature review. *J Bone Miner Res* 2004; 19:714-21. <http://amedeo.com/lit.php?id=15068493>
39. Enache-Angoulvant A, Hennequin C. Invasive *Saccharomyces* infection: a comprehensive review. *Clin Infect Dis* 2005, 41:1559-68. <http://amedeo.com/lit.php?id=16267727>
40. Eron JJ, Yetzer ES, Ruane PJ, et al. Efficacy, safety, and adherence with a twice-daily combination lamivudine/zidovudine tablet formulation, plus a protease inhibitor, in HIV infection. *AIDS* 2000;14:671-81. <http://amedeo.com/lit.php?id=10807190>
41. Falco V, Rodriguez D, Ribera E, et al. Severe nucleoside-associated lactic acidosis in human immunodeficiency virus-infected patients: report of 12 cases and review of the literature. *Clin Infect Dis* 2002; 34:838-46. <http://amedeo.com/lit.php?id=11850865>
42. <http://www.fda.gov/cder/drug/advisory/nevirapine.htm>
43. Foster R, Taylor C, Everall IP. More on abacavir-induced neuropsychiatric reactions. *AIDS*. 2004;18:2449. <http://amedeo.com/lit.php?id=15622330>
44. Gallant JE, Staszewski S, Pozniak R, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004; 292:191-201. <http://amedeo.com/lit.php?id=15249568>
45. Gallant J, Parish M, Keruly J, et al. Decline in Renal Function Associated with Tenofovir DF Compared with Nucleoside Reverse Transcriptase Inhibitor Treatment. Abstract 820. 12th CROI. February 22-25, 2005. Boston, MA. [http://www.retroconference.org/Search\\_Abstract\\_2005/AbstractSearch.aspX](http://www.retroconference.org/Search_Abstract_2005/AbstractSearch.aspX)
46. Garcia-Silva J, Almagro M, Pena-Penabad C, et al. Indinavir-induced retinoid-like effects: incidence, clinical features and management. *Drug Saf* 2002; 25:993-1003. <http://amedeo.com/lit.php?id=12408731>
47. Haas DW, Heather JR, Richard BK, et al. Pharmacogenetics of efavirenz and central nervous system side effects: an Adult AIDS Clinical Trials Group study. *AIDS* 2004, 18:2391-2400. <http://amedeo.com/lit.php?id=15622315>
48. Haas S, Rockstroh JK, Spengler U, et al. Nucleoside induced hepatopathy in HIV patients Diagnostic value of liver biopsy Assessment. *Pathologe* 2004; 25:406-11. <http://amedeo.com/lit.php?id=15179522>
49. Hansen AB, Mathiesen S, Gerstoft J. Severe metabolic acidosis and renal failure in an HIV-1 patient receiving tenofovir. *Scand J Infect Dis* 2004; 36:389-92. <http://amedeo.com/lit.php?id=15287389>



50. Heiser CR, French N, Slotten R, et al. Dietary supplementation and exercise reduces diarrhoea, increases muscular strength, and improves quality of life in HIV-positive men receiving nelfinavir. *Antiviral Therapy* 2002; 7:L40. <http://www.aegis.com/conferences/4thLipo/59.html>
51. Heiser CR, Ernst JA, Barrett JT, et al. Probiotics, soluble fiber, and L-Glutamine (GLN) reduce nelfinavir (NFV)- or lopinavir/ritonavir (LPV/r)-related diarrhea. *J Int Assoc Physicians AIDS Care (Chic Ill)* 2004, 3:121-9. <http://amedeo.com/lit.php?id=15768732>
52. Henry DH, Volberding PA, Leitz G. Epoetin Alfa for Treatment of Anemia in HIV-Infected Patients Past, Present, and Future. *JAIDS* 2004; 37:1221-7. <http://amedeo.com/lit.php?id=15385728>
53. Hetherington S, Hughes AR, Mosteller M, et al. Genetic variations in HLA-B region and hypersensitivity reactions to abacavir. *Lancet* 2002; 359:1121-2. <http://amedeo.com/lit.php?id=11943262>
54. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002; 34:1137-42. <http://amedeo.com/lit.php?id=11915004>  
Hicks CB, Cahn P, Cooper DA, et al. Durable efficacy of tipranavir-ritonavir in combination with an optimised background regimen of antiretroviral drugs for treatment-experienced HIV-1-infected patients at 48 weeks in the Randomized Evaluation of Strategic Intervention in multi-drug reSistant patients with Tipranavir (RESIST) studies: an analysis of combined data from two randomised open-label trials. *Lancet* 2006, 368:466-75. <http://amedeo.com/lit.php?id=16890833>
55. Highleyman L. Managing nausea, vomiting, and diarrhea. *BETA* 2002;15:29-39. <http://hiv.net/link.php?id=15>
56. Hocqueloux L, Alberti C, Feugeas JP, et al. Prevalence, risk factors and outcome of hyperlactataemia in HIV-infected patients. *HIV Med.* 2003; 4:18-23. <http://amedeo.com/lit.php?id=12534955>
57. Izzedine H, Isnard-Bagnis C, Hulot JS, et al. Renal safety of tenofovir in HIV treatment-experienced patients. *AIDS* 2004; 18:1074-6. <http://amedeo.com/lit.php?id=15096814>
58. Jackson JB, Musoke P, Fleming T, et al. Intrapartum and neonatal single-dose nevirapine compared with zidovudine for prevention of mother-to-child transmission of HIV-1 in Kampala, Uganda: 18-month follow-up of the HIVNET 012 randomised trial. *Lancet* 2003, 362:859-68. <http://amedeo.com/lit.php?id=13678973>
59. John M, Moore CB, James IR, et al. Chronic hyperlactatemia in HIV-infected patients taking antiretroviral therapy. *AIDS* 2001; 15:795-7. <http://amedeo.com/lit.php?id=11371686>
60. Johnson MO, Stallworth T, Neilands TB. The Drugs or the Disease? Causal Attributions of Symptoms Held by HIV-Positive Adults on HAART. *AIDS and Behavior* 2003; 7:1. <http://amedeo.com/lit.php?id=14586196>
61. Kohli-Pamnani A, Huynh P, Lobo F. Amprenavir-induced maculopapular exanthem followed by desensitization in a patient with late-stage human immunodeficiency virus. *Ann Allergy Asthma Immunol* 2006, 96:620-3. <http://amedeo.com/lit.php?id=16680935>
62. Knobel H, Miro JM, Domingo P, et al. Failure of a Short-Term Prednisone Regimen to Prevent Nevirapine-Associated Rash: A Double-Blind Placebo-Controlled Trial: The GESIDA 09/99 Study. *J Acquir Immune Defic Syndr* 2001; 28:14-18. <http://amedeo.com/lit.php?id=11579272>
63. Kopp JB. Renal Dysfunction in HIV-1-infected Patients. *Curr Infect Dis Rep* 2002; 4:449-460. <http://amedeo.com/lit.php?id=12228033>
64. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide an HIV-1 Fusion Inhibitor, for Drug-Resistant HIV Infection in North and South America. *N Engl J Med* 2003; 348:2175-85. <http://amedeo.com/lit.php?id=12637625>
65. Lawson-Ayayin S, Bonnet F, Bernardin E, et al. Avascular Necrosis in HIV-Infected Patients: A Case-Control Study from the Aquitaine Cohort, 1997-2002, France. *Clin Infect Dis* 2005, 40:1188-93. <http://amedeo.com/lit.php?id=15791521>
66. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of Enfuvirtide in Patients Infected with Drug-Resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; 348:2186-95. <http://amedeo.com/lit.php?id=12773645>
67. Lichtenfeld M, Spengler U, Rockstroh J. Hepatotoxizität der antiretroviralen Therapie. *Arzneimitteltherapie* 2001; 19:250-8.
68. Lochet P, Peyriere H, Lotthe A, et al. Long-term assessment of neuropsychiatric adverse reactions associated with efavirenz. *HIV Med* 2003; 4:62-66. <http://amedeo.com/lit.php?id=12534961>
69. Loiseau-Peres S, Delaunay C, Poupon S, et al. Osteopenia in patients infected by the HIV. A case control study. *Joint Bone Spine* 2002; 69:482-5. <http://amedeo.com/lit.php?id=12477232>
70. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B\*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002; 359:727-32. <http://amedeo.com/lit.php?id=11888582>
71. Martin AM, Nolan D, Gaudieri S, et al. Predisposition to abacavir hypersensitivity conferred by HLA-B\*5701 and a haplotypic Hsp70-Hom variant. *Proc Natl Acad Sci U S A* 2004; 101:4180-5. <http://amedeo.com/lit.php?id=15024131>

## 298 Management of Side Effects

72. Martin AM, Krueger R, Almeida CA, et al. A sensitive and rapid alternative to HLA typing as a genetic screening test for abacavir hypersensitivity syndrome. *Pharmacogenet Genomics* 2006; 16:353-7. <http://amedeo.com/lit.php?id=16609367>
73. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet* 2004; 364:65-7. <http://amedeo.com/lit.php?id=15234858>
74. Marzolini C, Telenti A, Decosterd LA, et al. Efavirenz plasma levels can predict treatment failure and central nervous system side effects in HIV-1-infected patients. *AIDS* 2001; 15:71-75. <http://amedeo.com/lit.php?id=11192870>
75. Mauss S, Berger F, Schmutz G. Antiretroviral therapy with tenofovir is associated with mild renal dysfunction. *AIDS* 2005; 19:93-5. <http://amedeo.com/lit.php?id=15627039>
76. Meraviglia P, Angeli E, Del Sorbo F, et al. Risk factors for indinavir-related renal colic in HIV patients: predictive value of indinavir dose/body mass index. *AIDS* 2002; 16:2089-93. <http://amedeo.com/lit.php?id=12370513>
77. Miller KD, Masur H, Jones ED, et al. High prevalence of osteonecrosis of the femoral head in HIV-infected adults. *Ann Intern Med* 2002; 137:17-25. <http://amedeo.com/lit.php?id=12093241>
78. Mondy K, Tebas P. Emerging bone problems in patients infected with HIV. *Clin Infect Dis* 2003; 36:S101-5. <http://amedeo.com/lit.php?id=12652379>
79. Montaner JS, Cahn P, Zala C, et al. Randomized, controlled study of the effects of a short course of prednisone on the incidence of rash associated with nevirapine in patients infected with HIV-1. *J AIDS* 2003; 33:41-6. <http://amedeo.com/lit.php?id=12792354>
80. Montessori V, Harris M, Montaner JS. Hepatotoxicity of nucleoside reverse transcriptase inhibitors. *Semin Liver Dis*. 2003; 23:167-72. <http://amedeo.com/lit.php?id=12800069>
81. Moyle G, Boffito M. Unexpected drug interactions and adverse events with antiretroviral drugs. *Lancet* 2004, 364:8-10. <http://amedeo.com/lit.php?id=15234836>
82. Negro E, Puig J, Masmija J et al. CD4 cell count changes after reduction of ddl dosage in patients receiving standard doses of ddl and TDF based regimens. *ICAAC* 2004 (Washington) H-561.
83. Negro E, Molto J, Munoz-Moreno JA, et al. Safety and efficacy of once-daily didanosine, tenofovir and nevirapine as a simplification antiretroviral approach. *Antivir Ther* 2004, 9:335-42.
84. Ouagari Z, Tubiana R, Mohand HA, et al. Skin rash associated with atazanavir: report of three cases. *AIDS*. 2006, 20:1207-8. <http://amedeo.com/lit.php?id=16691076>
85. Parsonage MJ, Wilkins EG, Snowden N, et al. The development of hypophosphataemic osteomalacia with myopathy in two patients with HIV infection receiving tenofovir therapy. *HIV Med* 2005, 6:341-6. <http://amedeo.com/lit.php?id=16156882>
86. Pirmohamed M, Park BK. HIV and drug allergy. *Curr Opin Allergy Clin Immunol* 2001; 1:311-6. <http://amedeo.com/lit.php?id=11964706>
87. Rauch A, Nolan D, Martin A, et al. Prospective genetic screening decreases the incidence of abacavir hypersensitivity reactions in the Western Australian HIV cohort study. *Clin Infect Dis* 2006, 43:99-102. <http://amedeo.com/lit.php?id=16758424>
88. Rotger M, Taffe P, Bleiber G, et al. Gilbert syndrome and the development of antiretroviral therapy-associated hyperbilirubinemia. *J Infect Dis* 2005; 192:1381-6. <http://amedeo.com/lit.php?id=16170755>
89. Rifkin BS, Perazella MA. Tenofovir-associated nephrotoxicity: Fanconi syndrome and renal failure. *Am J Med* 2004; 117:282-4. <http://amedeo.com/lit.php?id=15308442>
90. Roling J, Schmid H, Fischereider M, et al. HIV-associated renal diseases and highly active antiretroviral therapy-induced nephropathy. *Clin Infect Dis* 2006; 42:1488-95. <http://amedeo.com/lit.php?id=16619164>
91. Rollot F, Nazal EM, Chauvelot-Moachon L, et al. Tenofovir-related Fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome: the role of lopinavir-ritonavir-didanosine. *Clin Infect Dis* 2003; 37:e174-6. <http://amedeo.com/lit.php?id=14689363>
92. Rotunda A, Hirsch RJ, Scheinfeld N, et al. Severe cutaneous reactions associated with the use of HIV medications. *Acta Derm Venereol* 2003; 83:1-9. <http://amedeo.com/lit.php?id=12636014>
93. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe Hepatotoxicity Associated with Nevirapine Use in HIV-Infected Subjects. *J Infect Dis* 2005, 191:825-829. <http://amedeo.com/lit.php?id=15717255>
94. Saumoy M, Vidal F, Peraire J, et al. Proximal tubular kidney damage and tenofovir: a role for mitochondrial toxicity? *AIDS* 2004; 18:1741-2. <http://amedeo.com/lit.php?id=15280790>
95. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS* 2002; 16:1257-63. <http://amedeo.com/lit.php?id=12045491>
96. Schmid H, Mühlbayer D, Bogner J, et al. Macroenzyme Creatine Kinase Type 2 Accumulation in Sera from HIV- infected Patients: Significant Association with Tenofovir Disoproxil Fumarate-containing

- Treatment. 12th Conference on Retroviruses and Opportunistic Infections, Boston 2005. Poster No. 827. <http://www.retroconference.org/2005/CD/Abstracts/24226.htm>
97. Schwarze S. Die "dunkle Seite der HAART" - Nebenwirkungen und wie man sie in den Griff bekommt. In: Hoffman C, Jäger H (Hrsg.): AIDS. Die Auseinandersetzung geht weiter. Landsberg/ Lech: Verlag Moderne Industrie, 2002. S. 214-5.
  98. Scott JD, Wolfe PR, Bolan RK, et al. Serious renal impairment occurs rarely with use of tenofovir DF. *HIV Clin Trials* 2006, 7:55-8. <http://amedeo.com/lit.php?id=16798620>
  99. Shahar E, Moar C, Pollack S. Successful desensitization of enfuvirtide-induced skin hypersensitivity reaction. *AIDS* 2005, 19:451-2. <http://amedeo.com/lit.php?id=15750403>
  100. Sherman DS, Fish DN. Management of Protease Inhibitor - Associated Diarrhea. *Clin Infect Dis* 2000; 30:908-14. <http://amedeo.com/lit.php?id=10854364>
  101. Shere-Wolfe KD, Verley JR. Marked elevation of the creatine phosphokinase level in a patient receiving tenofovir. *Clin Infect Dis* 2002; 35:1137. <http://amedeo.com/lit.php?id=12384851>
  102. Stern JO, Robinson PA, Love J, et al. A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients. *J Acquir Immune Defic Syndr* 2003, 34:S21-33 <http://amedeo.com/lit.php?id=14562855>
  103. Sulkowski MS, Thomas DL, Mehta SH, et al. Hepatotoxicity associated Nevirapine nevirapine or Efavirenz-containing antiretroviral therapy: role of Hepatitis C and B Infection. *Hepatology* 2002; 35:182-9. <http://amedeo.com/lit.php?id=11786975>
  104. Sulkowski MS. Hepatotoxicity associated with antiretroviral therapy containing HIV-1 Protease Inhibitors. *Semin Liver Dis* 2003; 23:183-194. <http://amedeo.com/lit.php?id=12800071>
  105. Sulkowski MS. Drug-induced liver injury associated with antiretroviral therapy that includes HIV-1 protease inhibitors. *Clin Infect Dis* 2004; 38:S90-7. <http://amedeo.com/lit.php?id=14986280>
  106. Tan D, Walmsley S, Shen S, et al. Mild to Moderate Symptoms Do Not Correlate with Lactate Levels in HIV-Positive Patients on Nucleoside Reverse Transcriptase Inhibitors. *HIV Clin Trials* 2006, 7:107-15. <http://amedeo.com/lit.php?id=16880167>
  107. Tashima KT, Carpenter CC. Fusion inhibition-a major but costly step forward in the treatment of HIV-1. *N Engl J Med* 2003; 348:2249-50. <http://amedeo.com/lit.php?id=12773653>
  108. Tebas P, Powderly WG, Claxton S, et al. Accelerated bone mineral loss in HIV-infected patients receiving potent antiretroviral therapy. *AIDS* 2000; 14:F63-7. <http://amedeo.com/lit.php?id=10770534>
  109. The Grupo Estudio Syndrome Immunodeficiencias Adquirida 26/02 Study Group. Failure of Cetirizine to Prevent Nevirapine-Associated Rash: A Double-Blind Placebo-Controlled Trial for the GESIDA 26/01 Study. *J Acquir Immune Defic Syndr* 2004; 37:1276-1281. <http://amedeo.com/lit.php?id=15385735>
  110. Trotta MP, Ammassari A, Melzi S, et al. Treatment-related factors and highly active antiretroviral therapy adherence. *J Acquir Immune Defic Syndr* 2002; 31:S128-31. <http://amedeo.com/lit.php?id=12562035>
  111. Turner MJ, Angel JB, Woodend K. The efficacy of calcium carbonate in the treatment of protease inhibitor-induced persistent diarrhea in HIV-infected patients. *HIV Clin Trials* 2004; 5:19-2 <http://amedeo.com/lit.php?id=15002083>
  112. Vrouenraets SM, Treskes M, Regez RM, et al. Hyperlactataemia in HIV-infected patients: the role of NRTI-treatment. *Antivir Ther* 2002; 7:239-44. <http://amedeo.com/lit.php?id=12553477>
  113. Walker UA. Lactic acidosis in HIV-patients-diagnosis and treatment. *MMW Fortschr Med* 2004; 146 Spec No 1:65-7. <http://amedeo.com/lit.php?id=15373054>
  114. Walker UA, Venhoff N, Koch EC, et al. Uridine abrogates mitochondrial toxicity related to nucleoside analogue reverse transcriptase inhibitors in HepG2 cells. *Antivir Ther* 2003; 8:463-70. <http://amedeo.com/lit.php?id=14640394>
  115. Wilde JT. Protease inhibitor therapy and bleeding. *Haemophilia* 2000; 6:487-90. <http://amedeo.com/lit.php?id=11012690>
  116. Wohl DA, McComsey G, Tebas P, et al. Current concepts in the diagnosis and management of metabolic complications of HIV infection and its therapy. *Clin Infect Dis* 2006, 43:645-53. <http://amedeo.com/lit.php?id=16886161>
  117. Wood R. Nevirapine toxicity-implications for management of South African patients. *S Afr Med J* 2005, 95:253-7. <http://amedeo.com/lit.php?id=15889848>
  118. Zimmermann AE, Pizzoferrato T, Bedford J, et al. Tenofovir-associated acute and chronic kidney disease: a case of multiple drug interactions. *Clin Infect Dis* 2006;42:283-90. <http://amedeo.com/lit.php?id=16355343>



## 7. Lipodystrophy Syndrome

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### Background

The HIV lipodystrophy syndrome, which includes metabolic complications and altered fat distribution, is of major importance in HIV therapy. The metabolic abnormalities may harbor a significant risk of developing cardiovascular disease, with as yet unknown consequences. In addition, several studies report a reduced quality of life in patients with body habitus changes leading to reduced treatment adherence. Despite the impact of lipodystrophy syndrome on HIV management, little is known about the pathogenesis, its prevention, diagnosis and treatment. Current data indicate a rather multifactorial pathogenesis where HIV infection, its therapy, and patient-related factors are major contributors. The lack of a clear and easy definition reflects the clinical heterogeneity, limits a clear diagnosis and impairs the comparison of results among clinical studies. Therapeutic and prevention strategies have so far been of only limited clinical success. Thus, general recommendations include dietary changes and life style modifications, altering antiretroviral drug therapy (replacement of protease inhibitors with NNRTI or replacement of stavudine and zidovudine with e.g. abacavir or tenofovir), and finally, the use of metabolically active drugs. Here we summarize the pathogenesis, diagnosis and treatment options of the HIV lipodystrophy syndrome.

### Clinical manifestation

Lipodystrophy was originally described as a condition characterized by regional or generalized loss of subcutaneous fat. The non-HIV-associated forms, such as congenital or familial partial lipodystrophy, have a very low prevalence. Generally, these forms are associated with complex metabolic abnormalities and are difficult to treat. The term “lipodystrophy syndrome” in association with HIV, was introduced to describe a complex medical condition including the apparent abnormal fat redistribution and metabolic disturbances seen in HIV-patients receiving protease inhibitor therapy (Carr 1998). But, even years after its first description, there is still no consensus on a case definition for lipodystrophy syndrome in HIV patients. Thus, the diagnosis of lipodystrophy in clinical practice often relies on a more individual interpretation than on an evaluated classification. Finally, changes in the fat distribution have to be considered as being rather dynamic processes. In most cases, lipoatrophy is clinically diagnosed when significant fat loss has already occurred.

HIV-associated lipodystrophy includes both clinical and metabolic alterations. The most prominent clinical sign is a loss of subcutaneous fat (lipoatrophy) in the face (periorbital, temporal), limbs, and buttocks. Prospective studies have demonstrated an initial increase in limb fat during the first months of therapy, followed by a progressive decline over the ensuing years (Mallon 2003). Peripheral fat loss can be accompanied by an accumulation of visceral fat, which can cause mild gastrointes-

tinal symptoms. Truncal fat increases initially after therapy and then remains stable (Mallon 2003). Visceral obesity, as a singular feature of abnormal fat redistribution, appears to occur in only a minority of patients. Fat accumulation may also be found as dorsocervical fat pads (“buffalo hump”) within the muscle and the liver. Female HIV patients sometimes complain about painful breast enlargement, which has been attributed to the lipodystrophy syndrome. Whether gynecomastia in male patients is a component of the syndrome remains unclear. There is now accumulating evidence that the major clinical components – lipoatrophy, central adiposity and the combination of both – result from different pathogenetic developmental processes.

The prevalence of lipodystrophy syndrome has been estimated to be between 30 and 50 %, based on cross-sectional studies. A prospective study over an 18-month period after initiation of therapy revealed a prevalence of 17 % (Martinez 2001). Lipodystrophy, and in particular lipoatrophy, has been observed most frequently in patients receiving a combination regimen of nucleoside analogues and protease inhibitors, although almost all antiretroviral drug combinations can be associated with fat redistribution. The risk of the syndrome increases with the duration of treatment, the age of the patient and the level of immunodeficiency. Lipodystrophy has been observed during the therapy of both the acute and chronic states of HIV infection and even following post-exposure prophylaxis. Children can be affected, like adults, with clinical fat redistribution shortly after initiation or change of antiretroviral therapy. The evolution of the individual clinical components of the lipodystrophy syndrome is variable. Subcutaneous fat loss has been observed during exclusive therapy with NRTIs but probably develops faster under a combination of NRTIs and protease inhibitors. The nucleoside analogue linked most strongly to lipoatrophy is stavudine, particularly when used in combination with didanosine. Tenofovir combined with lamivudine and efavirenz is associated with less loss of limb fat than stavudine in a similar combination in therapy-naïve HIV patients (Gallant 2004). Single case reports even describe body habitus changes compatible with the lipodystrophy phenotype in antiretroviral therapy-naïve patients.

Frequently, complex metabolic alterations are associated with the described body shape alterations. These include peripheral and hepatic insulin resistance, impaired glucose tolerance, type 2 diabetes, hypertriglyceridemia, hypercholesterolemia, increased free fatty acids (FFA), and decreased high density lipoprotein (HDL). Often these metabolic abnormalities appear or deteriorate before the manifestation of fat redistribution. The prevalence of insulin resistance and glucose intolerance has been reported in the literature at 20 to 50% depending on the study design and measurement methods. Frank diabetes is less frequent with a prevalence of between 1 and 6 %. Lipodystrophic patients present with the highest rates of metabolic disturbances.

Hyperlipidemias are a frequently observed side effect of antiretroviral therapy, especially in combinations that include protease inhibitors. Given that many HIV patients present with already decreased HDL levels, these are not further reduced by antiretroviral drugs. Hypertriglyceridemias, especially in patients with evidence of body-fat abnormalities, are the leading lipid abnormality either alone or in combination with hypercholesterolemia. Several weeks after initiation or change of HIV therapy, lipid levels usually reach a plateau and remain stable. All protease inhibitors can potentially lead to hyperlipidemia, although to different extents. For exam-

ple, atazanavir (Reyataz™) appears to be less frequently associated with dyslipidemia and insulin resistance. In contrast, ritonavir (Norvir™) often leads to hypertriglyceridemia correlating to the drug levels.

The therapy-induced dyslipidemias are characterized by increased low density lipoproteins (LDL) and triglyceride-rich very low density lipoproteins (VLDL). Detailed characterization revealed an increase of apolipoprotein B, CIII and E. Raised levels of lipoprotein(a) have been described in protease inhibitor recipients. Mild hypercholesterolemia can occur during therapy with efavirenz (Sustiva™) but is not typical under therapy with nevirapine (Viramune™). Stavudine-based, antiretroviral therapy is associated with early and statistically significant increases in total triglycerides and cholesterol or NRTIs. It is important to note that HIV infection itself is associated with disturbed lipid metabolism. During disease progression, the total cholesterol, LDL, and HDL levels decline and the total triglyceride level rises. The latter is presumably caused by increased cytokine concentrations (TNF $\alpha$ , IFN $\gamma$ ) and an enhanced lipogenesis in addition to impaired postprandial triglyceride clearance.

Recently, more signs and symptoms have been described in association with the lipodystrophy syndrome. Their pathogenetic relationship to fat redistribution and metabolic changes has not yet been fully evaluated. Thus, future studies need to assess whether conditions such as dry skin, ingrown toenails, aseptic hip necrosis, osteopenia and osteoporosis are linked to the lipodystrophy syndrome or are caused by independent drug or disease-related effects.

## **HAART, lipodystrophy syndrome and cardiovascular risk**

The fat redistribution and disturbances in glucose and fat metabolism resemble a clinical situation that is known as the “metabolic syndrome” in HIV-negative patients. This condition includes symptoms such as central adipositas, insulin resistance and hyperinsulinemia, hyperlipidemia (high LDL, Lp(a) hypertriglyceridemia and low HDL) and hypercoagulopathy. Given the well-established cardiovascular risk resulting from this metabolic syndrome, there is growing concern about a potential therapy-related increased risk of myocardial infarction in HIV patients. These fears are further sustained by reports of arterial hypertension on HAART (Seaberg 2005), a high rate of smoking among HIV patients and increased levels of tissue plasminogen activator (tPA) and plasminogen activator inhibitor-1 (PAI-1) in patients with lipodystrophy. Although many of the, mainly retrospective, studies dealing with this issue are inconclusive, data from a large international study (D:A:D study) provide evidence for an increased relative risk of myocardial infarction during the first 7 years of HAART (Friis-Møller 2003, El-Sadr 2005). The incidence of myocardial infarction increased from 1.39/1,000 patient years in those not exposed to HAART, to 2.53/1,000 patient years in those exposed for < 1 year, to 6.07/1,000 patient years in those exposed for  $\geq$  6 years (RR compared to no exposure: 4.38 [95 % CI 2.39 to 8.04],  $p = 0.0001$ ). After adjustment for other potential risk factors, there was a 1.17-fold [1.11 to 1.24] increased risk of myocardial infarction per additional year of combined ART exposure (El-Sadr 2005). It is, however, of note that older age, male gender, smoking, diabetes mellitus, and pre-

existing coronary artery disease were still associated with a higher risk of sustaining cardiovascular events than HAART in this study. Although the CHD risk profile in D:A:D patients worsened over time, the risk of myocardial infarction decreased over time after controlling for these changes (Sabin 2005). Several other studies used ultrasonography to measure the thickness of the carotid intima media or endothelial function to predict the cardiovascular risk. Some of these investigations found abnormal test results (e.g. reduced flow-mediated dilation) that correlated either with the use of protease inhibitors or the presence of dyslipidemia (Currier 2003). Long-term follow-up results will be necessary to substantiate these preliminary observations. While there is some indication of an increased rate of coronary artery disease during HAART, the benefit of suppressed viral replication and improved immune function resulting in reduced morbidity and mortality, clearly argues for the use of antiretroviral drugs according to current international guidelines. It seems obvious however, that pre-existing cardiovascular risk factors in individual patients need to be considered more carefully before starting or switching HAART.

Recommendations such as the National Cholesterol Education Program (NECP) have been proposed for non-HIV-infected patients with similar risk constellations. These guidelines are being proposed by some authors for HIV patients as well (Dube 2000, Schambelan 2002, Grinspoon 2005). According to these recommendations, the overall cardiovascular risk in HIV-infected patients can be determined from specific risk factors by using the Framingham equation. Prediction of coronary heart disease using this equation, however, may have some limitations. A 10-year CHD risk estimation at any time point is determined by the individual's past and expected future lipid levels (best assessed as area under the curve). Hyperlipidemia in many treated HIV patients, however, does not follow the 10-year time course seen in the "normal population" due to frequent therapy changes that may lower total cholesterol, increase HDL, and improve atherogenic risk. Thus, the validity of this calculation for the long-term cardiovascular risk assessment in young patients with changing lipid levels and medication regimens requires further studies.

Clearly, more clinical studies are necessary to assess whether these recommendations are also applicable in the presence of HIV and to determine the clinical value of lipid lowering drug therapy in these patients. Most importantly, the information about drug interactions of lipid lowering and antiretroviral drugs is still incomplete. The accumulation of pre-existing and drug-related risk factors will get more clinical attention, because, by improving the HIV-associated morbidity and mortality, HAART consequently increases an additional relevant cardiovascular risk factor: the age of patients who are effectively treated with antiretroviral drugs.

## Pathogenesis

For a better understanding of the pathogenesis of the complex metabolic abnormalities, it is useful to separate individual aspects of the lipodystrophy syndrome: adipocytes/fat redistribution, lipid metabolism, and carbohydrate metabolism. This is because it is very likely that the lipodystrophy syndrome is not a stereotypic syndrome but rather an amalgam of miscellaneous clinical features, with perhaps multifactorial causes. Studies published during recent years provide evidence for two fundamental assumptions: firstly, lipoatrophy and lipoaccumulation result from divergent or only partially overlapping pathogenetic reasons. Secondly, NRTIs,



NNRTIs, PIs, and even drugs within each class contribute to the lipodystrophy syndrome and its individual features by different, probably overlapping and certainly synergistic mechanisms.

## **NRTI and lipodystrophy**

The patterns of fat redistribution in patients who are exclusively receiving NRTIs are unlike those observed in patients during PI therapy. Peripheral fat loss is the major symptom observed in NRTI therapy (particularly using stavudine and didanosine combinations), although a few clinical studies have described a minimal intra-abdominal fat increase in these patients, which is clearly less than under PIs. Given that, commonly, only a mild increase in triglycerides has been observed, exclusive NRTI therapy seems to be of minor impact on lipid metabolism. Postprandially elevated FFA in patients with lipodystrophy, together with *in vitro* experiments, have led to the hypothesis that NRTIs could impair fatty acid binding proteins (FABP) which are responsible for cellular fat uptake and intracellular fat transport. In contrast, addition of stavudine (Zerit™) to a dual PI regimen does not result in a further increase in the total cholesterol or triglyceride levels.

It is well established that long-term NRTI therapy can cause mitochondrial toxicity. The clinical manifestation of this side effect presents in symptoms such as hepatic steatosis, severe hyperlactatemia, and polyneuropathy. As an explanation for these symptoms, the “pol- $\gamma$  hypothesis” has been proposed, which was later extended to reveal the lipoatrophy observed under NRTIs (Brinkmann 1999). To maintain an adequate bioenergetic level for accurate cell function, all metabolically active cells depend on a persistent polymerase  $\gamma$ -mediated mitochondrial (mt) DNA synthesis. Mitochondria require a constant supply of nucleosides for this process. The mitochondrial DNA polymerase  $\gamma$  retains both DNA- as well as RNA-dependent DNA polymerase activity. The latter is perhaps responsible for the HIV reverse transcriptase activity and therefore its susceptibility for interactions with NRTIs. Experimental data revealed that, for NRTI uptake into mitochondria, the subsequent phosphorylation and then incorporation into the DNA, certain pharmacodynamic requirements need to be fulfilled. These requirements, which include thymidine kinase activity and deoxynucleotide transport specificity of the mitochondrial membrane, are apparently different for zidovudine (Retrovir™) and stavudine (Zerit™), which partially explains the prevailing association between lipoatrophy and stavudine therapy. The postulated mechanisms of NRTI-induced mitochondrial dysfunction consist of competitive inhibition, incorporation into the mtDNA resulting in mtDNA depletion, impairment of mitochondrial enzymes, uncoupling of oxidative phosphorylation and induction of apoptosis. Depletion of mtDNA and structural changes in the mitochondria, resulting in increased rates of apoptosis in subcutaneous adipocytes, have been confirmed by some studies. Despite the experimental link between mitochondrial toxicity and fat tissue as one potential target organ, the degree to which mitochondrial damage contributes to fat distribution abnormalities and its specificity remains unknown. In contrast, mitochondrial damage is widely believed to be responsible for other NRTI-related side effects, such as myopathy, hyperlactatemia, microvesicular steatosis, and steatohepatitis with lactic acidosis (Nolan & Mallal 2004).

## Protease inhibitors and lipodystrophy

PIs account for the majority of metabolic abnormalities associated with lipodystrophy syndrome. Numerous studies report increases in the levels of total triglycerides and triglyceride-rich lipoproteins (VLDL) accompanied by raised LDL levels after initiation of PI therapy (Walli 1998). Conversely, these parameters improved substantially in most studies after discontinuation of the PI or on switching to abacavir (Ziagen™) or nevirapine (Viramune™). The hyperlipidemic changes are frequently associated with hyperinsulinemia and/or insulin resistance.

It has been proposed, based on *in vitro* experiments, that PIs such as saquinavir (Invirase™), indinavir (Crixivan™), and ritonavir (Norvir™) are able to inhibit proteasomal degradation of apolipoprotein B leading to intracellular stockpiling of this lipoprotein and excessive release in response to FFA (Liang 2001). Using stable isotopes *in vivo*, other authors demonstrate a dramatic increase in FFA turnover together with increased lipolysis and decreased clearance of triglyceride-rich VLDL and chylomicrons (Shekar 2002). These conditions point towards an impaired post-prandial insulin-mediated lipid metabolism, since insulin, on the one hand, normally inhibits lipolysis and, on the other hand, increases uptake of FFA, triglyceride synthesis, and fat oxidation in favor of glucose oxidation.

So far, it remains unclear whether impaired insulin action eventually leads to dyslipidemia, or whether hyperlipidemia is responsible for reduced insulin function and insulin resistance in the periphery. Presumably, both mechanisms are important given that some PIs (e.g. indinavir) have been shown to induce insulin resistance without changes occurring in lipid metabolism after short-term administration (Noor 2001, Noor 2002), whereas other PIs (e.g. ritonavir) have been demonstrated to cause mainly hypertriglyceridemia due to increased hepatic synthesis without major changes occurring in glucose metabolism (Purnell 2000). However, comparative clinical studies on the association of different PIs with insulin resistance are still lacking.

It is reasonable to speculate that lipid abnormalities and, in particular increased FFA levels, contribute substantially to the peripheral and central insulin resistance of skeletal muscles and the liver, presumably due to the increased storage of lipids in these organs (Gan 2002). Given this hypothesis, the visceral adiposity could reflect the adaptation of the body in response to raised FFA concentrations and an attempt to minimize the lipotoxic damage to other organs.

Several *in vitro* experiments have indicated that almost all PIs can potentially lead to insulin resistance in adipocytes. Short-term administration of indinavir caused an acute and reversible state of peripheral insulin resistance in healthy volunteers, which was determined in an euglycemic-hyperinsulinemic clamp. These effects are most likely caused by the inhibition of glucose transport mediated by GLUT-4, the predominant transporter involved in insulin-stimulated cellular glucose uptake in humans (Murata 2002). A common structural component found in most PIs has been proposed to cause GLUT-4 inhibition (Hertel 2004). In some patients with lipodystrophy, additional impairment of glucose phosphorylation may contribute to insulin resistance (Behrens 2002). This is presumably due to an impaired insulin-mediated suppression of lipolysis and subsequently increased FFA levels (Behrens 2002, van der Valk 2001) and accumulation of intramyocellular lipids. Peripheral

insulin resistance may also account for an increase in the resting energy expenditure in HIV lipodystrophy and a blunted insulin-mediated thermogenesis.

Indinavir may also induce insulin resistance by inhibiting the translocation, processing or phosphorylation of the sterol regulatory element-binding protein 1c (SREBP-1c) (Caron 2001, Bastard 2002). Either directly or via the peroxisome proliferator activated receptor  $\gamma$  (PPAR $\gamma$ ), SREBP-1 regulates FFA uptake and synthesis, adipocyte differentiation and maturation, and glucose uptake by adipocytes. Similarly, the function of these factors has been proposed to be disturbed in inherited forms of lipodystrophy. Finally, hypoadiponectinemia, as found in patients with abnormal fat distribution, may contribute to insulin resistance (Addy 2003).

## Diagnosis

Both the lack of a formal definition and uncertainty about the pathogenesis and possible long-term consequences, leads to a continuing discussion about appropriate guidelines for the assessment and management of HIV lipodystrophy syndrome and its metabolic abnormalities. Outside clinical studies, the diagnosis relies principally on the occurrence of apparent clinical signs and the patient reporting them. A standardized data collection form may assist in diagnosis (Grinspoon 2005). This appears sufficient for the routine clinical assessment, especially when the body habitus changes develop rather rapidly and severely. For clinical investigations however, especially in epidemiological and interventional studies, more reliable measurements are required. But so far, no technique has demonstrated sufficient sensitivity, specificity or predictive value to definitively diagnose the HIV lipodystrophy syndrome by comparison with results obtained from a "normal" population. A recent multicenter study to develop an objective and broadly applicable case definition proposes a model including age, sex, duration of HIV infection, HIV disease stage, waist-to-hip ratio, anion gap, serum HDL cholesterol, trunk to peripheral fat ratio, percentage leg fat, and intra-abdominal to extra-abdominal fat ratio. Using these parameters, the diagnosis of lipodystrophy had a 79 % sensitivity and 80 % specificity.

Although this model is largely for research and contains detailed body composition data, alternative models and scoring systems, incorporating only clinical and metabolic data, also gave reasonable results (for more information, see <http://www.med.unsw.edu.au/nchechr>).

Despite individual limitations, several techniques are suitable for measuring regional fat distribution. These include dual energy x-ray absorptiometry (DEXA), computer tomography (CT), magnetic resonance imaging (MRI) and sonography. Anthropometric measurements are safe, portable, cheap and much easier to perform than imaging techniques. Waist circumference alone, as well as sagittal diameter, are more sensitive and specific measures than waist-to-hip ratio. Repeated measurements of skin fold thickness can be useful for individual long-term monitoring but need to be performed by an experienced person.

The main imaging techniques (MRI, CT, DEXA) differentiate tissues on the basis of density. Single-slice measurements of the abdomen and extremities (subcutaneous adipose tissue = SAT, visceral adipose tissue = VAT) and more complex three-

dimensional reconstructions have been used to calculate regional or total body fat. Limitations of these methods include most notably their expense, availability and radiation exposure (CT). Consequently, CT and MRI should only be considered in routine clinical practice for selected patients (e.g. extended dorso-cervical fat pads, differential diagnosis of non-benign processes and infections).

Table 1. HIV Lipodystrophy: Case definition and scoring system

Parameter		OR	95% CI	p value	Score*
<b>Demographic</b>					
Gender	male	1.0			0
	female	9.33	3.86-22.52	< 0.001	22
Age	≤40 years	1.0			0
	>40 years	2.02	1.20-3.4	0.008	7
Duration of HIV infection	≤ 4 years	1.0			0
	> 4 years	3.11	1.69-5.71	< 0.001	11
CDC Category	A	1.0			0
	B	1.32	0.73-2.39	0.361	3
	C	1.92	1.02-3.61	0.043	7
<b>Clinic</b>					
Waist : hip ratio	0.1	1.34	1.06-1.69	0.014	multiply by 29
<b>Metabolic</b>					
HDL cholesterol	0.1 mM	0.87	0.81-0.94	<0.001	multiply by -14
Anion gap	1 mM	1.10	1.04-1.166	0.001	multiply by 1
<b>Body composition</b>					
VAT:SAT	≤ 0.45	1.0			0
	0.45-0.83	0.82	0.38-1.76	0.613	-2
	0.83-1.59	1.40	0.62-3.18	0.416	3
	> 1.59	3.70	1.44-9.55	0.007	13
Trunk: limb fat ratio	1.0	1.72	1.12-2.66	0.014	multiply by 5
leg fat ratio	> 21.4	1.0			-16
	14.5-21.4	1.27	0.57-2.87	0.559	-14
	8.8-14.5	2.32	1.00-5.40	0.051	-8
	≤ 8.8	5.04	1.90-13.35	0.001	0

According to Carr & Law (2003). This model has a sensitivity of 79% (95% CI, 70-85 %) and a specificity of 80% (95 % CI, 71-87 %).

\* The final lipodystrophy score is obtained by adding individual scores for every variable and subtraction of 43 (constant). A final score of  $\geq 0$  for a patient indicates the diagnosis of lipodystrophy, a score of  $< 0$  means no lipodystrophy. CDC, U.S. Centers for Disease Control and Prevention; HDL, high-density lipoprotein; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.

Table 2. Proposed grading scale for lipodystrophy based on lipodystrophy case definition cores relative to the subjective physician assessment-derived total lipodystrophy severity score (according to Carr & Law 2003).

Grading scale	Lipodystrophy-score
0	< 0
1	0-9.9
2	10-14.9
3	15-22.9
4	≥ 23

DEXA is appropriate for examining appendicular fat, which is comprised almost entirely of SAT, and has been successfully employed in epidemiological studies. However, SAT and VAT cannot be distinguished by DEXA, which therefore limits the evaluation of changes in truncal fat. Application of sonography to measure specific adipose compartments, including those in the face, requires experienced investigators and has been minimally applied in HIV infection so far. Bioelectrical impedance analysis estimates the whole body composition and cannot be recommended for measurement of abnormal fat distribution.

Patients should routinely be questioned and examined for cardiovascular risk factors, such as smoking, hypertension, adiposity, type 2 diabetes, and family history. For an accurate assessment of blood lipid levels, it is recommended to obtain blood after a fasting of at least 8 hours. Total cholesterol and triglycerides together with LDL and HDL cholesterol should be obtained prior to the initiation of, or switch to, a new potent antiretroviral therapy and repeated 3 to 6 months later. Fasting glucose should be assessed with at least a similar frequency. The oral glucose tolerance test (OGTT) is a reliable and accurate instrument for evaluating insulin resistance and glucose intolerance. An OGTT may be indicated in patients with suspected insulin resistance such as those with adipositas (BMI > 27 kg/m<sup>2</sup>), a history of gestational diabetes and a fasting glucose level of 110 to 126 mg/dl (impaired fasting glucose). An intravenous glucose tolerance test or hyperinsulinemic-euglycemic clamp appears only feasible in clinical studies. The diagnosis of diabetes is based on fasting glucose levels > 126 mg/dl, glucose levels of > 200 mg/dl independent of fasting status, or a 2-hour OGTT glucose level above 200 mg/dl. Additional factors that could lead to or assist in the development of hyperlipidemia and/or insulin resistance always need to be considered (e.g. alcohol consumption, thyroid dysfunction, liver and kidney disease, hypogonadism, concurrent medication such as steroids,  $\beta$ -receptor blockers, thiazides, etc.).

## Therapy

So far, most attempts to improve or even reverse the abnormal fat distribution by modification of the antiretroviral treatment have shown only modest clinical success. In particular, peripheral fat loss appears to be resistant to most therapeutic interventions. The metabolic components of the syndrome may be easier to improve (Table 3).

## Lifestyle changes

Dietary interventions are commonly accepted as the first therapeutic option for hyperlipidemia, especially hypertriglyceridemia. Use of NCEP guidelines may reduce total cholesterol and triglycerides by 11 or 21 %, respectively. Whenever possible, dietary restriction of the total fat intake to 25-35 % of the total caloric intake should be a part of the treatment in conjunction with lipid-lowering drugs. Consultation with professional and experienced dieticians should be considered for HIV-infected patients and their partners. Patients with excessive hypertriglyceridemia (>1000 mg/dl) may benefit from a very low fat diet and alcohol abstinence to reduce the risk of pancreatitis, especially if there is a positive family history or concurrent medications that may harbor a risk of developing pancreatitis. Regular exercise may have beneficial effects, not only on triglycerides and insulin resistance, but probably also on fat redistribution (reduction in truncal fat and intramyocellular fat) and should be considered in all HIV-infected patients (Driscoll 2004a). All patients should be advised and supported to cease smoking in order to reduce the cardiovascular risk. Cessation of smoking is more likely to reduce cardiovascular risk than any choice or change of antiretroviral therapy or use of any lipid-lowering drug.

Table 3. Therapeutic options for HIV-associated lipodystrophy and related metabolic complications

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Lifestyle changes (reduce saturated fat and cholesterol intake, increase physical activity, cease smoking)
Change antiretroviral therapy [replacement of PI, replacement of stavudine (Zerit™) or zidovudine (Retrovir™)]
Statins [e.g. Atorvastatin (Sortis™), Pravastatin (Pravasin™), Fluvastatin (Lescol™)]
Fibrates [e.g. Gemfibrozil (Gevilon™) or Bezafibrat (Cedur™)]
Metformin (e.g. Glucophage™)
Thiazolidinediones [rosiglitazone (Avandia™), pioglitazone (Actos™)]
Recombinant human growth hormones (e.g. Serostim™)
Surgical intervention

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## Specific interventions

Given the extensive indications that PIs are the culprits substantially contributing to the metabolic side effects, numerous attempts have tried to substitute the PI component of a regimen with nevirapine, efavirenz, or abacavir. Similarly, given the close association of stavudine-based therapy with lipoatrophy, replacement of this thymidine nucleoside analogue by, for example, abacavir or tenofovir has been evaluated in several studies. Indeed, these “switch studies” have demonstrated substantial improvement, although not normalization, of serum lipids (total and LDL cholesterol, triglycerides) and/or insulin resistance in many patients. In patients with hyperlipidemia, substitution of PIs with alternative PIs that have less metabolic side effects (e.g. atazanavir) has also been proven to be a successful strategy (Martinez 2005, Moebius 2005). Protease inhibitor cessation has not been shown to improve lipoatrophy. However, stopping administration of the thymidine nucleoside analogue stavudine or zidovudine usually leads to a slow recovery (over months and

years) measured by DEXA and moderate clinical increase in limb fat (Moyle 2005). Under restricted inclusion criteria and study conditions, most patients maintained complete viral suppression after changes to the HAART regimen, but not all of these studies included control groups with unchanged antiretroviral therapy. Recently, a pilot study evaluating the effect of uridine (NucleomaxX™) on lipodystrophy in HIV patients continuing their HAART regimen described a significant increase in subcutaneous fat after only three months (Sutinen 2005). Further studies with uridine, a sugar cane extract, will be necessary to fully assess the effectiveness and safety of this compound for patients with the lipodystrophy syndrome.

The most advantageous changes of metabolic parameters have been observed after replacement of the PI by nevirapine or abacavir. This option is, however, not always suitable, and the clinical benefit of effective viral suppression and improved immune function needs to be considered in view of the drug history, current viral load, and resistance mutations (Martinez 2003). When options are limited, antiretroviral drugs that may lead to elevation of lipid levels should not be withheld for fear of further exacerbating lipid disorders.

Table 4. Preliminary treatment recommendations and LDL cholesterol goals for HAART-associated hyperlipidemias

Risk Category	Recommendations		
	"aimed for" LDL	diet if LDL	Lipid-lowering drugs if LDL
CHD or risk equivalent ≥ 2 RF and 10-years risk ≤ 20%	< 100 mg/dl	≥ 100 mg/dl	≥ 130 mg/dl
10-year risk 10-20%	< 130 mg/dl	≥ 130 mg/dl	≥ 130 mg/dl
10-year risk <10%	< 130 mg/dl	≥ 130 mg/dl	≥ 160 mg/dl
0-1 risk factors	< 160 mg/dl	≥ 160 mg/dl	≥ 160 mg/dl

Coronary heart disease (CHD) includes history of myocardial infarction, unstable angina, stable angina, coronary artery procedures, or evidence of clinically significant myocardial ischemia. CHD risk equivalents include clinical manifestations of non-coronary forms of atherosclerotic disease, diabetes, and >2 risk factors with 10-year risk for hard CHD >20%. Risk factors (RF) include: age (male ≥ 45 years, female ≥ 55 years or premature menopause without hormone replacement), positive family history for premature CHD (in first-degree relatives < 55 years and first-degree female relatives < 65 years), cigarette smoking, hypertension (blood pressure ≥ 140/90 mmHg or taking antihypertension drugs), HDL < 40 mg/dl (1.0 mmol/l). If HDL cholesterol is over > 60 mg/dl (1.6 mmol/l), subtract one risk factor from the total (adapted from Dubé 2000 and Schambelan 2002).

Lipid lowering agents should be considered for the treatment of severe hypertriglyceridemia, elevated LDL or a combination of both. The clinical benefit, however, of lipid lowering or insulin-sensitizing therapy in HIV patients with lipodystrophy remains to be demonstrated. In light of the potentially increased cardiovascular risk to recipients of antiretroviral therapy, an American AIDS clinical trial group (ACTG) published recommendations based on the National Cholesterol Education Program (NCEP) for primary and secondary prevention of coronary artery disease in seronegative patients (Table 4). In addition, more detailed recommendations by an International AIDS Society-USA Panel have been published to provide guidelines for physicians actively involved in HIV care. However, these recom-

recommendations should be considered as being rather preliminary, given the so far limited numbers, sizes and durations of the clinical studies they are based on. It appears reasonable to measure fasting lipid levels annually before and 3-6 months after antiretroviral therapy is initiated or changed. Whenever possible, the antiretroviral therapy least likely to worsen lipid levels should be selected for patients with dyslipidemia. Decision on lipid lowering therapy can be based on estimating the 10-year risk for myocardial infarction according to the Framingham equation (<http://hin.nhlbi.nih.gov/atp/iii/calculator.asp>). It remains to be shown, however, whether this long-term risk calculation is applicable for HIV-infected patients given the changing lipid levels and medication regimens during HIV therapy.

HMG-CoA reductase inhibitors have been successfully used in combination with dietary changes in HIV patients with increased total and LDL cholesterol. These drugs may decrease total and LDL cholesterol by about 25 % (Grinspoon 2005). Many of the statins (as well as itraconazole, erythromycin, diltiazem, etc.) share common metabolism pathways with PIs via the cytochrome P450 3A4 system, thereby potentially leading to additional side effects due to increased plasma levels of statins which can then cause liver and muscle toxicity. Based on limited pharmacokinetic and clinical studies, atorvastatin (Sortis™), fluvastatin (Lescol™), and pravastatin (Pravasin™), carefully administered at increasing doses, are the preferred agents for a carefully monitored therapy in HIV-infected patients on HAART. Lovastatin (Mevinacor™) and simvastatin (Zocor™) should be avoided due to their potential interaction with PIs.

Fibric acid analogues such as gemfibrozil or fenofibrate are particularly effective in reducing the triglyceride levels by up to 50 % (Rao 2004, Badoui 2004, Miller 2002, Calza 2003) and should be considered in patients with severe hypertriglyceridemia (>1000 mg/dl). Fibric acid analogues retain a supportive effect on lipoprotein lipase activity and can thereby lower LDL levels. Despite their potentially synergistic effect, co-administration of fibric acid analogues and statins in patients on HAART should only be used carefully in selected individuals, since both can cause rhabdomyolysis. Niacinic acid has been shown to only minimally improve the hyperlipidemia induced by HAART. It does, however, increase peripheral insulin resistance (Gerber 2004). Extended-release niacin (Niaspan™) has been shown to have beneficial effects mainly on triglycerides and was well tolerated at a dose of 2,000 mg daily in a study with 33 individuals (Dube 2005). Finally, it should be stressed that the long-term effects of lipid-lowering agents and their impact on cardiovascular outcomes, especially in HIV patients with moderate or severe hypertriglyceridemia, are unknown.

Metformin has been evaluated for the treatment of lipodystrophy syndrome. Some studies have revealed a positive effect on the parameters of insulin resistance and the potential reduction of intra-abdominal (but also subcutaneous) fat, although not clinically obvious. Together with exercise training, metformin has been described to reverse the muscular adiposity in HIV-infected patients (Driscoll 2004b). Metformin, like all biguanides, can theoretically precipitate lactic acidosis but this adverse interaction has not been described. Use of metformin should be avoided in patients with creatinine levels above 1.5 mg/dl, increased aminotransferase levels, or hyperlactatemia. Thiazolidinediones, such as rosiglitazone (Avandia™) or pioglitazone (Actos™), exhibit the potency to improve insulin sensitivity via stimulation of



the PPAR $\gamma$  and other mechanisms. Rosiglitazone has been successfully used to treat abnormal fat distribution in genetic lipodystrophies. Three published studies on HIV patients, however, revealed no or only a minimal improvement in the abnormal fat distribution. But, insulin sensitivity was increased at the expense of increased total cholesterol and triglycerides (Carr 2004, Hadigan 2004, Sutinen 2003, Cavalcanti 2005). Thus, at least rosiglitazone cannot be recommended for general treatment of lipoatrophy in HIV patients at this time (Grinspoon 2005). It also reduces the bioavailability of nevirapine, but not of efavirenz and lopinavir (Oette 2005). Recently, a randomized double-blind placebo-controlled trial (ANRS 113) revealed a significant increase in subcutaneous fat 48 weeks after treatment with pioglitazone 30 mg once daily without demonstrating negative effects on lipid parameters (Slama 2006).

Recombinant growth hormone (e.g. Serostim<sup>TM</sup>) at doses of 4-6 mg/d sc over a time course of 8-12 weeks has been demonstrated in some small studies to be a successful intervention for reducing visceral fat accumulation, but it also reduces subcutaneous fat (Kotler 2004). Unfortunately, these improvements have been shown to consistently reverse after the discontinuation of growth hormone therapy. Studies with lower maintenance doses have not been performed yet. The possible side effects associated with growth hormone therapy include arthralgia, peripheral edema, insulin resistance and hyperglycemia.

Surgical intervention (liposuction) for the treatment of local fat hypertrophy has been successfully performed, but appears to be associated with an increased risk of secondary infection, and recurrence of the fat accumulation is possible. For the treatment of facial lipoatrophy, repeated subcutaneous injection of substances such as poly-L-lactic acid (Sculptra<sup>TM</sup>, New-Fill<sup>TM</sup>), a resorbable molecule that promotes collagen formation, has been effectively used in HIV patients (Valantin 2003, Lafaurie 2003, Guaraldi 2004, Mest 2004, Casavantes 2004). In 2004, Sculptra<sup>TM</sup> was approved by the Food and Drug Administration as an injectable filler to correct facial fat loss in people with human immunodeficiency virus. We recommend consultation with experienced specialists for surgical treatments and injection therapy. Further evaluation in long-term follow-up studies is necessary to fully assess the value of these methods.

## References

1. Addy CL, Gavrilu A, Tsiodras S, Brodovicz K, Karchmer AW, Mantzoros CS. Hypoadiponection is associated with insulin resistance, hypertriglyceridemia, and fat redistribution in human immunodeficiency virus –infected patients treated with highly active antiretroviral therapy. *J Clin Endocrinol Metab* 2003; 88:627-36.
2. Badiou S, Merle De Boever C, Dupuy AM, et al. Fenofibrate improves the atherogenic lipid profile and enhances LDL resistance to oxidation in HIV-positive adults. *Atherosclerosis* 2004; 172:273-279.
3. Bastard JP, Caron M, Vidal H, Jan V, Auclair M, Vigouroux C et al. Association between altered expression of adipogenic factor SREBP1 in lipoatrophic adipose tissue from HIV-1-infected patients and abnormal adipocyte differentiation and insulin resistance. *Lancet* 2002; 359:1026-1031.
4. Behrens G, Dejam A, Schmidt H, Balks HJ, Brabant G, Korner T, Stoll M, Schmidt RE. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 1999; 13:F63-70.
5. Behrens GM, Stoll M, Schmidt RE. Lipodystrophy syndrome in HIV infection: what is it, what causes it and how can it be managed? *Drug Saf* 2000; 23:57-76.
6. Behrens GMN, Boerner A-R, Weber K, et al. Impaired glucose phosphorylation and transport in skeletal muscle causes insulin resistance in HIV-1 infected patients with lipodystrophy. *J Clin Invest* 2002; 110:1319-1327.

## 314 Lipodystrophy Syndrome

7. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999;354:1112-1115.
8. Calza L, Manfredi R, Chiodo F. Statins and fibrates for the treatment of hyperlipidaemia in HIV-infected patients receiving HAART. *AIDS* 2003; 17:851-859.
9. Caron M, Auclair M, Vigouroux C, Glorian M, Forest C, Capeau J. The HIV protease inhibitor indinavir impairs sterol regulatory element-binding protein-1 intranuclear localization, inhibits preadipocyte differentiation, and induces insulin resistance. *Diabetes* 2001; 50:1378-1388.
10. Carr A, Emery S, Law M, Puls R, Lundgren JD, Powderly WG. An objective case definition of lipodystrophy in HIV-infected adults: a case-control study. *Lancet* 2003; 361:726-35.
11. Carr A, Law M. An objective lipodystrophy severity grading scale derived from the Lipodystrophy Case Definition Score. *J Acquir Immune Defic Syndr* 2003;33:571-576.
12. Carr A, Samaras K, Burton S, Law M, Freund J, Chisholm DJ, Cooper DA. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998; 12:F51-8.
13. Carr A, Samaras K, Thorisdottir A, Kaufmann GR, Chisholm DJ, Cooper DA. Diagnosis, prediction, and natural course of HIV-1 protease-inhibitor-associated lipodystrophy, hyperlipidaemia, and diabetes mellitus: a cohort study. *Lancet* 1999; 353:2093-9.
14. Carr A, Workman C, Carey D, et al. No effect of rosiglitazone for treatment of HIV-1 lipodystrophy: randomised, double-blind, placebo-controlled trial. *Lancet* 2004; 363:429-38.
15. Casavantes LC, Gottlieb M. Bio-Alcamid, a high-volume injectable posthesis for facial reconstruction in HIV-related lipodystrophy: a report on 100 patients. *Antivir Ther* 2004; 9:L37.
16. Cavalcanti R, Kain K, Shen S, Raboud J, Walmsley S. A randomized placebo controlled trial of rosiglitazone for the treatment of HIV lipodystrophy. Abstract 854, 12<sup>th</sup> CROI 2005, Boston
17. Currier J, Kendall M, Henry K, et al. Carotid intima-media thickness in HIV-infected and uninfected adults: ACTG 5078. Abstract 131, 10<sup>th</sup> CROI 2003, Boston.
18. Driscoll SD, Meininger GE, Lareau MT et al. Effects of exercise training and metformin on body composition and cardiovascular indices in HIV-infected patients. *AIDS* 2004a; 18:465-473.
19. Driscoll SD, Meininger GE, Ljungquist K, et al. Differential effects of metformin and exercise on muscle adiposity and metabolic indices in HIV-infected patients. *J Clin Endocrinol Metab* 2004b, 89: 2171-2178. <http://amedeo.com/lit.php?id=15126538>
20. Dube MP, Sprecher D, Henry WK, et al. Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with HIV and receiving antiretroviral therapy: recommendations of the Adult ACTG Cardiovascular Disease Focus Group. *Clin Infect Dis* 2000; 31:1216-24.
21. Dube MP, Wu JW, Aberg JA et al. Safety and efficacy of extended-release niacin for the treatment of dyslipidaemia in patients with HIV infection: a prospective, multicentre study (ACTG 5148). *Antiviral Therapy* 2005; 10: L9.
22. El-Sadr W, Reiss P, de Wit S et al. Relationship between prolonged exposure to combination ART and myocardial infarction: effect of sex, age, and lipid changes. Abstract 42, 12<sup>th</sup> CROI 2005, Boston.
23. Friis-Moller N, Sabin CA, Weber R, et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; 349:1993-2003.
24. Gallant JE, Staszewski S, Pozniak AL, DeJesus E, Suleiman JM, Miller MD et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naive patients: a 3-year randomized trial. *JAMA* 2004; 292:191-201.
25. Gan SK, Samaras K, Thompson CH, et al. Altered myocellular and abdominal fat partitioning predict disturbance in insulin action in HIV PI-related lipodystrophy. *Diabetes* 2002; 51:3163-9.
26. Gerber MT, Mondy KE, Yarasheski KE, et al. Niacin in HIV-infected individuals with hyperlipidemia receiving potent antiretroviral therapy. *Clin Infect Dis* 2004; 39:419-25.
27. Grinspoon S, Carr A. Cardiovascular risk and body-fat abnormalities in HIV-infected adults. *N Engl J Med* 2005; 352:48-62.
28. Guaraldi G, Orlando G, De Fazio D, et al. Prospective, partially-randomized, 24-week study to compare the efficacy and durability of different surgical techniques and interventions for the treatment of HIV-related facial lipodystrophy. *Antivir Ther* 2004; 9:L9
29. Hadigan C, Yawetz S, Thomas A, et al. Metabolic effects of rosiglitazone in HIV lipodystrophy: a randomized, controlled trial. *Ann Intern Med* 2004; 140:786-94.
30. Hertel J, Struthers H, Horj CB, Hruz PW. A structural basis for the acute effects of HIV protease inhibitors on GLUT4 intrinsic activity. *J Biol Chem* 2004, 279:55147-52.
31. John M, Nolan D, Mallal S. Antiretroviral therapy and the lipodystrophy syndrome. *Antivir Ther* 2001;6:9-20.

32. Kotler DP, Muurahainen N, Grunfeld C, Wanke C, Thompson M, Saag M, et al. Effects of growth hormone on abnormal visceral adipose tissue accumulation and dyslipidemia in HIV-infected patients. *J Acquir Immune Defic Syndr* 2004; 35:239-52.
33. Lafaurie M, Dolivo M, Boulu D, et al. Treatment of facial lipoatrophy with injections of poly lactic acid in HIV-infected patients. Abstract 720, 10<sup>th</sup> CROI 2003, Boston.
34. Liang J-S, Distler O, Cooper DA, et al. HIV protease inhibitors protect apolipoprotein B from degradation by the proteasome: A potential mechanism for protease inhibitor-induced hyperlipidemia. *Nat Med* 2001; 7:1327-1331.
35. Mallon PW, Miller J, Cooper DA, Carr A. Prospective evaluation of the effects of antiretroviral therapy on body composition in HIV-1-infected men starting therapy. *AIDS* 2003; 17:971-9.
36. Mallal SA, John M, Moore CB, James IR, McKinnon EJ. Contribution of nucleoside analogue reverse transcriptase inhibitors to subcutaneous fat wasting in patients with HIV infection. *AIDS* 2000; 14:1309-16.
37. Martinez E, Azuaje C, Antela A, et al. Effects of switching to ritonavir-boosted atazanavir in HIV-infected patients receiving antiretroviral therapy with hyperlipidemia. Abstract 850, 12<sup>th</sup> CROI 2005, Boston.
38. Martinez E, Mocroft A, Garcia-Viejo MA, Perez-Cuevas JB, Blanco JL, Mallolas J et al. Risk of lipodystrophy in HIV-1-infected patients treated with protease inhibitors: a prospective cohort study. *Lancet*. 2001; 357:592-8.
39. Martinez E, Arnaiz JA, Podzamec D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with HIV infection. *N Engl J Med* 2003; 349:1036-46.
40. Meininger G, Hadigan C, Laposata M, et al. Elevated concentrations of free fatty acids are associated with increased insulin response to standard glucose challenge in HIV-infected subjects with fat redistribution. *Metabolism* 2002; 51:260-266.
41. Mest DR, Humble G. Safety and efficacy of intradermal poly-L-lactic acid (Sculptra™) injections in patients with HIV-associated facial lipoatrophy. *Antivir* 2004; 9:L36.
42. Miller J, Brown D, Amin J et al. A randomized, double-blind study of gemfibrozil for the treatment of protease inhibitor-associated hypertriglyceridaemia. *AIDS* 2002, 16:2195-2200.
43. Moebius U, Lubach-Ruitman M, Castro-Frenzel B, et al. Switching to atazanavir improves metabolic disorders in patients with severe hyperlipidemia. *J Acquir Immune Defic Syndr* 2005; 39:174-180.
44. Moyle G, Sabin C, Carteledge J, et al. A 48-week, randomized, open-label comparative study of tenofovir DF vs abacavir as substitutes for a thymidine analog in persons with lipoatrophy and sustained virological suppression on HAART. Abstract 44LB, 12<sup>th</sup> CROI 2005, Boston.
45. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiological concentrations. *AIDS* 2002; 16:859-863.
46. Nolan D, John M, Mallal S. Antiretroviral therapy and the lipodystrophy syndrome, part 2: concepts in aetiopathogenesis. *Antivir Ther* 2001; 6:145-60.
47. Nolan D, Mallal S. Complications associated with NRTI therapy: update on clinical features and possible pathogenic mechanisms. *Antivir Ther* 2004; 9:849-63.
48. Noor MA, Lo JC, Mulligan K, Schwarz JM, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS* 2001; 15:F11-F18.
49. Noor MA, Seneviratne T, Aweeka FT, et al. Indinavir acutely inhibits insulin-stimulated glucose disposal in humans: a randomized, placebo-controlled study. *AIDS* 2002; 16:F1-F8.
50. Oette M, Kurowski M, Feldt T, et al. Impact of rosiglitazone treatment on the bioavailability of antiretroviral compounds in HIV-positive patients. *J Antimicrob Chemother* 2005; 56:416-419.
51. Purnell JQ, Zambon A, Knopp RH, et al. Effect of ritonavir on lipids and post-heparin lipase activities in normal subjects. *AIDS* 2000; 14:51-57.
52. Rao A, D'Amico S, Balasubramanyam A, Maldonado M. Fenofibrate is effective in treating hypertriglyceridemia associated with HIV lipodystrophy. *Am J Med Sci* 2004, 327:315-318.
53. Sabin C, Morfeldt L, Friis-Møller N, et al. Changes over time in the use of antiretroviral therapy and risk factors of cardiovascular disease in the D:A:D study. Abstract 866, 12<sup>th</sup> CROI 2005, Boston.
54. Saint-Marc T, Partisani M, Poizot-Martin I, et al. Fat distribution evaluated by computed tomography and metabolic abnormalities in patients undergoing antiretroviral therapy: preliminary results of the LIPOCO study. *AIDS*. 2000; 14:37-49.
55. Schambelan M, Benson CA, Carr A, et al. Management of metabolic complications associated with antiretroviral therapy for HIV-1 infection: recommendations of an International AIDS-Society-USA panel. *J Acquir Immune Defic Syndr* 2002; 31:257-275.
56. Seaberg E, Riddler S, Margolick J, et al. The effect of HAART initiation on blood pressure. Abstract 872, 12<sup>th</sup> CROI 2005, Boston.

## 316 Lipodystrophy Syndrome

57. Slama L, Lanoy L, Valentin MA, et al. Effect of pioglitazone on HIV-1 related lipodystrophy: a randomized double-blind placebo-controlled trial (ANRS 113) with 130 patients. Abstract 151LB, 13<sup>th</sup> CROI 2006, Denver.
58. Sekhar RV, Jahoor F, White AC, et al. Metabolic basis of HIV-lipodystrophy syndrome. *Am J Physiol Endocrinol Metab* 2002, 283:E332-7.
59. Sutinen J, Hakkinen AM, Westerbacka J, et al. Rosiglitazone in the treatment of HAART-associated lipodystrophy – a randomized double-blinded placebo controlled study. *Antivir Ther* 2003; 8:199-207.
60. Sutinen J, Walker UA, Sevastianova K, Hakkinen AM, Ristola M, Yki-Jarvinen H. Uridine supplementation increases subcutaneous fat in patients with HAART-associated lipodystrophy: a randomized, placebo-controlled trial. *Antiviral Therapy* 2005; 10:L7
61. Valantin MA, Aubron-Olivier C, Ghosn J, et al. Polylactic acid implants (New-Fillá) in the correction of facial lipodystrophy in HIV—infected patients (VEGA study): results at 72 weeks. Abstract 719, 10<sup>th</sup> CROI 2003, Boston.
62. van der Valk M, Bisschop PH, Romijn JA, et al. Lipodystrophy in HIV-1-positive patients is associated with insulin resistance in multiple metabolic pathways. *AIDS* 2001; 15:2093-2100.
63. Walli R, Herfort O, Michl GM, et al. Treatment with protease inhibitors associated with peripheral insulin resistance and impaired oral glucose tolerance in HIV-1-infected patients. *AIDS* 1998; 12:F167-F173.

## 8. Mitochondrial Toxicity of Nucleoside Analogs

Ulrich A. Walker and Grace A. McComsey

### Introduction

Two years after the introduction of protease inhibitors into the armamentarium of antiviral therapy, reports of HIV-infected individuals experiencing clinically relevant changes in body metabolism began to surface. These “metabolic” symptoms were initially summarized under the term “lipodystrophy” (Carr 1998). Today, ten years after the introduction of highly active antiretroviral therapy (HAART), this lipodystrophy syndrome is increasingly understood as the result of overlapping, but distinct effects of the different drug components within the HAART antiretroviral cocktail. The main pathogenetic mechanism through which nucleoside analogs are thought to contribute to the metabolic changes and organ toxicities is mitochondrial toxicity (Brinkman 1999).

### Pathogenesis of mitochondrial toxicity

NRTIs are prodrugs (Kakuda 2000) because they require activation in the cell through phosphorylation before they are able to inhibit their target, e.g. HIV reverse transcriptase. In addition to impairing the HIV replication machinery, the NRTI-triphosphates also inhibit a human polymerase called “gamma-polymerase”, which is responsible for the replication of mitochondrial DNA (mtDNA). Thus, the inhibition of gamma-polymerase by NRTIs leads to a decline (depletion) in mtDNA, a small circular molecule normally present in multiple copies in each mitochondrion and in hundreds of copies in most human cells (Lewis 2003). The only biological task of mtDNA is to encode for enzyme subunits of the respiratory chain, which is located in the inner mitochondrial membrane. Therefore, by causing mtDNA-depletion, NRTIs also lead to a defect in respiratory chain function.

An intact respiratory chain is the prerequisite for numerous metabolic pathways. The main task of the respiratory chain is to oxidatively synthesize ATP, our chemical currency of energy. In addition, the respiratory chain consumes NADH and FADH as end products of fatty acid oxidation. This fact explains the micro- or macrovesicular accumulation of intracellular triglycerides, which often accompanies mitochondrial toxicity. Last but not least, a normal respiratory function is also essential for the synthesis of DNA, because the de novo synthesis of pyrimidine nucleosides depends on an enzyme located in the inner mitochondrial membrane. This enzyme is called dihydroorotate dehydrogenase (DHODH) (Löffler 1997). The clinical implications of this fact are detailed below.

The onset of mitochondrial toxicity follows certain principles (Walker 2002b):

1. Mitochondrial toxicity is concentration dependent. High NRTI-concentrations cause a more pronounced mtDNA-depletion compared to low concentrations. The

clinical dosing of some nucleoside analogs is close to the limit of tolerance with respect to mitochondrial toxicity.

2. The onset of mitochondrial toxicity requires prolonged time. Changes in mitochondrial metabolism are observed only if the amount of mtDNA-depletion exceeds a certain threshold, an effect observed solely with prolonged NRTI-exposure. As a consequence of this effect, the onset of mitochondrial toxicity is typically not observed in the first few months of HAART. Furthermore, long-term NRTI exposure may also lead to mitochondrial effects despite relatively low NRTI concentrations.

3. There are significant differences in the relative potencies of nucleoside and nucleotide analogs in their ability to interact with gamma-polymerase. The hierarchy of gamma-polymerase inhibition for the active NRTI metabolites has been determined as follows: zalcitabine (HIVID<sup>TM</sup>) > didanosine (Videx<sup>TM</sup>) > stavudine (Zerit<sup>TM</sup>) > lamivudine (Epivir<sup>TM</sup>) ≥ abacavir (Ziagen<sup>TM</sup>) ≥ tenofovir (Viread<sup>TM</sup>) ≥ emtricitabine (Emtriva<sup>TM</sup>).

4. Zidovudine may be peculiar because its active triphosphate is only a weak inhibitor of gamma-polymerase. However, another mechanism can explain how zidovudine could cause mtDNA-depletion independent from gamma-polymerase inhibition. Zidovudine is an inhibitor of mitochondrial thymidine kinase type 2 (TK2), and, as such, interferes with the synthesis of natural pyrimidine nucleotides, thus potentially impairing the formation of mtDNA (McKee 2004). Indeed, inborn defects of TK2 are known to cause mtDNA-depletion in muscle tissue of humans (Saada 2001). It has also been demonstrated recently that zidovudine can be non-enzymatically converted into stavudine within the body, at least within some cells (Becher 2003, Bonora 2004).

5. Mitochondrial toxicity is tissue specific. Tissue specificity is explained by the fact that the uptake of the NRTI-prodrugs into cells and their mitochondria, as well as activation by phosphorylation may be different among individual cell types.

6. There may be additive or synergistic mitochondrial toxicities if two or more NRTIs are used in combination.

7. Some data suggest that mitochondrial transcription may also be impaired without mtDNA-alterations (Mallon 2005, Galluzzi 2005). However, the mechanism and clinical significance of this observation are not yet understood.

## Clinical manifestations

MtDNA-depletion may manifest clinically in one or several main target tissues (Fig. 1).

In the *liver* mitochondrial toxicity is associated with increased lipid deposits, resulting in micro or macrovesicular steatosis. Steatosis may be accompanied by elevated liver transaminases. Such steatohepatitis may progress to liver failure and lactic acidosis, a potentially fatal, but fortunately rare complication. Although steatohepatitis and lactic acidosis were already described in the early 90s in patients receiving didanosine monotherapy (Lambert 1990), mitochondrial liver toxicity is now observed under treatment with all NRTIs that have a relatively strong potential to inhibit gamma-polymerase, especially with the so called “D-drugs” didanosine (Videx<sup>TM</sup>), stavudine (Zerit<sup>TM</sup>) and zalcitabine (HIVID<sup>TM</sup>). However, liver

complications were also described with zidovudine (Retrovir™). It has been demonstrated in the hepatic tissue of HIV patients, that each of the D-drugs leads to a time dependent mtDNA-depletion. On electron microscopy, morphologically abnormal mitochondria were observed.

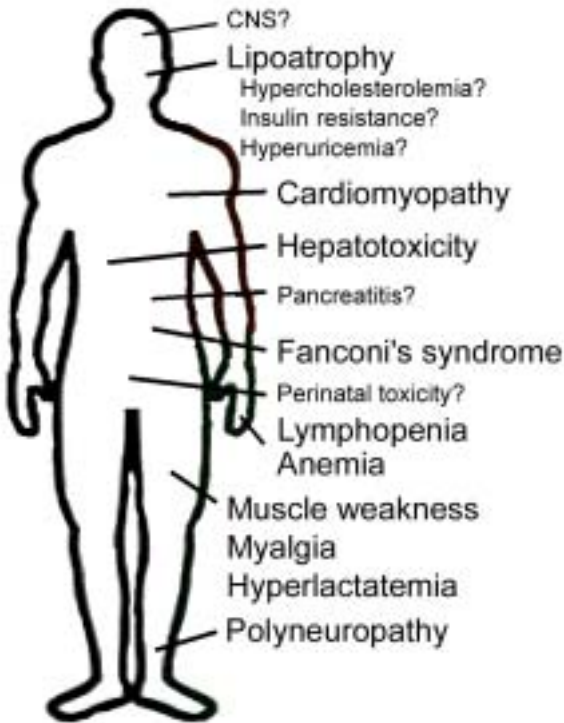


Figure 1: Organ manifestations of mitochondrial toxicity.

A typical complication of mitochondrial toxicity is an *elevation in serum lactate*. Such hyperlactatemia was more frequently described with prolonged stavudine treatment (Saint-Marc 1999, Carr 2000), especially when combined with didanosine. The toxicity of didanosine is also increased through the interactions with ribavirin and hydroxyurea. The significance of asymptomatic hyperlactatemia is unclear. When elevated lactate levels are associated with symptoms, these are often non-specific such as nausea, right upper quadrant abdominal tenderness or myalgias. In the majority of cases, levels of bicarbonate and the anion gap ( $\text{Na}^+ - [\text{HCO}_3^- + \text{Cl}^-]$ ) are normal, although liver transaminases are mildly increased in the majority of cases (Lonergan 2000a). Therefore, the diagnosis relies on the logistically more cumbersome direct determination of serum lactate. In order to avoid artifacts, venous blood must be drawn without the use of a tourniquet from resting patients. The blood needs to be collected in fluoride tubes and transported to the laboratory on ice for immediate analysis. Non-mitochondrial causes must also be

considered in the differential diagnosis of lactic acidosis (Table 1) and underlying organ toxicities should be looked for.

Table 1. Causes of hyperlactatemia/ lactic acidosis

Type A lactic acidosis	Type B lactic acidosis
( <i>Tissue hypoxia</i> )	( <i>Other mechanisms</i> )
Shock	Thiamine deficiency
Carbon monoxide poisoning	Alkalosis (pH>7.6)
Heart failure	Epilepsy
	Adrenalin (iatrogenic, endogenous)
	Liver failure
	Neoplasm (lymphoma, solid tumors)
	Intoxication (nitroprusside, methanol, methylene glycol, salicylates)
	Fructose
	Rare enzyme deficiencies
	mtDNA mutations
	mtDNA depletion

A *mitochondrial myopathy* in antiretrovirally treated HIV patients was first described with high dose zidovudine therapy (Arnaudo 1991). Skeletal muscle weakness may manifest under dynamic or static exercise. The serum CK is often normal or only minimally elevated. Muscle histology helps to distinguish this form of NRTI toxicity from HIV myopathy, which may also occur simultaneously. On histochemical examination, the muscle fibers of the former are frequently negative for cytochrome c-oxidase and carry ultrastructurally abnormal mitochondria, whereas those of the latter are typically infiltrated by CD8+ T-lymphocytes. Exercise testing may detect a low lactate threshold and a reduced lactate clearance, but in clinical practice these changes are difficult to distinguish from lack of aerobic exercise (detraining).

Prolonged treatment with D-drugs may also frequently lead to a predominantly symmetrical, sensory and distal *polyneuropathy* of the lower extremities (Simpson 1995, Moyle 1998). An elevated serum lactate level may help to distinguish this axonal neuropathy from its HIV-associated phenocopy, although in most cases the lactate level is normal. The differential diagnosis may also take into account the fact that the mitochondrial polyneuropathy mostly occurs weeks or months after initiation of D-drugs. In contrast, the HIV-associated polyneuropathy generally does not worsen and may indeed improve with prolonged antiretroviral treatment.

In its more narrow sense, the term “lipodystrophy” denotes a change in the distribution of body fat. Some subjects affected with lipodystrophy may experience abnormal fat accumulation in certain body areas (most commonly abdomen or dorso-cervical region), whereas others may develop fat wasting (Bichat’s fat pad in the cheeks, temporal fat, or subcutaneous fat of the extremities). Both fat accumulation and fat loss may at times occur simultaneously in the same individuals. Fat wasting (also called *lipoatrophy*) is partially reversible and generally observed not earlier than one year after the initiation of antiretroviral therapy. In the affected subcutaneous tissue, ultrastructural abnormalities of mitochondria and reduced mtDNA levels



have been identified, in particular in subjects treated with stavudine (Walker 2002a). In vitro and in vivo analyses of fat cells have also demonstrated diminished intracellular lipids, reduced expression of adipogenic transcription factors (PPAR-gamma and SREBP-1), and increased apoptotic indices. NRTI treatment may also impair some endocrine functions of adipocytes. For example, they may impair the secretion of adiponectin and through this mechanism may promote insulin resistance. Stavudine has been identified as a particular risk factor, but other NRTIs such as zidovudine may also contribute. When stavudine is replaced by another NRTI, mtDNA-levels and apoptotic indices improve (McComsey 2005a) along with an objectively measurable, albeit small increase of subcutaneous adipose tissue (McComsey 2004a). In contrast, switching away from protease inhibitors did not ameliorate lipoatrophy or adipocyte apoptosis. Taken together, the available data are consistent with a predominant effect of mitochondrial toxicity in the pathogenesis of lipoatrophy.

Some studies have suggested an effect of NRTIs on the mtDNA levels in blood (Coté 2003, Miro 2003). The functional consequence of such mitochondrial toxicity on *lymphocytes* is still unknown. In this context, it is important to note that a delayed loss of CD4<sup>+</sup> and CD8<sup>+</sup> T-lymphocytes was observed, when didanosine plasma levels were increased by comedication with tenofovir or by low body weight (Negredo 2004). Recent in vitro investigations with exposure of mitotically stimulated T-lymphocytes to slightly supratherapeutic concentrations of didanosine also detected a substantial mtDNA-depletion with a subsequent late onset decline of lymphocyte proliferation and increased apoptosis (Setzer 2005a, Setzer 2005b). Thus, mitochondrial toxicity is the most likely explanation for the late onset decline of lymphocytes observed with didanosine. The data suggest that the mitochondrial toxicity of NRTIs on lymphocytes has immunosuppressive properties.

Asymptomatic elevations in *serum lipase* are not uncommon under HAART, but of no value in predicting the onset of pancreatitis (Maxson 1992). The overall frequency of pancreatitis has been calculated as 0.8 cases/ 100 years of NRTI-containing HAART. Clinical pancreatitis is associated with the use of didanosine in particular. Didanosine reexposure may trigger a relapse and should be avoided. A mitochondrial mechanism has been cited to explain the onset of pancreatitis, but this assumption remains unproven.

New studies have also raised the question, whether or not zidovudine can be used safely to reduce the risk of HIV vertical transmission. Pregnant monkeys were treated with zidovudine plus lamivudine for a period of 10 weeks prior to delivery and zidovudine was found to be incorporated into mtDNA. The NRTI combination was also associated with mtDNA-depletion in skeletal muscle, heart and brain (Gerschenson 2004). Perinatally acquired lesions were shown to persist for months after cessation of NRTI exposure in some models (Walker 2004a).

Mitochondrial symptoms were found at increased frequency in *infants* perinatally exposed to NRTIs (Blanche 1999). Hyperlactatemia is not infrequently observed and may persist for several months after delivery (Noguera 2003). Very low mtDNA levels were measured in the placenta, as well as in the peripheral cord blood of neonates (Shiramizu 2003, Divi 2005). Other clinical trials in contrast did not detect an increased perinatal risk in association with perinatal zidovudine prophylaxis although key parameters of mitochondrial dysfunction were not assessed.

Long-term follow-up data are urgently needed. The present information however does not justify deviating from the currently recommended strategy to use zidovudine to prevent vertical HIV transmission.

The existence of mitochondrial damage to the *kidney* is controversial. Supratherapeutic doses of the nucleotide analog reverse transcriptase inhibitor tenofovir (Viread<sup>TM</sup>) induced a Fanconi syndrome with tubular phosphate loss and consecutive osteomalacia in animals (Tenofovir review team 2001). Tenofovir is taken up into the renal tubules by means of a special anion transporter and it cannot be ruled out that an excessively high intracellular drug concentration may lead to a clinically relevant gamma-polymerase inhibition and mtDNA depletion, despite the fact that tenofovir has only a low potency to impair the replication of mtDNA. Decreased mtDNA levels have recently been found in renal biopsies from patients exposed to tenofovir plus didanosine, a NRTI combination that for several reasons is no longer recommended (Côté 2005). Renal mtDNA levels from individuals treated with tenofovir did not differ from those who remained untreated. However, the glomerular and tubular function was not assessed in this study. Furthermore, information about the indication for renal biopsy was not provided, and a didanosine-only control group was not included. It should be noted that neither the trials leading to the approval of tenofovir, nor the subsequent field data were able to prove the mitochondrial toxicity of tenofovir in the renal tubules. However, most trials only measured creatinine clearance and serum phosphate (Izzedine 2005), even though a compromise in renal function is not expected in Fanconi's syndrome and normal serum phosphate levels may be preserved by increased phosphate mobilization from bone, thus masking increased renal loss. More sensitive methods have recently revealed a diminished renal phosphate resorption and an elevated alkaline phosphatase in patients treated with tenofovir (Kinai 2005). Cases of phosphate diabetes were also reported under treatment with other nucleoside analogues.

## Monitoring and diagnosis

There is currently no method to reliably predict the mitochondrial risk of an individual patient. Routine screening of asymptomatic NRTI-treated subjects with lactate levels is not warranted, since elevated lactate levels in asymptomatic subjects are not predictive of clinical mitochondrial toxicity (McComsey 2004b). In contrast, there should be a low threshold to promptly check lactate levels in subjects who experience symptoms consistent with mitochondrial toxicity. The determination of mtDNA-levels in PBMCs is subject to systematic errors and high variability; the method is not internationally standardized. Quantifying mtDNA within affected tissues is likely to be more sensitive; however this form of monitoring is invasive and not prospectively evaluated with regard to clinical endpoints.

Once symptoms are established, histological examination of a biopsy may contribute to the correct diagnosis. The following findings in tissue biopsies point towards a mitochondrial etiology: ultrastructural abnormalities of mitochondria, diminished histochemical activities of cytochrome c-oxidase, the detection of intracellular and more specifically microvesicular steatosis, and the so-called ragged-red fibers.

## Treatment and prophylaxis of mitochondrial toxicity

### Drug interactions

Drug interactions may precipitate mitochondrial symptoms and must be taken into account. The mitochondrial toxicity of didanosine (Videx<sup>TM</sup>) for example is augmented through drug interactions with ribavirin, hydroxyurea and allopurinol (Ray 2004). When didanosine is combined with tenofovir (Viread<sup>TM</sup>), the didanosine dose must be reduced to 250 mg once daily. The thymidine analog brivudine is a herpes virostatic that may sensitize for NRTI-related mitochondrial toxicity because one of its metabolites is an inhibitor of DHODH (see below). Brivudine should therefore not be combined with antiretroviral pyrimidine analogues.

### Mitochondrial toxins

An impairment of mitochondrial metabolism may also result from ibuprofen, valproic acid and acetyl salicylic acid as these substances impair the mitochondrial utilization of fatty acids. Numerous cases have been described, in which a life-threatening lactic acidosis was triggered by valproic acid, both in HIV-infected patients and in patients with inherited mutations of mtDNA. Acetyl salicylic acid may damage mitochondria and such damage to liver organelles may result in Reye's syndrome.

Amiodarone and tamoxifen also inhibit the mitochondrial synthesis of ATP. Acetaminophen and other drugs impair the antioxidative defense (glutathione) of mitochondria, allowing for their free radical mediated damage. Aminoglycoside antibiotics and chloramphenicol not only inhibit the protein synthesis of bacteria, but under certain circumstances may also impair the peptide transcription of mitochondria as our bacteria-like endosymbionts. Adefovir and cidofovir are also inhibitors of gamma-polymerase. Alcohol as a mitochondrial toxin is advised against.

The most important clinical intervention is probably the discontinuation of the NRTI(s) responsible for mitochondrial toxicity. Several studies have demonstrated that switching stavudine (Zerit<sup>TM</sup>) to a less toxic alternative led to an objective and progressive improvement in lipoatrophy (McComsey 2004, Madruga 2005, Martin 2004, Moyle 2005, Milinkovic 2005, Tebas 2005). In contrast, a switch from protease inhibitors to NNRTIs was not associated with an improvement of lipoatrophy. These findings stress the importance of mitochondrial toxicity in the pathogenesis of these fat abnormalities.

### Uridine

The supplementation of uridine is a new, but promising strategy. As outlined above, any respiratory chain impairment also results in the inhibition of DHODH, an essential enzyme for the synthesis of uridine and its derived pyrimidines (Fig 2). This decrease in intracellular pyrimidine pools leads to a relative excess of the exogenous pyrimidine nucleoside analogs, with which they compete at gamma-polymerase. A vicious circle is closed and contributes to mtDNA-depletion. By supplementing uridine either prophylactically or therapeutically, this vicious circle

may be interrupted, resulting in increased mtDNA-levels. Indeed, uridine abolished in hepatocytes all the effects of mtDNA-depletion and normalized lactate production, cell proliferation, the rate of cell death and intracellular steatosis. (Walker 2003). In contrast, vitamin cocktails were not beneficial in this model. New data indicate that uridine is able to also prevent the loss of mtDNA, lipids and mitochondrial functions in adipocytes exposed to stavudine (Walker 2004a). Adipocyte apoptosis was also prevented.

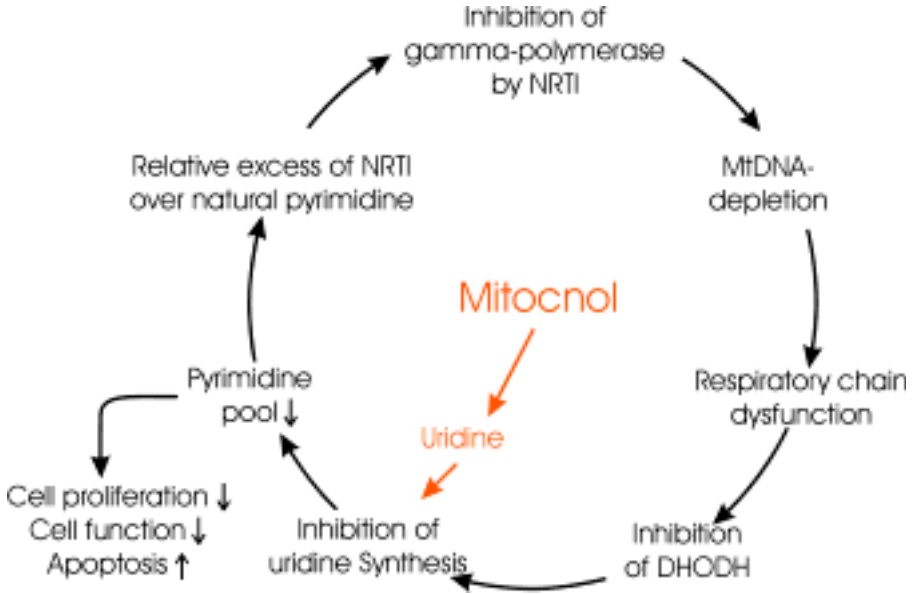


Figure 2: Suggested mechanism of Mitocnol (NucleomaxX™) in the prevention and treatment of mitochondrial toxicity.

The oral substitution of uridine as a pyrimidine precursor is well tolerated by humans, even at high doses (van Groeningen 1986, Kelsen 1997). A food supplement called Mitocnol was shown to have a more than 8-fold uridine bioavailability over conventional uridine (Venhoff 2005). After positive experiences in individual cases of mitochondrial toxicity (Walker 2004d), data from clinical trials are now surfacing. Mitocnol was studied in a randomized placebo-controlled double-blind trial in lipoatrophic subjects under continued therapy with stavudine or zidovudine where it has shown improvement in objectively measured subcutaneous fat (Sutinen 2005). The effect of Mitocnol on subcutaneous fat gain was more rapid and quantitatively more pronounced in comparison with switch strategies (e.g. the replacement of stavudine and zidovudine by antivirals with a reduced potential of mitochondrial toxicity (Fig 3).

A second trial has also suggested Mitocnol to be efficacious with regard to patient and physician assessed lipoatrophy scores, although fat and PBMC mtDNA levels were unchanged (McComsey 2005b). A third trial examined the effect of Mitocnol on the function of hepatic mitochondria by means of a  $^{13}\text{C}$  methionine breath test

(Banasch 2006). Mitocnol improved mitochondrial liver function despite unchanged therapy with thymidine analogs. The effect of a 3-day course of Mitocnol was noticeable after 2 weeks, persisted over several weeks, and was reproducible on Mitocnol reexposure.

Mitocnol is well tolerated and adverse events have not been observed so far. In one study, a small HDL decline was noted, while in another HDL-cholesterol was unchanged (McComsey 2005b). There are no known negative interactions of uridine with the efficacy of the antiretroviral treatment (Sommadossi 1988, Koch 2003, McComsey 2005, Sutinen 2005). In Europe and North America, Mitocnol is available as a dietary supplement called NucleomaxX<sup>®</sup> and can be acquired in pharmacies and the internet ([www.nucleomaxX.com](http://www.nucleomaxX.com)).

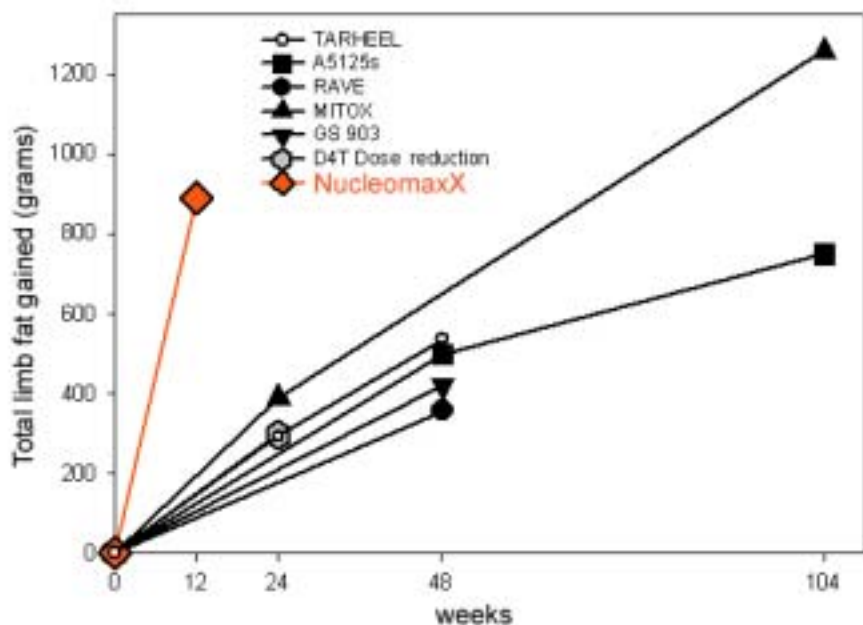


Figure 3: Subcutaneous fat gain with Mitocnol under stavudine and zidovudine treatment (in comparison with NRTI-sparing strategies).

In symptomatic hyperlactatemia and in lactic acidosis, all NRTIs should be immediately discontinued (Brinkman 2000). The supplementation of vitamin cocktails has been recommended, but there are no data that demonstrate the efficacy of this intervention with respect to mtDNA-depletion (Walker 1995, Venhoff 2002). After discontinuation of NRTIs, normalization of lactate may require several weeks. More mitochondrial friendly NRTIs may then be reintroduced, but patients should be monitored closely (Loneragan 2003). The proposed supportive treatment of hyperlactatemia and lactic acidosis is summarized in Table 2.

Table 2. Supportive treatment of lactate elevation in HIV-infected patients (non-pregnant adults)

Lactate 2-5 mmol/L + symptoms	Lactate > 5 mmol/L or lactic acidosis
Discontinue mitochondrial toxins	Discontinue NRTIs and all mitochondrial toxins
Consider vitamins and NucleomaxX (36g TID on 3 consecutive days/ month)	Intensive care Maintain hemoglobin > 100 g/L Avoid vasoconstrictive agents Oxygen Correct hypoglycemia Bicarbonate controversial – 50-100 mmol if pH<7.1 Coenzyme Q <sub>10</sub> (100 mg TID) Vitamin C (1 g TID) Thiamine (Vit. B <sub>1</sub> , 100 mg TID) Riboflavin (Vit. B <sub>2</sub> , 100 mg QD) Pyridoxine (Vit. B <sub>6</sub> , 60 mg QD) L-acetyl carnitine (1 g TID) NucleomaxX (36 g TID until lactate <5 mmol/L)

## References

1. Arnaudo E, Dalakas M, Shanske S, Moraes CT, DiMauro S, Schon EA. Depletion of muscle mitochondrial DNA in AIDS patients with zidovudine-induced myopathy. *Lancet* 1991;337:508-510. <http://amedeo.com/lit.php?id=1671889>
2. Banasch M, Goetze O, Knyhala K et al. Uridine supplementation enhances hepatic mitochondrial function in thymidine-analogue treated HIV-infected patients. *AIDS* 2006; 20:1554-1556. <http://amedeo.com/lit.php?id=16847412>
3. Becher F, Pruvost AG, Schlemmer DD et al. Significant levels of intracellular stavudine triphosphate are found in HIV-infected zidovudine-treated patients. *AIDS* 2003;17:555-561. <http://amedeo.com/lit.php?id=12598776>
4. Blanche S, Tardieu M, Rustin P et al. Persistent mitochondrial dysfunction and perinatal exposure to antiretroviral nucleoside analogues. *Lancet* 1999;354:1084-1089. <http://amedeo.com/lit.php?id=10509500>
5. Bonora S, Boffito M, D'Avolio A et al. Detection of stavudine concentrations in plasma of HIV-infected patients taking zidovudine. *AIDS* 2004;18:577-578. <http://amedeo.com/lit.php?id=15090817>
6. Brinkman K, Smeitink JA, Romijn JA, Reiss P. Mitochondrial toxicity induced by nucleoside-analogue reverse-transcriptase inhibitors is a key factor in the pathogenesis of antiretroviral-therapy-related lipodystrophy. *Lancet* 1999;354:1112-1115. <http://amedeo.com/lit.php?id=10509516>
7. Brinkman K, Vrouenraets S, Kauffman R, Weigel H, Frissen J. Treatment of nucleoside reverse transcriptase inhibitor-induced lactic acidosis. *AIDS* 2000;14:2801-2802. <http://amedeo.com/lit.php?id=11125906>
8. Carr A, Miller J, Law M, Cooper DA. A syndrome of lipotrophy, lactic acidemia and liver dysfunction associated with HIV nucleoside analogue therapy: contribution to protease inhibitor-related lipodystrophy syndrome. *AIDS* 2000;14:F25-F32. <http://amedeo.com/lit.php?id=10716495>
9. Carr A, Samaras K, Burton S et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS* 1998;12:F51-F58. <http://amedeo.com/lit.php?id=9619798>
10. Coté HC, Yip B, Asselin JJ et al. Mitochondrial:nuclear DNA ratios in peripheral blood cells from human immunodeficiency virus (HIV)-infected patients who received selected HIV antiretroviral drug regimens. *J Infect Dis* 2003;187:1972-1976. <http://amedeo.com/lit.php?id=12792876>
11. Côté H, Magil A, Harrigan PR, et al. Kidney mitochondrial DNA levels in HIV patients with renal dysfunction on tenofovir-containing therapy are markedly reduced with concurrent didanosine therapy. Abstract TuPe2.3C19, 3<sup>rd</sup> IAS 2005, Rio de Janeiro.
12. Divi RL, Walker VE, Wade NA et al. Mitochondrial damage and DNA depletion in cord blood and umbilical cord from infants exposed in utero to Combivir. *AIDS* 2004, 18:1013-1021. <http://amedeo.com/lit.php?id=15096804>
13. Galluzzi L, Pinti M, Troiano L et al. Changes in mitochondrial RNA production in cells treated with nucleoside analogues. *Antivir Ther* 2005, 10:191-195. <http://amedeo.com/lit.php?id=15751778>

14. Gerschenson M, Nguyen V, Ewings EL et al. Mitochondrial toxicity in fetal *Erythrocebus* patas monkeys exposed transplacentally to zidovudine plus lamivudine. *AIDS Res Hum Retroviruses* 2004;20:91-100. <http://amedeo.com/lit.php?id=15000702>
15. Izzedine H, Hulot JS, Vittecoq D et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naïve HIV-1-infected patients. Data from a double-blind randomized active-controlled multicentre study. *Nephrol Dial Transplant* 2005, 20:743-746. <http://amedeo.com/lit.php?id=15741212>
16. Kakuda TN. Pharmacology of nucleoside and nucleotide reverse transcriptase inhibitor-induced mitochondrial toxicity. *Clin Ther* 2000;22:685-708. <http://amedeo.com/lit.php?id=10929917>
17. Kelsen DP, Martin D, O'Neil J et al. Phase I trial of PN401, an oral prodrug of uridine, to prevent toxicity from fluorouracil in patients with advanced cancer. *J Clin Oncol* 1997;15:1511-1517. <http://amedeo.com/lit.php?id=9193347>
18. Kinai E, Hanabusa E. Renal tubular toxicity associated with tenofovir assessed using urine-beta 2 microglobulin, percentage of tubular reabsorption of phosphate and alkaline phosphatase levels. *AIDS* 2005, 19:2031-2033. <http://amedeo.com/lit.php?id=16260911>
19. Koch EC, Schneider J, Weiss R, Penning B, Walker JA. Uridine excess does not interfere with the antiretroviral efficacy of nucleoside analogue reverse transcriptase inhibitors. *Antivir Ther* 2003;8:485-487. <http://amedeo.com/lit.php?id=14640397>
20. Lambert JS, Seidlin M, Reichman RC et al. 2',3'-dideoxyinosine (ddI) in patients with the acquired immunodeficiency syndrome or AIDS-related complex. A phase I trial. *N Engl J Med* 1990;322:1333-1340. <http://amedeo.com/lit.php?id=2139173>
21. Lewis W, Day BJ, Copeland WC. Mitochondrial toxicity of NRTI antiviral drugs: an integrated cellular perspective. *Nature Rev Drug Discovery* 2003, 2:812-822. <http://amedeo.com/lit.php?id=14526384>
22. Loneragan JT, Barber RE, Mathews WC. Safety and efficacy of switching to alternative nucleoside analogues following symptomatic hyperlactatemia and lactic acidosis. *AIDS* 2003;17:2495-2499. Abstract: <http://amedeo.com/lit.php?id=14600521>
23. Loneragan JT, Behling C, Pfander H, Hassanein TI, Mathews WC. Hyperlactatemia and hepatic abnormalities in 10 human immunodeficiency virus-infected patients receiving nucleoside analogue combination regimens. *Clin Infect Dis* 2000a;31:162-166. <http://amedeo.com/lit.php?id=10913415>
24. Löffler M, Jöckel J, Schuster G, Becker C. Dihydroorotat-ubiquinone oxidoreductase links mitochondria in the biosynthesis of pyrimidine nucleotides. *Mol Cell Biochem* 1997;174:125-129. <http://amedeo.com/lit.php?id=9309676>
25. Madruga JVR, Casseti I, Suleiman JMAH, et al. Improvement in lipotrophy and lipid abnormalities following switch from stavudine (d4T) to tenofovir DF (TDF) in combination with lamivudine (3TC) and efavirenz (EFV) in HIV-infected patients: a 48 week follow-up from study 903e. Abstract ZePe2.2B12, 3<sup>rd</sup> IAS 2005, Rio de Janeiro.
26. Mallon PW, Unemori P, Sedwell R et al. In vivo, nucleoside reverse-transcriptase inhibitors alter expression of both mitochondrial and lipid metabolism genes in the absence of depletion of mitochondrial DNA. *J Infect Dis* 2005, 191:1686-1696. <http://amedeo.com/lit.php?id=15838796>
27. Martin A, Smith DE, Carr A et al. Reversibility of lipotrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS* 2004;18:1029-1036. <http://amedeo.com/lit.php?id=15096806>
28. Maxson CJ, Greenfield SM, Turner JL. Acute pancreatitis as a common complication of 2',3'-dideoxyinosine therapy in the acquired immunodeficiency syndrome. *Am J Gastroenterol* 1992;87:708-713. <http://amedeo.com/lit.php?id=1590305>
29. McComsey GA, Ward DJ, Hesselthaler SM et al. Improvement in lipotrophy associated with HAART in HIV-infected patients switched from stavudine to abacavir or zidovudine: the results of the TARHEEL study. *Clin Infect Dis* 2004a;38:263-270. <http://amedeo.com/lit.php?id=14699460>
30. McComsey GA, Yau L. Asymptomatic hyperlactataemia: predictive value, natural history and correlates. *Antivir Ther* 2004b;9:205-212. <http://amedeo.com/lit.php?id=15134182>
31. McComsey GA, Paulsen DM, Loneragan TJ, et al. Improvements in lipotrophy, mitochondrial DNA content and adipose tissue apoptosis levels after replacement of stavudine with either abacavir or zidovudine. *AIDS* 2005a;19:15-23 <http://amedeo.com/lit.php?id=15627029>
32. McComsey GA, Setzer B, O'Riordan M, et al. NucleomaxX improves clinical lipotrophy without any change in fat mitochondrial DNA levels. *Antivir Ther* 2005b, 10:L49-L50.
33. McKee EE, Bentley AT, Hatch M, et al. Phosphorylation of thymidine and AZT in heart mitochondria: elucidation of a novel mechanism of AZT cardiotoxicity. *Cardiovasc Toxicol* 2004, 4:155-167. <http://amedeo.com/lit.php?id=15371631>
34. Milinkovic A, Lopez S, Miro O, et al. A randomized open study comparing the impact of reducing stavudine dose versus switching to tenofovir on mitochondrial function, metabolic parameters, and subcutaneous fat in HIV-infected patients receiving antiretroviral therapy containing stavudine. Abstract 857, 12<sup>th</sup> CROI 2005, Boston.

## 328 Mitochondrial Toxicity of Nucleoside Analogs

35. Miro O, Lopez S, Pedrol E et al. Mitochondrial DNA depletion and respiratory chain enzyme deficiencies are present in peripheral blood mononuclear cells of HIV-infected patients with HAART-related lipodystrophy. *Antivir Ther* 2003;8:333-338. <http://amedeo.com/lit.php?id=14526764>
36. Moyle GJ, Sadler M. Peripheral neuropathy with nucleoside antiretrovirals: risk factors, incidence and management. *Drug Safety* 1998;19:481-494. <http://amedeo.com/lit.php?id=9880091>
37. Moyle G, Sabin C, Cartledge J, et al. A randomized, open-label comparative trial of abacavir or tenofovir DF as replacement for a thymidine analogue in persons with lipodystrophy and suppressed HIV RNA on HAART: the RAVE study. Abstract 44, 12<sup>th</sup> CROI 2005, Boston.
38. Negro E, Moltó J, Burger D et al. Unexpected CD4 cell count decline in patients receiving didanosine and tenofovir-based regimens despite undetectable viral load. *AIDS* 2004;18:459-463. <http://amedeo.com/lit.php?id=15047506>
39. Noguera A, Fortuny C, Sanchez E et al. Hyperlactatemia in HIV-infected children receiving antiretroviral treatment. *Pediatr Infect Dis J* 2003;22:778-782. <http://amedeo.com/lit.php?id=14506367>
40. Ray AS, Olson L, Fridland A. Role of purine nucleoside phosphorylase in interactions between 2',3'-dideoxyinosine and allopurinol, ganciclovir, or tenofovir. *Antimicrob Agents Chemother* 2004;48:1089-1095. <http://amedeo.com/lit.php?id=15047506>
41. Saada A, Shaag A, Mandel H, Nevo Y, Eriksson S, Elpeleg O. Mutant mitochondrial thymidine kinase in mitochondrial DNA depletion myopathy. *Nat Genet* 200, 29:342-344 <http://amedeo.com/lit.php?id=11687801>
42. Saint-Marc T, Touraine JL. The effects of discontinuing stavudine therapy on clinical and metabolic abnormalities in patients suffering from lipodystrophy. *AIDS* 1999;13:2188-2189. <http://amedeo.com/lit.php?id=10546885>
43. Setzer B, Schlesier M, Thomas AK, Walker UA. Mitochondrial toxicity of nucleoside analogues in primary human lymphocytes. *Antivir Ther* 2005a; 10:327-34 <http://amedeo.com/lit.php?id=15865227>
44. Setzer B, Schlesier M, Walker UA. Effects of didanosine-related mtDNA-depletion of human mtDNA in human T-lymphocytes. *J Infect Dis* 2005b, 191:848-855. <http://amedeo.com/lit.php?id=15717258>
45. Shiramizu B, Shikuma KM, Kamemoto L et al. Placenta and cord blood mitochondrial DNA toxicity in HIV-infected women receiving nucleoside reverse transcriptase inhibitors during pregnancy. *J Acquir Immune Defic Syndr* 2003;32:370-374. <http://amedeo.com/lit.php?id=12640193>
46. Simpson DM, Tagliati M. Nucleoside analogue-associated peripheral neuropathy in HIV infection. *J Acquir Immune Defic Syndr* 1995;9:153-161. <http://amedeo.com/lit.php?id=7749792>
47. Sommadossi JP, Carlisle R, Schinazi RF, Zhou Z. Uridine reverses the toxicity of 3'-azido-3'-deoxythymidine in normal human granulocyte-macrophage progenitor cells in vitro without impairment of antiretroviral activity. *Antimicrob Agents Chemother* 1988;32:997-1001. <http://amedeo.com/lit.php?id=3190201>
48. Sutinen J, Walker UA, Häkkinen AM, et al. Uridine for the treatment of HAART-associated lipodystrophy, a randomized, placebo-controlled trial. *Antivir Ther* 2005, 10:L7.
49. Tebas P, Zhang H, Yarasheski K, et al. Switch to PI-containing/nucleoside reverse transcriptase inhibitor-sparing regimen increases appendicular fat and serum lipid levels without affecting glucose metabolism or bone mineral density. The results of a prospective randomized trial, ACTG 5125S. Abstract 40, 12<sup>th</sup> CROI 2005, Boston.
50. Tenofovir review team. Memorandum. [www.fda.gov](http://www.fda.gov/ohrms/dockets/ac/01/slides/3792s1_02_FDA-tenofovir.ppt) 2001. [http://www.fda.gov/ohrms/dockets/ac/01/slides/3792s1\\_02\\_FDA-tenofovir.ppt](http://www.fda.gov/ohrms/dockets/ac/01/slides/3792s1_02_FDA-tenofovir.ppt)
51. van Groenigen CJ, Leyva A, Kraal I, Peters GJ, Pinedo HM. Clinical and pharmacokinetic studies of prolonged administration of high-dose uridine intended for rescue from 5-FU toxicity. *Cancer Treatment Reports* 1986;70:745-750. <http://amedeo.com/lit.php?id=3731137>
52. Venhoff N, Setzer B, Lebrecht D, Walker UA. Dietary supplements in the treatment of NRTI-related mitochondrial toxicity. *AIDS* 2002;16:800-802. <http://amedeo.com/lit.php?id=11964542>
53. Venhoff N, Zilly M, Lebrecht D et al. Uridine pharmacokinetics of Mitocnol, a sugar cane extract. *AIDS* 2005; 19: 739-740. <http://amedeo.com/lit.php?id=15821404>
54. Walker UA, Byrne E. The therapy of respiratory chain encephalomyopathy: a critical review of the past and current perspective. *Acta Neurol Scand* 1995;92:273-280. <http://amedeo.com/lit.php?id=8848932>
55. Walker UA, Auclair M, Lebrecht D, Kornprobst M, Capeau J, Caron M. Uridine abrogates the adverse effects of stavudine and zalcitabine on adipose cell functions. *Antivir Ther* 2004a;9:L21-L22.
56. Walker UA, Bickel M, Lütke Volksbeck SI et al. Evidence of nucleoside analogue reverse transcriptase inhibitor-associated genetic and structural defects of mitochondria in adipose tissue of HIV-infected patients. *J AIDS* 2002a;29:117-121. <http://amedeo.com/lit.php?id=11832679>
57. Walker UA, Setzer B, Venhoff N. Increased long-term mitochondrial toxicity in combinations of nucleoside analogue reverse-transcriptase inhibitors. *AIDS* 2002b;16:2165-2173. <http://amedeo.com/lit.php?id=12409738>



58. Walker UA, Venhoff N, Koch E, Olschewski M, Schneider J, Setzer B. Uridine abrogates mitochondrial toxicity related to nucleoside analogue reverse transcriptase inhibitors in HepG2 cells. *Antivir Ther* 2003;8:463-470. <http://amedeo.com/lit.php?id=14640394>
59. Walker DM, Poirier MC, Campen MJ et al. Persistence of mitochondrial toxicity in hearts of female B6C3F1 mice exposed in utero to 3'-azido-3'-deoxythymidine. *Cardiovasc Toxicol* 2004a, 4:133-153. <http://amedeo.com/lit.php?id=15371630>
60. Walker UA, Langmann P, Miehle N, Zilly M, Klinker H, Petschner F. Beneficial effects of oral uridine in mitochondrial toxicity. *AIDS* 2004b;18:1085-1086. <http://amedeo.com/lit.php?id=15096820>
61. Walker UA, Bäuerle J, Laguno M et al. Depletion of mitochondrial DNA in liver under antiretroviral therapy with didanosine, stavudine, or zalcitabine. *Hepatology* 2004c, 39:311-317. <http://amedeo.com/lit.php?id=14767983>
62. Walker UA, Langmann P, Miehle N, Zilly M, Klinker H, Petschner F. Beneficial effects of oral uridine in mitochondrial toxicity. *AIDS* 2004d, 18:1085-1086. <http://amedeo.com/lit.php?id=15096820>



## 9. HIV Resistance Testing

Eva Wolf

The development of resistant viral strains is one of the main reasons for failure of antiretroviral therapy. If there is resistance to several drug classes, the number of alternative treatment regimens is limited and the virological success of subsequent therapies, or so-called salvage regimens, may be short-lived.

The rapid development of resistant variants is due to the high turnover of HIV – approximately 10 million new viral particles are produced every day (Perelson 1996) – and the exceptionally high error rate of HIV reverse transcriptase. This leads to a high mutation rate and constant production of new viral strains, even in the absence of treatment. In the presence of antiretroviral drugs, resistant strains are selected for as the dominant species (Drake 1993).

### Assays for resistance testing

There are two established assays for measuring resistance or sensitivity of HIV to specific antiretroviral drugs – the genotypic and the phenotypic resistance tests (Wilson 2003). Both assays are commercially available. Examples of commercially available genotypic resistance tests are: HIV-1 TrueGene™, *Bayer Healthcare Diagnostics*; or ViroSeq™, *Celera Diagnostics/Abbott Laboratories*. Other genotypic resistance assays such as Virco™TYPE HIV-1, *Virco*, GenoSure (Plus), *LabCorp*, or GeneSeq, *Monogram Biosciences (formerly Virologic)* are established in the laboratories of the respective manufacturers and are used in clinical trials. Phenotypic resistance tests include: Antivirogram™, *Virco*; PhenoSense™, *Monogram Biosciences (formerly ViroLogic)*; and Phenoscript™, *Viralliance*.

Disadvantages of phenotypic testing include the lengthy procedure and high expense of the assay. The cost of genotyping ranges from 350 to 500 Euro, depending on the assay and laboratory used. It is approximately twice as much for phenotyping.

The drawback with both methods is that a minimum amount of virus is necessary in order to perform the test. A viral load below 500-1,000 copies/ml often does not allow any detection of resistance.

### Phenotyping

Phenotypic resistance tests involve direct quantification of drug sensitivity. Viral replication is measured in cell cultures under the selective pressure of increasing concentrations of antiretroviral drugs and is compared to viral replication of wild-type virus.

Drug concentrations are expressed as IC<sub>50</sub> values (50 % inhibitory concentration). The IC<sub>50</sub> is the concentration of drug required to inhibit viral replication by 50 %. The sensitivity of the virus is expressed as the IC<sub>50</sub> divided by the IC<sub>50</sub> of a wild type reference virus (fold-change value) and compared to the so-called cut-off value. The cut-off value indicates by which factor the IC<sub>50</sub> of an HIV isolate can be

increased in comparison to that of the wild type, whilst still being classified as sensitive. Determination of the cut-off is crucial for the interpretation of the results!

### **Cut-off definitions**

Three different cut-offs are currently used. The *technical cut-off* is a measure of the methodological variability of the assay. The *biological cut-off* involves the inter-individual variability of wild type virus isolates from ART-naïve HIV patients. If the IC<sub>50</sub> is below the biological cut-off, virological success is very likely. However, an IC<sub>50</sub> above the biological cut-off does not allow prediction of the virological response to a drug.

In contrast, the *clinical cut-off* indicates up to which levels of IC<sub>50</sub> virological success can still be expected. Clinical cut-offs for boosted protease inhibitors (PIs) are higher than cut-offs for unboosted PIs. But, through boosting with ritonavir, drug levels may overcome certain levels of resistance.

The VircoType and PhenoSense reports have included lower and upper clinical cut-offs (Bacheler 2004). The lower clinical cut-off is the fold-change in IC<sub>50</sub> and indicates a slightly reduced virological response. A fold-change above the upper clinical cut-off indicates resistance, and a fold-change between the two cut-offs indicates partial resistance.

## **Genotyping**

Genotypic assays are based on the analysis of mutations associated with resistance. These are determined by the direct sequencing of the amplified HIV genome or by specific hybridization techniques with wild-type or mutant oligonucleotides. Genotype tests only detect viral mutants comprising at least 20 to 30 % of the total population and provide an indirect measurement of drug resistance. Mutations that are associated with reduced sensitivity have been well described for most HIV drugs, but the high number of different resistance patterns, which may also contain compensatory mutations, makes the determination of the degree of resistance to particular drugs difficult.

The interpretation of genotypic resistance patterns is based on the correlation between the geno- and the phenotype. Data is available from *in vitro* studies, clinical observations and duplicate testing, in which genotypically localized mutations were investigated for phenotypic resistance.

### **Ruled-based interpretation systems**

For the phenotypic interpretation of genotypic mutation patterns, rule-based interpretation systems are commonly available. Expert panels (e.g. the French ANRS AC11 Resistance group) have developed algorithms based on literature and clinical outcomes.

### **Virtual phenotype**

One further approach to predict phenotype from genotype is the so-called "virtual" phenotype: a genotypic mutation pattern is interpreted with the aid of a large database of samples of paired genotypic and phenotypic data (Winters 2004). The genotypic interpretation systems vircoTYPE and geno2pheno are both based on a

virtual phenotype. For the VircoType interpretation, genotypes matching the patient's virus were identified through a database search. The  $IC_{50}$  results of each of the matching viruses were averaged, thus producing the probable phenotype of the patient's virus. In the updated version of VircoTYPE, all mutations and mutation pairs of the patient's virus that contribute to specific drug resistance according to the new multiple linear regression modeling are identified. They are then included in the respective linear regression model using the drug specific resistance weight factors of the observed mutations and mutation pairs. The outcome variable of the regression model is the predicted fold-change comparing the  $IC_{50}$  of the patient's virus to the  $IC_{50}$  of the wild type reference virus.

In addition, machine learning approaches such as decision trees and support vector machines (as implemented by the geno2pheno system) can be applied to predict phenotypic drug resistance (Beerenwinkel 2003, Larder 2005).

Some of the most important databases for resistance profiles and interpretational systems are available free of charge on the following websites:

- Stanford-Database: <http://hiv.net/link.php?id=24>
- Los Alamos-Database: <http://hiv.net/link.php?id=25>
- geno2pheno: <http://hiv.net/link.php?id=26>
- HIV Genotypic Drug Resistance Interpretation – ANRS AC11:  
<http://hiv.net/link.php?id=138>
- HIV-GRADE: <http://www.hiv-grade.de/cms/grade/homepage.html>

Some commercial suppliers of resistance tests also provide interpretation guidelines for their systems (e.g. TruGene™, GeneSeq™, Retrogram™).

The discussion about genotypic resistance in this chapter focuses on the sequencing of the reverse transcriptase, the protease and the env (gp41) gene and on the respective resistance patterns that emerge with treatment.

Most data are derived from patients with subtype B viruses (representing only 12 % of the worldwide HIV-infected population). However, by now, non-subtype B viruses have also been investigated for the development of resistance (van de Vijver 2004). Resistance pathways and patterns may differ in the various subtypes.

## Background

Within the nucleotide sequences of the HIV genome, a group of three nucleotides, called a codon, defines a particular amino acid in the protein sequence. Resistance mutations are described using a number, which shows the position of the relevant codon, and two letters: the letter preceding the number corresponds to the amino acid specified by the codon at this position in the wild-type virus; the letter after the number describes the amino acid that is produced from the mutated codon. M184V indicates a mutation in codon 184 of the reverse transcriptase gene leading to a valine for methionine substitution in the reverse transcriptase enzyme.

## Mechanisms of resistance

**Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs)** are pro-drugs that only become effective after being converted to triphosphates. Nucleotide analogs require only two instead of three phosphorylation steps. Phosphorylated NRTIs compete with naturally occurring dNTPs (deoxynucleotide triphosphates). The incorporation of a phosphorylated NRTI into the proviral DNA blocks further elongation of the proviral DNA and leads to interruption of the chain.

There are two main biochemical mechanisms that lead to NRTI resistance (De Mendoza 2002). *Sterical inhibition* is caused by mutations enabling the reverse transcriptase to recognize structural differences between NRTIs and dNTPs. Incorporation of NRTIs is then prevented in favor of dNTPs (e.g. in the presence of the mutations M184V, Q151M, L74V, or K65R; Naeger 2001, Clavel 2004).

*Phosphorylysis* via ATP (adenosine triphosphate) or pyrophosphate leads to the excision of the NRTIs already incorporated in the growing DNA chain. This is the case with the following mutations: M41L, D67N, K70R, L210W, T215Y and K219Q (Meyer 2000). Phosphorylysis leads to cross-resistance between NRTIs, the degree of which may differ between substances (AZT, d4T > ABC > ddC, ddI > 3TC). Contrary to the excision mutations, K65R leads to a decreased excision of all NRTIs when compared to the wild type, resulting in a greater stability once incorporated. For K65R, the combined effect of its opposing mechanisms - on the one hand decreased incorporation and on the other, decreased excision - results in a decreased susceptibility to most NRTIs but an increased susceptibility to AZT (White 2005).

**Non-nucleoside RT inhibitors (NNRTIs)** also inhibit the viral enzyme reverse transcriptase (RT). NNRTIs are small molecules that bind to the hydrophobic pocket close to the catalytic domain of the RT. Mutations at the NNRTI binding site reduce the affinity of the NNRTI to the RT and thus lead to loss of antiviral activity of NNRTI and treatment failure.

**Protease inhibitors (PIs)** hinder the cleavage of viral precursor gal-pol-polyprotein by the enzyme protease, thereby producing immature, non-infectious viral particles. PI resistance usually develops slowly, as several mutations must first accumulate. This is also referred to as the genetic barrier. For PIs, a distinction is made between *major* (or *primary*) and *minor* (or *secondary*) mutations.

*Major mutations* are responsible for phenotypic resistance. They are selected for early on in the process of resistance to one drug, and are located within the active site of the target enzyme, the HIV protease. They reduce the ability of the protease inhibitor to bind to the enzyme. Major or primary mutations may also lead to a reduced activity of the protease. *Minor mutations* (often referred to as secondary mutations) are located outside the active site and usually occur after major mutations. Minor mutations can be particularly found at polymorphic sites of non-B subtypes. Minor mutations compensate for the reduction in viral fitness caused by major mutations (Johnson 2004). However, the differentiation of major and minor mutations can only provide an approximate estimation of the degree of resistance.

**Fusion inhibitors** differ from NRTIs, NNRTIs and PIs, which block the replication of HIV in the infected cell. Instead, fusion inhibitors prevent HIV from entering its target cells. The first step in cell entry occurs when the HIV envelope glycoprotein,

gp120, binds to the CD4 receptor and the chemokine coreceptors, CCR5 or CXCR4, of the target cell. Interactions between the two heptad repeat regions HR1 and HR2 within the transmembrane glycoprotein subunit gp41 lead to a conformational change in gp41, enable fusion of the viral and cellular membranes and thereby entry of HIV into the host cell.

The fusion inhibitor T-20 (enfuvirtide), a synthetic peptide consisting of 36 amino acids, mimics the C-terminal HR2 domain of gp41 and competitively binds to HR1. Thus, interactions between HR1 and HR2 are blocked and the conformational change of gp41 that is necessary for fusion of virions to host cells is inhibited. A single amino acid substitution in gp41 can reduce the efficacy of T-20.

## Transmission of resistant HIV strains

The prevalence of mutations already present in treatment-naïve patients differs among demographic regions. High prevalences of more than 20 % were observed in big US cities with large populations of homosexual men and a long period of access to antiretroviral treatment. In San Francisco, the resistance prevalence among patients with acute or recent infections was between 18 and 27 % during the period 1996-2002. Comparably high rates of resistance transmission were observed in Madrid from 1997 to 1999 and in 2002 (Grant 2003, Wensing 2003a, De Mendoza 2003). In a multicentric evaluation in 40 US cities, 14 % of 371 isolates from treatment-naïve patients had at least one resistance mutation (Ross 2004).

In 2003, the first results of the CATCH-Study (which later transferred into the European SPREAD study) were published. Data from more than 1,600 newly diagnosed HIV patients from 17 European countries were evaluated. From 1996 until 2002, the prevalence of primary mutations was 10 % (Wensing 2003b). These data were confirmed by the SPREAD study, which gathered data from 2,008 patients (Strategy to Control Spread of HIV Drug Resistance). The goal of the SPREAD study is to monitor primary resistances in newly infected and ART-naïve HIV patients and their clinical implications. Whereas the proportion of NRTI mutations, which was 13 % at the start of the observation, decreased by half over time, the frequency of NNRTI resistance mutations increased from 2.3 to 9.8 %. The frequency of PI resistance remained stable at 3-4 %. From 1996 to 2002, primary resistance was mainly observed in subtype B infections. Resistance mutations were present in 12.9 % of patients with subtype B infection compared to only 4.8 % in non-B subtypes. However, an increase over time was also observed in non-B subtypes (from 2.0 % in 1996-1998 to 8.2 % in 2000-2001).

Transmission rates of resistant virus are possibly underestimated in the different regions. Minority viral populations below 25 % are not detected by standard sequencing techniques. Forty-nine virus isolates of acute seroconverters were tested for the presence of L90M, K103N and M184V by quantitative real-time polymerase chain reaction using specific oligonucleotides for the three key resistance mutations. In 10 out of 49 patients these mutants were detected. In 5 of these 10 patients the detected population represented a minor viral quasi-species and was not detected by direct sequencing (Metzner 2005).

Transmitted primary resistance can persist for a long time. In a Spanish seroconverters study, 10 patients with primary resistance mutations were followed over a median time of 41 months. The following mutations were detected: T215Y in three isolates, T215N/S/C in four, M41L in six, L74V in one, I54V in one, V82S/A in two, and L90M in two isolates. In only three of 10 cases (partial) reversion (of T215Y) was observed: T215Y revertants (T215S) were detected in two patients, and wild type virus was detected in one patient after 7 years (De Mendoza 2005).

The clinical relevance of primary resistance has been shown in several studies. Transmitted resistance mutations can limit further treatment options and reduce treatment response rates (Harzic 2002, Little 2002, Riva 2002, Hanna 2001, Balotta 2000). A retrospective study with 202 patients showed that, when initiating treatment without information on pre-existing resistance, patients with pre-existing mutations had a slower treatment response and a higher risk of treatment failure (Little 2002). However, on careful consideration of any pre-existing resistance, primary treatment success is often possible (Oette 2005, Little 2002, Hanna 2001).

In early 2005, a patient from New York caused a sensation. He was infected with a multidrug resistant virus harboring 7 relevant NRTI mutations, 2 NNRTI mutations and 12 PI mutations. After 4 to 20 months (the exact time of infection is unknown), the patient's CD4 count had decreased to 80 cells/ $\mu$ l. The replication capacity of this resistant virus was comparable to that of wild type virus. Only two available antivirals, T-20 and efavirenz were still active. Even though the transmission of multidrug resistant virus and rapid clinical progression are rare events, this case report demonstrates the possible clinical consequences of primary drug resistance (Markowitz 2005).

## Clinical studies

The clinical importance of performing resistance testing before making changes to the therapy, has been demonstrated in several prospective, controlled studies, both for genotypic (Durant 1999, Baxter 1999, Tural 2001) and phenotypic resistance testing (Cohen 2000). Patients whose physicians had access to information about any existing mutations before the therapy was changed usually had more significant decreases in the viral load than patients in whom treatment was changed without knowledge of the resistance profile.

With regard to the ongoing development of new antivirals with different resistance profiles, the clinical relevance of resistance testing might be even higher than that shown in studies several years ago.

## Interpretation of genotypic resistance profiles

### NRTIs

For several NRTIs, such as lamivudine, and for NNRTIs, a high degree of resistance can develop following only a single mutation (Havlir 1996, Schuurman 1995). For this reason, such drugs should only be used in highly effective regimens. However, the lamivudine-specific mutation, M184V, also reduces viral replication capacity (often referred to as reduced viral fitness) by 40–60 % (Sharma 1999,



Miller 2003). After 52 weeks on lamivudine monotherapy, the viral load remained 0.5 logs below the initial levels, despite early development of the M184V mutation (Eron 1995). When compared to treatment interruptions, continuous monotherapy with 3TC delays virological and immunological deterioration (Castagna 2005).

FTC (emtricitabine) has the same resistance pattern as 3TC. Treatment failure is associated with the M184V mutation (van der Horst 2003).

Thymidine analog mutations, mostly referred to as "TAMs", include the mutations M41L, D67N, K70R, L210W, T215Y and K219Q, which were initially observed on zidovudine therapy (Larder 1989). It is now known that these mutations can also be selected for by stavudine (Loveday 1999). Three or more TAMs are associated with a relevant reduction in the sensitivity to stavudine (Shulman 2001, Calvez 2002, Lafeuillade 2003). The term "NAMs" (nucleoside analog mutations) is also used instead of TAMs, as these mutations are associated with cross-resistance to all other nucleoside analogs, with the exception of 3TC and FTC.

Viral mutants, isolated from patients in whom treatment on AZT, 3TC or abacavir has failed, usually have a measurable phenotypic resistance. Two TAMs result in a 5.5-fold, three TAMs in a 29-fold and four TAMs or more in a > 100-fold reduced sensitivity to zidovudine. The use of abacavir in cases where there is a more than 7-fold reduction in sensitivity no longer promises success. This usually requires at least 3 TAMs in addition to the M184V mutation (Harrigan 2000).

A score, which has been developed in the context of the Narval study (ANRS 088), seems to have a good predictive value concerning virological response to abacavir. Virological response is poor if 5 mutations out of M41L, D67N, L74V, M184V, L210W, and T215Y/F are present (Brun-Vézinet 2003).

The virological response to ddI depends on the number of specific TAMs. In the Jaguar study, using treatment-experienced patients, T215Y/F, M41L and L210W – to a lesser extent also D67N and K219Q – were associated with a reduced efficacy (Marcelin 2005). The virological response was not dependent on the presence of the mutations M184V and K70R.

The development of a measurable phenotypic resistance to d4T or ddI has been observed less frequently, and has been more moderate in character (Larder 2001). The clinical cut-off for stavudine lies below the biological cut-off of 1.8. Presumably, this is also the case for ddI (Shulman 2004). Since most interpretation systems still use biological cut-offs, phenotypic resistance might be underestimated.

Clinical data indicates that tenofovir is effective even in the presence of NAMs such as D67, K70R, T215Y/F or K219Q/E. However, if three or more NAMs include M41L or L210W, a reduced virological response can be expected (Antinou 2003).

The lamivudine-associated mutation, M184V, as well as the L74V mutation, observed on didanosine treatment, and the NNRTI-specific mutations, L100I and Y181C, may have an antagonistic effect on the development of resistance (Vandamme 1999).

M184V induces re-sensitization to AZT, resulting in a 50-60 % reduction of IC<sub>50</sub>. Re-sensitization to stavudine results in a 30 % reduction of IC<sub>50</sub>. However, re-sensitization is of clinical relevance only if there are no more than three other AZT- or d4T-associated mutations present (Shafer 1995, Naeger 2001, Underwood 2005).

In one genotypic and phenotypic resistance study consisting of 9,000 samples, a combination of M41L, L210W and T215Y decreased the susceptibility to AZT by more than 10-fold in 79 % of cases. If the M184V mutation was also present, only 52 % had a more than 10-fold decreased susceptibility to AZT (Larder 1999a). The M184V mutation also increases the sensitivity to tenofovir (Miller 2001, Miller 2004a). In contrast, the presence of M184V plus multiple NAMs or mutations at positions 65, 74 or 115 increased the resistance to ddI, ddC and abacavir (Harrigan 2000, Lanier 2001).

So-called multidrug resistance (MDR) to all nucleoside analogs – except lamivudine – is established if one of the following combinations occurs: T69SSX, i.e. the T69S mutation plus an insertion of 2 amino acids (SS, SG or SA) between positions 69 and 70, plus a AZT-associated mutation or Q151M, plus a further MDR mutation (V75I, F77L or F116Y; Masquelier 2001).

The MDR mutation, Q151M, alone leads to intermediate resistance to AZT, d4T, ddI, ddC and abacavir (Shafer 2002a). It is relatively uncommon, with a prevalence of less than 5 %. In contrast, Q151M does not lead to the loss of activity of tenofovir. Instead, the T69S insertion induces an approximately 20-fold increase in the resistance to tenofovir (Miller 2001, Miller 2004a).

The insertion T69SSX together with the mutation M184V, as well as the mutation Q151M together with M184V, leads to a 70 % reduction in the viral replication capacity (Miller 2003).

The L74V mutation emerges on ddI or abacavir and leads to a 2- to 5-fold increase in the resistance to ddI (Winters 1997). The loss of efficacy by a factor of around 2-3 for abacavir is not considered clinically relevant and requires further mutations (Tisdale 1997, Brun-Vézinet 2003).

L74V/I with or without M184V leads to a reduction in  $IC_{50}$  of about 70 %; phenotypic susceptibility increases by a factor of 3 (Underwood 2005).

The K65R mutation can emerge while on tenofovir, abacavir or ddI and leads to an intermediate resistance to tenofovir, abacavir, ddI, 3TC, FTC, and possibly d4T (Shafer 2002a, Garcia-Lerma 2003). There is no cross-resistance with AZT (Miller 2004b). In antiretroviral combinations containing AZT, the incidence of the K65R mutation is lower. K65R emerges very rarely together with TAMs on the same genome. K65R and TAMs represent two antagonistic resistance pathways. Genotypes harboring K65R and L74V are also very unlikely (Wirten 2005). Since abacavir was mostly used as part of the combination AZT+3TC+abacavir or in the presence of multiple TAMs, K65R was rare prior to the use of tenofovir. Similar to large clinical trials using tenofovir within divergent (PI- or NNRTI-containing) treatment regimens, the incidence of K65R stabilized at  $\leq 5$  %. However, virological failure of triple NRTI combinations such as Tenofovir+3TC+ABC or Tenofovir+3TC+ddI was often associated with the development of K65R (Farthing 2003, Gallant 2003, Landman 2003, Jemsek 2004). The main reason for the high failure rate seems to be the low genetic barrier of these regimens: the emergence of K65R induces a loss of sensitivity to all three drugs.

K65R increases the sensitivity to AZT and induces a resensitization to zidovudine in the presence of (few) TAMs. K65R alone increases sensitivity to AZT by a factor of 2, together with M184V/I by a factor of 2.5 (White 2005, Underwood 2005).

Vice versa, TAMs reduce the K65R-associated resistance to TDF, abacavir, ddI and ddC (Parikh 2004).

As with M184V, the mutation K65R leads to a reduction in the viral replication capacity. This is not the case with TAMs or L74V/I. The median replication capacities for viruses with M184V/I (n=792), K65R (n=72) or L74V/I (n=15) alone were 68 % (P < 0.0001), 72 % (p < 0.0001) and 88 % (p=0.16), respectively. With the exception of M184V, NAMs did not change the replication capacities of viruses containing K65R or L74V/I (McColl 2005). If both mutations, K65R and M184V, were present, a replication of only 29 % was observed (Miller 2003).

The V75T mutation, which is associated with an approximately 5-fold increase in the resistance to d4T, ddI and ddC, is only rarely observed (Lacey 1994).

In large patient cohorts, quantitative measurements of sensitivity have shown that up to 29 % of NRTI-experienced patients have a hypersusceptibility to NNRTIs (i.e. a reduction in the inhibitory concentration by a factor of 0.3 - 0.6). A reduction in the AZT or 3TC sensitivity correlated with an increased NNRTI susceptibility. Shulman et al. pheno- and genotyped 444 virus isolates from NRTI-experienced patients. Mainly the reverse transcriptase mutations T215Y, H208Y and V118I were predictive for efavirenz hypersusceptibility. A database analysis of pair wise geno- and phenotypes showed NNRTI hypersusceptibility for TAMs and for non-thymidine analog-associated NAMs. Hypersusceptibility for efavirenz was detected for 1-2 TAMs, multiple TAMs plus M184V and for non-thymidine analog-associated NAMs such as K65R, T69X, M184V and in particular for K65R+M184V (Whitcomb 2000, Shulman 2004b, Coakley 2005a). However, these results have not influenced treatment strategies so far.

## NNRTIs

A single mutation can confer a high degree of resistance to one or more NNRTIs. The relatively frequent K103N mutation leads to a 20- to 30-fold increase in resistance to all available NNRTIs (Petropoulos 2000). Further use of the approved first generation NNRTIs in the presence of this mutation is therefore not recommended.

V106A leads to a 30-fold increase in nevirapine resistance and intermediate efavirenz resistance. In contrast to subtype B viruses, the mutation V106M is more frequent in subtype C viruses. V106M is associated with high-level resistance not only to nevirapine but also to efavirenz (Grossman 2004).

A98G (which occurs more frequently in subtype C viruses), K101E and V108 lead to low-grade resistance to all available NNRTIs. Intermediate resistance to efavirenz and delavirdine and low-grade resistance to nevirapine result from the L101I mutation. Y181C/I causes a 30-fold increase in nevirapine resistance, and response to efavirenz is only temporary. G190A is associated with a high degree of nevirapine resistance and an intermediate resistance to efavirenz and delavirdine. G190S and Y188C/L/H are mutations that result in a high degree of nevirapine and efavirenz resistance (Shafer 2002b, De Mendoza 2002).

## PIs

The spectrum of PI mutations is very large. Although there is a moderate to high degree of cross-resistance between PIs, the primary mutations are relatively specific

for the individual drugs. If treatment is changed early on to another PI combination, i.e. before the accumulation of several mutations, the subsequent regimen may still be successful.

Most data on primary mutations selected for first in the presence of a PI, are derived from studies using unboosted PIs. In studies evaluating first-line triple therapy with boosted lopinavir, fosamprenavir or saquinavir, no patient with virological failure developed detectable major PI mutations, and the incidence of minor mutations was low (Gulick 2004, DeJesus 2004, Anaworanich 2005). Development of primary PI resistance in patients failing boosted PI therapy is rare (Conradie 2004, Friend 2004, Lanier 2003, Coakley 2005b).

Polymorphisms at positions 10, 20, 36, 63, 71, 77 and 93 do not lead to resistance per se, but compensate for the reduced protease activity caused by primary mutations (Nijhuis 1999).

The typical **nelfinavir**-specific resistance profile, with the D30N primary mutation and further secondary mutations, results in only a low degree of cross-resistance to other PIs (Larder 1999a). Virological failure on nelfinavir can also be associated with the emergence of L90M (Craig 1999). In subtype B viruses, treatment with nelfinavir generally leads to the emergence of D30N or M46I plus N88S. In subtype C, G and AE viruses, however, the mutations L90M and I84V occur more frequently. One reason for these different resistance pathways is the prevalence of natural polymorphisms: whereas the polymorphism M36I is present in only 30 % of subtype B viruses, M36I is present in 70 – 100 % of non-B subtypes (Gomes 2002, Gonzales 2004, Grossman 2004, Sugiura 2002, Hackett 2003).

A comparison between the replicative capacities of a virus with a single protease mutation (D30N or L90M) and that of the wild-type virus, demonstrated a significant loss of viral fitness in the presence of the D30N mutation selected by nelfinavir. In contrast, the L90M mutation only leads to a moderate reduction in the replicative capacity, which can be compensated for by the frequently occurring L63P polymorphism. Conversely, the L63P mutation hardly influences the reduced replicative capacity of D30N mutants (Martines 1999).

G48V mainly emerges on unboosted **saquinavir** and leads to a 10-fold decrease in the susceptibility to saquinavir – in combination with L90M it results in a high degree (over 100-fold) of decreased susceptibility to saquinavir (Jakobson 1995). Yet generally, any 4 mutations out of L10I/R/V, G48V, I54V/L, A71V/T, V77A, V82A, I84V and L90M, are required to reduce the efficacy of RTV-boosted saquinavir (Valer 2002). Marcelin et al. (2005) re-evaluated the genotypic interpretation of saquinavir resistance in a retrospective analysis of 138 PI-experienced patients. In this study, the mutations 10F/I/M/R/V, 15A/V, 20I/M/R/T, 24I, 62V, 73ST, 82A/F/S/T, 84V, and 90M were identified as those most strongly associated with virological response. The presence of 3 to 4 mutations was associated with a reduced response to boosted saquinavir.

Unboosted **indinavir** and/or ritonavir mainly selected for the major mutation V82A(T/F/S), which in combination with other mutations led to cross-resistance to other PIs (Shafer 2002c). Mutants that frequently developed on indinavir, harboring M46I, L63P, V82T, I84V or L10R, M46I, L63P, V82T, I84V, were just as fit as the wild-type virus.

The resistance pattern of **amprenavir** and **fosamprenavir** is somewhat different to that of other first generation PIs. In the course of failing treatment with unboosted amprenavir or fosamprenavir, the following mutations have been selected: I54L/M, I50V or V32I plus I47V – often together with the mutation M46I. In a small study, the corresponding virus isolates showed full susceptibility to saquinavir and lopinavir (Chapman 2004, Ross 2003).

A loss of sensitivity to (fos-) amprenavir and all other approved PIs can be anticipated if the mutation I84V (together with other mutations) is present (Snowden 2000, Schmidt 2000, Kempf 2001, Maguire 2002, MacManus 2003). Researchers on a small study, with 49 PI-experienced patients who were switched to boosted amprenavir, developed an algorithm that also included resistance mutations at positions 35, 41, 63 and 82 (Marcelin 2003). Several mutations are required to confer resistance to boosted (fos-)amprenavir (Table 3).

The response to **lopinavir** in PI-experienced patients correlates with the number of any of the following mutations: L10F/I/R/V, K20M/R, L24I, M46I/L, F53L, I54L/T/V, L63P, A71I/L/T/V, V82A/F/T, I84V, and L90M (Kempf 2000, Kempf 2001). Five mutations or less result in an increase in the IC<sub>50</sub> by a median factor of 2.7, with 6-7 mutations this factor is 13.5, and with at least 8 mutations it is 44. The good efficacy, even with several mutations, is due to the high plasma levels of boosted lopinavir, which – for the wild-type virus – are > 30-fold above the EC<sub>50</sub> concentration during the entire dose interval (Prado 2002).

In studies where boosted lopinavir is part of a first-line regimen, no primary PI-mutations have been observed to date. Very few case reports of primary lopinavir resistance have been published. In one patient, virological failure was associated with the occurrence of V82A followed by the mutations V32I, M46M/I and I47A. Phenotyping resulted in high-grade lopinavir resistance. Susceptibility to other PIs, especially saquinavir, was not affected (Friend 2004, Parkin 2004). In a second case, with some pre-existing polymorphisms (M36I, L63P and I93L), the mutations 54V and V82A, followed by L33F, were selected (Conradie 2004).

A different algorithm to predict lopinavir resistance also includes mutations at novel amino acid positions. Viruses with any 7 mutations out of L10F/I, K20I/M, M46I/L, G48V, I50V, I54A/M/S/T/V, L63T, V82A/F/S, G16E, V32I, L33F, E34Q, K43T, I47V, G48M/V, Q58E, G73T, T74S, and L89I/M display approximately a 10-fold increase in IC<sub>50</sub>. Mutations at positions 50, 54 and 82 particularly affect the phenotypic resistance (Parkin 2003, Jimenez 2005).

In-vivo selection of lopinavir resistance was described in 54 PI-experienced patients failing treatment with boosted lopinavir. Mutations at positions 82, 54 and 46 frequently emerged. Mutations such as L33F, I50V or V32I together with I47V/I were selected less frequently. New mutations at positions 84, 90 and 71 were not observed (Mo 2005).

Recently, the mutation I47A, which has rarely been observed since lopinavir has become available, has been associated with lopinavir resistance. I47A reduces the binding affinity to lopinavir and results in an 86- to > 110-fold loss in sensitivity. In contrast, I47A leads to saquinavir hypersusceptibility due to an enhanced binding affinity to saquinavir (Kagan 2005).

A German team reported that even with 5 - 10 PI-mutations, which normally confer broad PI-cross-resistance, resensitization is possible. The mutation L76V, which is primarily selected for by lopinavir and rarely by amprenavir, is associated with high-grade resistance to lopinavir and (fos-) amprenavir, but can lead to resensitization to atazanavir and saquinavir (Müller 2004).

The resistance profile of **atazanavir**, an aza-peptidomimetic PI, partly differs to that of other PIs. In patients, in whom first-line treatment with atazanavir failed, the mutation I50L – often combined with A71V – was primarily observed. On the one hand, I50L leads to a loss of sensitivity to atazanavir; on the other hand, I50L leads to an increased susceptibility to other currently approved PIs. Mutants harboring I50L plus A71V showed a 2- to 9-fold increase in the binding affinity to the HIV protease. Even in the presence of other major and minor PI mutations, I50L can increase susceptibility to other PIs (Colonna 2002, Colonna 2003, Weinheimer 2005, Yanchunas 2005). In PI-experienced patients, the I50L mutation was selected for in only one third of patients failing atazanavir (Colonna 2004).

In PI-experienced patients, at least partial cross-resistance to atazanavir is probable (Snell 2003). The accumulation of PI-mutations such as L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, L90M, and, in particular, I84V, leads to a loss of sensitivity to atazanavir. In the expanded access program using unboosted atazanavir, the number of the respective PI mutations correlated with the change in viral load. For unboosted atazanavir, the threshold for resistance is generally met if 3 or 4 PI mutations are present; for boosted atazanavir, resistance is likely with 6 or more mutations (Colonna 2004, Johnson 2004, Gianotti 2005).

**Tipranavir**, the first non-peptidic protease inhibitor, shows good efficacy against viruses with multiple PI mutations. In phenotypic resistance testing, 90 % of isolates with a high degree of resistance to ritonavir, saquinavir, indinavir and nelfinavir were still sensitive to tipranavir (Larder 2000). Although tipranavir has shown activity against viruses with up to 20 - 25 PI mutations, a reduced sensitivity can be anticipated if three or more PRAMs (protease inhibitor-resistance associated mutations) – also referred to as UPAMs (universal PI-associated mutations) – are present (Cooper 2003). PRAMs include the following mutations: L33I/V/F, V82A/F/L/T, I84V and L90M. On the other hand, a sufficient short term reduction in the viral load of 1.2 logs was seen after two weeks on treatment with boosted tipranavir plus an optimized backbone in patients with at least three PRAMs, compared to only 0.2-0.4 logs with boosted amprenavir, saquinavir or lopinavir plus an optimized backbone (Mayers 2004).

In a pooled analysis of 291 patients in three Phase II trials, the mutations, V82T, V82F and V82L, but not L90M or V82A, were associated with tipranavir-resistance. The mutations, D30N, I50V and N88D, were associated with an increased susceptibility for tipranavir (Kohlbrenner 2004).

In pooled data analyses of Phase II and III studies, the mutations I10V, I13V, K20M/R/V, L33F, E35G, M36I, N43T, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D and I84V were identified as being associated with a virological response to tipranavir (Schapiro 2005). The presence of 4 to 7 mutations leads to a reduced tipranavir response. The accumulation of 8 or more mutations is predictive for tipranavir failure.

In vitro, L33F and I84V were the first mutations that were selected for by tipranavir, but the respective loss in sensitivity was only two-fold. At the end of the selection experiments, virus isolates with 10 mutations (L10F, I13V, V32I, L33F, M36I, K45I, I54V, A71V, V82L, I84V) and sensitivity reduced by 87-fold, were observed (Doyon 2005). Similar resistance mutations were also found in clinical isolates of tipranavir-treated patients (L10F, I13V, K20M/R/V, L33F, E35G, M36I, K43T, M46L, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D, I84V) (Croom 2005).

## Fusion inhibitors

This section focuses on **enfuvirtide (T-20)** resistance. The gp41 genome has positions of high variability and highly conserved regions. There seems to be no differences between B and non-B subtypes. Polymorphic sites are observed in all regions of gp41. The heptad repeat 2 (HR2) region has the highest variability. Primary T-20 resistance is a rare phenomenon (Wiese 2005).

Loss of efficacy is generally accompanied by the appearance of mutations at the T-20 binding site, which is the heptad repeat 1 (HR1) region of gp41. In particular, mutations at positions 36 to 45 emerge, most frequently with substitutions at positions 36, 38, 40, 42, 43 and 45 (e.g. G36D/E/S, 38A/M/E, Q40H/K/P/R/T, N42T/D/S, N43D/K, or L45M/L).

The IC<sub>50</sub> fold change, which ranges from  $\leq 10$  to several hundred, depends on the position of the mutation and the substitution of the amino acid. The decrease in susceptibility is higher for double mutations than for a single mutation. For double mutations such as G36S+L44M, N42T+N43K, N42T+N43S or Q40H+L45M, a fold-change of  $> 250$  has been observed. Additional mutations in HR2 and envelope regions also contribute to T-20 resistance (Sista 2004, Mink 2005). In clinical isolates with G36D as a single mutation a 4- to 450-fold decrease in susceptibility was found. In the isolate showing a 450-fold decrease in susceptibility, a heterozygote change at position 126 in HR2 was observed (N/K).

In a small study, 6 out of 17 patients with virological failure developed the mutation S138A in the HR2 region of gp41 in addition – mostly combined with a mutation at position 43 in the HR1 region and a range of HR2 sequence changes at polymorphic sites (Xu 2004).

The replication capacity (RC) in the presence of HR1 mutations is markedly reduced when compared to wild type virus with a relative order of RC wild type  $> N42T > V38A > N42T, N43K \approx N42T, N43S > V38A, N42D \approx V38A, N42T$  (Lu 2004). Viral fitness and T-20 susceptibility are inversely correlated ( $r=0.99$ ,  $p < 0.001$ ) (Lu 2004).

## New drugs

The following chapter describes the resistance profiles of several newly developed antiretroviral drugs.

- **TMC 125 (Etravirine)**, a second generation NNRTI, is effective against both wild-type viruses of HIV-1 M subtypes A, B, C, D, F and recombinant forms AE, AG and DF, and viruses with NNRTI mutations such as L100I, K103N, Y188L and/or G190A/S. In 12 out of 16 patients who had failed on previous

efavirenz- or nevirapine-based regimens, viral load was reduced by more than 0.5 logs after 7 days on TMC 125 (Gazzard 2002). *In vitro* attempts showed that drug resistance to TMC 125 emerges significantly slower than to nevirapine or efavirenz. High-level resistance to TMC 125 emerged after 5 *in vitro* passages. The dominant virus population contained the RT mutations V179F (a new variant at this position) and Y181C. Further mutations were E138K, Y188H and M230L (Brillant 2004).

In a study on 25 virus isolates with one or two NNRTI-associated mutations, etravirine was still active in 18 isolates with only a small change in IC<sub>50</sub> (less than 4-fold). A more than 10-fold increase in IC<sub>50</sub> was observed in only 3 virus isolates. The corresponding resistance profile noted in one case was the combination L100I+K103N, and in the two other cases the single mutations Y181I and F227C. However, the prevalence of these mutations is small (3 % for L100I+K103N and ≤ 0.5 % for Y181I and F227C; Andries 2004). Etravirine has a higher genetic barrier than other NNRTIs due to its flexible binding to the reverse transcriptase. High-grade resistance is observed only with multiple mutations. After several *in-vitro* passages, the dominant virus population showed the RT mutation V179F (a new variant at this position) and Y181C. Further mutations that were selected for *in vitro* were L100I, E138K, Y188H, G190E, M230L, M230L and V179I (Brillant 2004, Vingerhoets 2005).

- **TMC 278 (Rilpivirin)**, another second generation NNRTI, also has a unique profile of activity against NNRTI-resistant viruses and displays a high genetic barrier comparable to that of TMC125 (Goebel 2005, De Béthune 2005).
- **TMC 114 (Darunavir, Prezista™)**, a non-peptidic protease inhibitor, shows good activity, both *in vitro* and *in vivo*, against a broad spectrum of PI resistant viruses. *In vitro*, resistance emerged more slowly against TMC 114 than against nelfinavir, amprenavir or lopinavir. Resistance against TMC 114 occurred with the mutations R41T and K70E, which were also associated with a reduction in replication capacity. One selected virus with a 10-fold reduction in susceptibility to TMC 114 showed a < 10-fold reduction to the current PIs (atazanavir not assessed), with the exception of saquinavir (De Meyer 2002, De Meyer 2003, De Meyer 2005).

Pooled data analyses of the clinical studies Power 1, 2 and 3 showed that the presence of specific baseline mutations was associated with reduced virological response (i.e. V11I, V32I, L33F, I47V, I50V, I54L/M, G73S, L76V, I84V, and L89V). The mutations V32I, L33F, I47V, I54L or L89V developed in ≥ 10 % of virological failures (De Béthune 2006). A preceding failure on lopinavir was not predictive for virological outcome on TMC 114 (Koh 2003, Peters 2004). Out of 447 PI-experienced patients with a median number of 8 PI mutations and a median of 3 major PI mutations, 30 to 47 % of patients in the different TMC114 study arms had a viral load of < 50 copies/ml compared to only 10 % in the control PI arm (Katlama 2005).

## Summary

With the aid of HIV resistance tests, antiretroviral treatment strategies can be improved. Pharmaco-economic studies have shown that these tests are also cost-



effective both in treatment-experienced and in ART-naïve patients (Sax 2005, Corzilius 2004, Weinstein 2001).

For several years, national and international HIV treatment guidelines have recommended the use of resistance testing (Salzberger 2004, US DHHS 2005, BHIVA 2005). With some delay, resistance tests are now covered by public health insurances in several countries.

Currently, both genotypic and phenotypic tests show good intra- and inter-assay reliability. However, the interpretation of genotypic resistance profiles has become very complex and requires constant updating of the guidelines. The determination of the thresholds associated with clinically relevant phenotypic drug resistance is crucial for the effective use of (virtual) phenotypic testing.

Even if treatment failure requires the consideration of other causal factors, such as compliance of the patient, metabolism of drugs and drug levels, resistance testing is of great importance in antiretroviral therapy.

Finally, it needs to be emphasized that – even with the benefit of well-interpreted resistance tests – only experienced HIV practitioners should start, stop or change antiretroviral therapy with respect to the clinical situation and the psychosocial context of the patient.

## Resistance tables

Table 1: Mutations on the reverse transcriptase gene leading to NRTI resistance (modified from ANRS – AC 11 Groupe Resistance, Sep. 2005, <http://hiv.net/link.php?id=138>, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2005))

RTI	Resistance mutations
Zidovudine	T215 Y/F (esp. with other TAMs) ≥ 3 of the following mutations: M41L, D67N, K70R, L210W, K219Q/E Q151M (esp. with A62V/F77L/F116Y) T69SSX (insertion)*
Stavudine	V75M/S/A/T T215Y/F (usually in combination with other TAMs) ≥ 3 TAMs* Q151M (esp. with A62V/F77L/F116Y) T69SSX (insertion)*
Abacavir	≥ (4-) 5 of the following mutations M41L, D67N, L74V, M184V, L210W T215Y/F K65R+L74V+115F+ M184V Q151M (esp. with A62V/F77L/F116Y) T69SSX (insertion)* K65R (resistance possible)
Lamivudine	M184V/I T69SSX (insertion)* K65R
Emtricitabine	M184V/I T69SSX (insertion)* K65R
Didanosine	L74V, esp. with T69D/N or TAMs Q151M (esp. with A62V/F77L/F116Y) T69SSX (insertion)* K65R (partial resistance, esp. with T69D/N) T215Y/F and ≥ 2 of the following mutations: M41L, D67N, K70R, L210W, K219Q/E
Tenofovir DF	T69SSX (insertion)* ≥ 3 TAMs with M41L or L210W (in part only partial resistance) (≥ 3 -) 6 of the following mutations: M41L, E44D, D67N, T69D/N/S, L74V, L210W, T215Y/F K65R (partial resistance)

TAMs = thymidine analog mutations

\* T69SSX in combination with T215Y/F and other TAMs leads to a high degree of resistance to all NRTIs and tenofovir

Table 2: Mutations on the reverse transcriptase gene leading to NNRTI resistance (modified from ANRS – AC 11 Groupe Resistance, Sep. 2005, <http://hiv.net/link.php?id=138>, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2005))

Mutations associated with a high degree of resistance in **bold font**.

<b>NNRTIs</b>	<b>Resistance mutations</b>
Efavirenz	L100I <b>K101E</b> <b>K103N(H/S/T)</b> <b>V106M</b> V108I (with other NNRTI mutations) Y181C(I) <b>Y188L(C)</b> <b>G190S/A (C/E/Q/T/V)</b> P225H (with other NNRTI mutations) <b>M230L</b>
Nevirapine	A98G L100I K101E <b>K103N (H/S/T)</b> <b>V106A/M</b> V108I <b>Y181C/I</b> <b>Y188C/L/H</b> <b>G190A/S (C/E/Q/T/V)</b> <b>M230L</b>
Delavirdine	A98G <b>L100I</b> K101E <b>K103N/T</b> <b>V106A/M</b> <b>Y181C</b> <b>Y188C/L</b> M230L <b>P236L</b>

## 348 HIV Resistance Testing

Table 3: Mutations on the protease gene leading to PI resistance (modified from ANRS – AC 11 Groupe Resistance, Sep. 2005, <http://hiv.net/link.php?id=138>, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2005))

PIs	Relevant resistance mutations and patterns	Further mutations associated with resistance
Indinavir	M46I/L V82A/F/S/T I84A/V when boosted with ritonavir, several mutations are required for a relevant loss of sensitivity	L10I/V/F, K20R/M/I, L24I, V32I, M36I, I54V/L/M/T, A71V/T, G73S/A, V77I and L90M ≥ 2 PRAMs*
Saquinavir	≥ 4 of the following mutations: L10I/R/V, G48V, I54V/L, A71V/T, V77I, V82A, I84V and L90M or ≥ 3-4 of: 10F/I/M/R/V, 15A/V, 20I/M/R/T, 24I, 62V, 73ST, 82A/F/S/T, 84V, and 90M	≥ 2 PRAMs*
Nelfinavir	D30N I84A/V N88S/D L90M	V82A/F/S/T and at least 2 of the following mutations: L10I, M36I, M46I/L, I54V/L/M/T, A71V/T, V77I ≥ 2 PRAMs*
Fosamprenavir	I50V (esp. with M46I/L) V32I plus I47V I54L/M I84V	
Fosamprenavir/Ritonavir (700/100 mg BID) or Amprenavir/Ritonavir (600/100 mg BID)	≥ 6 of the following mutations: L10F/I/V, K20M/R, E35D, R41K, I54V/L/M, L63P, V82A/F/T/S, I84V V32I plus I47V	G73S
Lopinavir/r	≥ 8 of the following mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, G73S, V82A/F/T, I84V, L90M	5-7 of the following mutations: L10F/I/R/V, K20M/R, L24I, V32I, L33F, M46I/L, I47V/A, I50V, F53L, I54L/T/V, L63P, A71I/L/V/T, G73S, V82A/F/T, I84V, L90M ≥ 2 PRAMs*
Atazanavir and Atazanavir/Ritonavir (300/100 mg QD)	I50L – frequently in combination with A71V – ≥ 3-4 of the following mutations for unboosted atazanavir and ≥ 6 of the following mutations for boosted atazanavir: L10I/V/F, K20R/M/I, L24I, L33I/F/V, M36I/L/V, M46I/L, M48V, I54V/L, L63P, A71V/T/I, G73C/S/T/A, V82A/F/S/T, I84V and L90M	N88S ≥ 2 PRAMs*

Tipranavir	<p>≥ 3 PRAMs*</p> <p>≥ 8 of the following mutations:</p> <p>I10V, I13V, K20M/R/V, L33F, E35G, M36I, N43T, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D und I84V</p>	<p>L10I/V, K20M/L/T, M46I, I54V, V82A/F/L/T</p> <p>4-7 of the following mutations: I10V, I13V, K20M/R/V, L33F, E35G, M36I, N43T, I47V, I54A/M/V, Q58E, H69K, T74P, V82L/T, N83D und I84V</p>
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\*PRAMs (protease inhibitor resistance associated mutations) include the following mutations: L33I/F/V, V82A/F/S/T, I84V and L90M. They lead to high PI cross-resistance.

Table 4: Mutations on the env (gp41) gene leading to T-20 resistance (modified from ANRS – AC 11 Groupe Resistance, Sep. 2005, <http://hiv.net/link.php?id=138>, and Drug Resistance Mutations Group of the International AIDS Society-USA (Johnson 2005))

Fusion inhibitors	Resistance mutations
T-20	<p>G36A/D/E/S/V</p> <p>38A/M/E/K/V</p> <p>Q40H/K/P/R/T</p> <p>N42T/D/S</p> <p>N43D/K/H/S</p> <p>N42T+N43S</p> <p>N42T+N43K</p> <p>G36S+L44M</p> <p>L44M</p> <p>L45M/L/Q</p>

The reduction in susceptibility is generally higher for double mutations than for single mutations.

## References

- Ananworanich J, Ruxrungtham K, Sirivichayakul S, et al. Resistance mutations in ARV-naïve patients treated with ritonavir-boosted saquinavir. Abstract WePe4.4C12, 3rd IAS 2005, Rio de Janeiro, Brazil. <http://www.hiv-knowledge.org/iasmmaps/transcri.htm>
- Andries K, Azijn H, Thielemans T, et al. TMC125, a novel next-generation nonnucleoside reverse transcriptase inhibitor active against nonnucleoside reverse transcriptase inhibitor-resistant HIV type 1. *Antimicrob Agents Chemother* 2004; 48: 4680-6. Abstract: <http://amedeo.com/lit.php?id=15561844>
- Antoniou T, Park-Wyllie L, Tseng AL. Tenofovir: A nucleotide analog for the management of HIV infection. *Pharmacotherapy* 2003; 23:29-43. <http://www.medscape.com/viewarticle/448280>
- Bachelor L, Winters B, Harrigan R, et al. Estimation of phenotypic clinical cut-offs for virco® Type HIV-1 through meta analyses of clinical trial and cohort data. Abstract 138, 7th Int Congress on Drug Ther HIV Infection. *Antiviral Therapy* 2004; 9:S154. [http://www.aegis.com/conferences/hivdrw/2004/Session\\_6.pdf](http://www.aegis.com/conferences/hivdrw/2004/Session_6.pdf)
- Balotta C, M Violin M, Facchi G, et al. Risk of HAART failure is related to the presence of transmitted mutations conferring resistance to RT inhibitors in HIV-1 newly infected individuals. 4th Int Workshop on HIV Drug Resistance & Treatment Strategies 2000, Sitges, Spain. *Antivir Ther* 2000;5 Suppl 3: 144.
- Baxter JD, Mayers DL, Wentworth DN, et al. A randomized study of antiretroviral management based on plasma genotypic antiretroviral resistance testing in patients failing therapy AIDS 2000; 14: Abstract: <http://amedeo.com/lit.php?id=10894268>
- Beerenwinkel N, Däumer M, Oette M, et al. Geno2pheno: estimating phenotypic drug resistance from HIV-1 genotypes. *Nucleic Acids Research* 2003, 13: 3850-3855. <http://nar.oupjournals.org/cgi/content/full/31/13/3850>
- BHIVA guidelines for the treatment of HIV-infected adults with antiretroviral therapy 2005. Available at: <http://www.bhiva.org/guidelines/2005/HIV/HIV05frameset.html>

## 350 HIV Resistance Testing

9. Brilliant J, Klumpp K, Swallow S, Cammack N, Heilek-Snyder G. In vitro resistance development for a second-generation NNRTI: TMC125. *Antivir Ther* 2004; 9:S20. [http://www.natap.org/2004/HIVDRW/hivdrw\\_13.htm](http://www.natap.org/2004/HIVDRW/hivdrw_13.htm)
10. Brun-Vézinet F, Descamps D, Ruffault A, et al. Clinically relevant interpretation of genotype for resistance to abacavir. *AIDS* 2003; 17: 1795-802. Abstract: <http://amedeo.com/lit.php?id=12891065>
11. Calvez V, Costagliola D, Descamps D, et al. Impact of stavudine phenotype and thymidine analogues mutations on viral response to stavudine plus lamivudine in ALTIS 2 ANRS trial. *Antivir Ther* 2002; 7:211-8. <http://amedeo.com/lit.php?id=12487389>
12. Castagna A, Danise A, Menzo S, et al. E-184V study: lamivudine monotherapy vs treatment interruption in failing HIV-1 infected subjects, harbouring the M184V mutation: 48-week final results. Abstract WeFo0204, 3rd IAS 2005, Rio de Janeiro, Brazil.
13. Chaix C, Grenier-Sennelier C, Durant J, et al. Economic Evaluation of drug resistance genotyping for the adaptation of treatment in HIV-infected patients in the VIRADAPT study. Abstract 105, 3rd International Workshop on HIV Drug Resistance and Treatment Strategies 1999, San Diego, CA, USA.
14. Chapman TM, Plosker GL, Perry CM. Fosamprenavir: a review of its use in the management of antiretroviral therapy-naïve patients with HIV infection. *Drugs* 2004; 64: 2101-24. <http://amedeo.com/lit.php?id=15341507>
15. Clavel F, Hance AJ. HIV Drug Resistance. *N Engl J Med* 2004; 350:1023-1035
16. Coakley E, Parkin N. Contribution of non-thymidine analog nucleoside RT inhibitor associated mutations to phenotypic hypersusceptibility to efavirenz. Abstract 704, 12th CROI 2005a, Boston, USA. Abstract: <http://www.retroconference.org/2005/cd/Abstracts/25329.htm>
17. Coakley E, Mass M, Parkin N. Atazanavir resistance in a protease inhibitor-naïve patient treated with atazanavir/ritonavir associated with development of high-level atazanavir resistance and the N88S mutation in protease. Abstract 716, 12th CROI 2005b, Boston, USA. Abstract: <http://www.retroconference.org/2005/cd/Abstracts/25331.htm>
18. Cohen C, Kessler H, Hunt S, et al. Phenotypic resistance testing significantly improves response to therapy: final analysis of a randomized trial (VIRA 3001). *Antiviral Ther* 2000, 5 (supl 3): 67. Abstract 84.
19. Colonna RJ, McLaren C and Kelleher T. Pathways to Atazanavir resistance in treatment-experienced patients on Atazanavir containing regimens. Abstract 3.1, 2nd Eur HIV Drug Res Workshop 2004, Rom.
20. Colonna RJ, Friborg J, Rose RE, et al. Identification of amino acid substitutions correlated with reduced atazanavir susceptibility in patients treated with atazanavir-containing regimens. *Antiviral Ther* 2002, 7:S4. Abstract 4.
21. Colonna RJ, Rose R, Ciani C, et al. Emerge of resistance and maintenance of susceptibility to other PI is associated with an I50L substitution in HIV protease. Abstract 597, 10th CROI 2003, Boston, USA.
22. Conradie F, Sanne I, Venter W, et al. Failure of lopinavir-ritonavir (Kaletra-) containing regimen in an antiretroviral-naïve patient. *AIDS* 2004, 18:1041-1085.
23. Cooper D, Hall D, Jayaweera D, et al. Baseline phenotypic susceptibility to tipranavir/ritonavir is retained in isolates from patients with multiple protease inhibitor experience (BI 1182.52). Abstract 596, 10th CROI 2003, Boston, USA.
24. Corzillius M, Mühlberger N, Sroczynski G, et al. Cost effectiveness analysis of routine use of genotypic antiretroviral resistance testing after failure of antiretroviral treatment for HIV. *Antivir Ther* 2004; 9:27-36. <http://amedeo.com/lit.php?id=15040534>
25. Craig C, Goddard C, Whittaker L, et al. HIV-1 genotype and phenotype during dual therapy (NV15436 sub-study). Abstract 103, 7th ECCATH 1999, Lisbon, Portugal.
26. Croom KF, Keam SJ. Tipranavir: a ritonavir-boosted protease inhibitor. *Drugs* 2005; 65: 1669-77 Abstract: <http://amedeo.com/lit.php?id=16060700>
27. De Béthune M, Andries K, Azijn H, et al. TMC278, a new potent NNRTI, with an increased barrier to resistance and good pharmacokinetic profile. Abstract 556, 12<sup>th</sup> CROI 2005, Boston, USA. Abstract: [http://www.retroconference.org/Search\\_Abstract\\_2005/Default.aspx](http://www.retroconference.org/Search_Abstract_2005/Default.aspx)
28. De Béthune MP, de Mever S, van Baelen B, et al. Impact of baseline and on-treatment PI mutations on TMC114 susceptibility and virological outcome: preliminary analysis of data from treatment experienced patients in Power 1, 2 and 3 studies. Abstract 51, 4th European HIV Drug Resistance Workshop 2006, Monte Carlo, Monaco.
29. DeJesus E, Iye P, Schurmann D, et al. The Solo Study: Sustained virological response in subjects receiving GW433908/Ritonavir with high viral load and low CD4 cell counts at study entry. Abstract TuPeB 4503, 15th IAC 2004; Bangkok. [http://www.iasociety.org/ejias/show.asp?abstract\\_id=2168446/](http://www.iasociety.org/ejias/show.asp?abstract_id=2168446/)
30. De Mendoza C, Gallego O, Soriano V. Mechanisms of resistance to antiviral drugs – clinical implications. *AIDS Rev* 2002, 4: 64-82. <http://amedeo.com/lit.php?id=12152520>

31. De Mendoza C, Rodriguez C, Corral A, et al. Evidence for a different transmission efficiency of viruses with distinct drug-resistant genotypes. Abstract 130, XII Int HIV Drug Res Workshop 2003, Los Cabos, Mexico. [http://www.mediscover.net/Journals\\_PDF/Session5.pdf](http://www.mediscover.net/Journals_PDF/Session5.pdf)
32. De Mendoza C, Rodriguez C, Corral A, et al. Long-term persistence of drug resistance mutations after HIV seroconversion. Abstract PE3.5/3. 10<sup>th</sup> European AIDS Conference (EACS) 2005, Dublin, Ireland.
33. De Meyer S, Azijn H, Van Ginderen M, et al. In vitro selection experiments demonstrate an increased genetic barrier to resistance development to TMC114 as compared with currently licensed protease inhibitors. Abstract 5, XI International HIV Drug Resistance Workshop 2002, Seville, Spain.
34. De Meyer S, Van Marck H, Veldemann J, et al. Antiviral activity of TMC114, a potent next-generation protease inhibitor, against >4000 recent recombinant clinical isolates exhibiting a wide range of (protease inhibitor) resistance profiles. *Antiviral Therapy* 2003; 8:S20
35. De Meyer S, Azijn H, Surleraux D, et al. TMC114, a novel HIV type 1 protease inhibitor active against protease inhibitor-resistant viruses, including a broad range of clinical isolates. *Antimicrob Agents Chemother* 2005; 49: 2314-21. Abstract: <http://amedeo.com/lit.php?id=15917527>
36. Doyon L, Tremblay S, Bourgon L, Wardrop E, Cordingley MG. Selection and characterization of HIV-1 showing reduced susceptibility to the non-peptidic protease inhibitor tipranavir. *Antiviral Res* 2005; 68: 27-35. Abstract: <http://amedeo.com/lit.php?id=16122817>
37. Drake JW. Rates of spontaneous mutation among RNA viruses. *PNAS* 1993, 90:4171-4175. <http://amedeo.com/lit.php?id=8387212>
38. Durant J, Clevenbergh P, Halfon P, et al. Drug-resistance genotyping in HIV-1 therapy: the VIRADAPT randomised controlled trial. *Lancet* 1999, 353:2195-99. <http://amedeo.com/lit.php?id=10392984>
39. Eberle J, Goebel FD, Postel N, et al. Amino acid changes in the HIV-1/gp41 HR1 region associated with ongoing viral replication selected by T-20 (enfuvirtide) therapy. Abstract 43, 3rd European Conference on Viral Diseases 2004, Regensburg, Germany.
40. Eron JJ, Benoit SL, Jemsek J, et al. Treatment with lamivudine, zidovudine, or both in HIV-positive patients with 200 to 500 CD4+ cells per cubic millimeter. *N Engl J Med* 1995, 333:1662-1669. <http://amedeo.com/lit.php?id=7477218>
41. Farthing C, Khanlou H, Yeh V, et al. Early virologic failure in a pilot study evaluating the efficacy of once daily abacavir (ABC), lamivudine (3TC), and tenofovir DF (TDF) in treatment naïve HIV-infected patients. LB 46, 2nd IAS Meeting 2003, Paris, France.
42. Friend J, Parkin N, Liegler T, et al. Isolated lopinavir resistance after virological rebound of a ritonavir/lopinavir-based regimen. *AIDS* 2004, 18:1965-1970.
43. Gallant JE, Rodriguez A, Weinberg W, et al. Early non-response to tenofovir DF (TDF) + abacavir (ABC) and lamivudine (3TC) in a randomized trial compared to efavirenz (EFV) + ABC and 3TC: ESS30009 unplanned interim analysis. LB H-1722a, 43rd ICAAC 2003, Chicago, USA.
44. Garcia-Lerma JG, MacInnes H, Bennett D, et al. A novel genetic pathway of HIV type 1 resistance to stavudine mediated by the K65R mutation. *J Virol*. 2003;77:5685-5693. <http://intapp.medscape.com/px/medlineapp/getdoc?pmi=12719561&cid=med>
45. Gianotti N, Seminari E, Guffanti M, et al. Evaluation of atazanavir C<sub>trough</sub>, atazanavir genotypic inhibitory quotient, and baseline HIV genotype as predictors of a 24-week virological response in highly drug-experienced, HIV-infected patients treated with unboosted atazanavir. *New Microbiol* 2005; 28: 119-25. Abstract: <http://amedeo.com/lit.php?id=16035256>
46. Goebel F, Yakovlev A, Pozniak A, et al. TMC 278: Potent anti-HIV activity in antiretroviral therapy-naïve patients. Abstract 160, 12th CROI 2005, Boston, USA. Abstract: [http://www.retroconference.org/Search\\_Abstract\\_2005/Default.aspx](http://www.retroconference.org/Search_Abstract_2005/Default.aspx)
47. Gomes P, Diogo I, Goncalves MF, et al. Different pathways to nelfinavir genotypic resistance in HIV-1 subtypes B and G. Abstract 46, 9th CROI 2002; Seattle, Washington.
48. Gonzalez LM, Brindeiro RM, Aguiar RS, et al. Impact of nelfinavir resistance mutations on in vitro phenotype, fitness, and replication capacity of HIV type 1 with Subtype B and C Proteases. *Antimicrob Agents Chemother* 2004, 48: 3552-55. <http://aac.asm.org/cgi/content/full/48/9/3552>
49. Grant GM, Liegler T, Spotts G, et al. Declining nucleoside reverse transcriptase inhibitor primary resistance in San Francisco, 2000-2002. Abstract 120, XII International HIV Drug Resistance Workshop, 2003, Los Cabos, Mexico.
50. Grossman Z, Istomin V, Averbuch D, et al; Israel AIDS Multi-Center Study Group. Genetic variation at NNRTI resistance-associated positions in patients infected with HIV-1 subtype C. *AIDS* 2004a; 18: 909-15. <http://amedeo.com/lit.php?id=15060438>
51. Grossman Z., Paxinos EE., Averbuch D, et al. Mutation D30N is not preferentially selected by human immunodeficiency virus type 1 subtype C in the development of resistance to nelfinavir. *Antimicrob Agents Chemother* 2004b; 48:2159-2165. <http://amedeo.com/lit.php?id=15155216>

## 352 HIV Resistance Testing

52. Gulick RM, da Silva B, McMillan F, et al. Lopinavir/ritonavir (LPV/r)-based therapy in antiretroviral (ARV)-naïve, HIV-infected patients: 6-Year Follow-up of Study 720. Abstract P28, VII International Congress on Drug Therapy in HIV Infection 2004, Glasgow, UK.
53. Hackett J Jr, Swanson P, Drews B, et al. Natural polymorphisms associated with resistance to protease inhibitors in non-subtype B HIV-1 strains. Abstract 814, 2nd IAS 2003, Paris, France.
54. Hanna GJ, Balaguera HU, Steger KA, et al. Drug-selected and non-clade B pol genotypes in chronically HIV-1-infected antiretroviral-naïve adults: response to antiretroviral therapy. *Antiviral Ther* 2001, 6(suppl1):111-112. Abstract 144. <http://www.medscape.com/viewarticle/436299>
55. Harrigan PR, Stone C, Griffin P, et al. Resistance profile of the HIV type 1 reverse transcriptase inhibitor abacavir (1592U89) after monotherapy and combination therapy. *J Infect Dis* 2000, 181:912-920. <http://amedeo.com/lit.php?id=10720512>
56. Harzic M, Pellegrin I, Deveau C, et al. Genotypic drug resistance during HIV-1 primary infection in France (1996-1999): frequency and response to treatment. *AIDS* 2002; 16: 793-796. <http://amedeo.com/lit.php?id=11964538>
57. Havlir DV, Gamst A, Eastman S, Richman DD. Nevirapine-resistant HIV: kinetics of replication and estimated prevalence in untreated patients. *J Virol* 1996, 70:7894-7899. <http://amedeo.com/lit.php?id=8892912>
58. Jacobsen H, Yasargil K, Winslow DL, et al. Characterization of HIV type 1 mutants with decreased sensitivity to protease inhibitor Ro 31-8959. *Virology* 1995, 206:527-534. <http://amedeo.com/lit.php?id=7831807>
59. Jemsek J, Hutcherson P, and E Harper E. Poor virologic responses and early emergence of resistance in treatment naïve, HIV-infected patients receiving a once daily triple nucleoside regimen of didanosine, lamivudine, and tenofovir. DF. Abstract 51, 11th CROI 2004, San Francisco, USA. <http://64.251.206.31/2004/AbstractSearch/AbstractSearch.aspx>
60. Jimenez JL, Resino S, Martinez-Colom A, Bellon JM, Munoz-Fernandez MA. Mutations at codons 54 and 82 of HIV protease predict virological response of HIV-infected children on salvage lopinavir/ritonavir therapy. *J Antimicrob Chemother* 2005; Abstract: <http://amedeo.com/lit.php?id=16195257>
61. Johnson VA, Brun-Vézinet F, Bonaventura C, et al. Update of the drug resistance mutations in HIV-1: Fall 2005. Special contribution - drug resistance mutations in HIV. *Top HIV Med* 2005, 13:115-131. <http://www.iasusa.org/pub/topics/2005/issue4/125.pdf>.
62. Kagan RM, Shenderovich MD, Heseltine PN, Ramnarayan K. Structural analysis of an HIV-1 protease I47A mutant resistant to the protease inhibitor lopinavir. *Protein Sci* 2005; 14: 1870-8. Abstract: <http://amedeo.com/lit.php?id=15937277>
63. Katlama C, Berger D, Bellon N. Efficacy of TMC114/r in 3-Class experienced patients with limited treatment options: 24-week planned interim analysis of 2 96-week multinational dose-finding trials. Abstract 164LB, 12th CROI 2005, Boston, USA. Abstract: <http://www.retroconference.org/2005/cd/Abstracts/25794.htm>
64. Kempf D, Xu Y, Brun S, et al. Baseline genotype and phenotype do not predict response to ABT-378/Ritonavir in PI-experienced patients at 24 and 48 weeks. Abstract 731, 7th CROI 2000, San Francisco, USA.
65. Kempf DJ, Isaacson JD, King MS, et al. Identification of genotypic changes in HIV protease that correlate with reduced susceptibility to the protease inhibitor lopinavir among viral isolates from protease inhibitor-experienced patients. *J Virol* 2001, 75:7462-9. <http://amedeo.com/lit.php?id=11462018>
66. Koh Y, Nakata H, Maeda K, et al. TMC114 (UIC96017): a novel nonpeptidic protease inhibitor potent against multi-PI resistant HIV in vitro. Abstract 553, 10th CROI 2003, Boston, USA.
67. Kohlbrenner V, Hall D, Schapiro J, et al. Development of a tipranavir mutation score: analysis of protease mutations associated with phenotypic drug susceptibility and antiviral response in Phase II clinical trials. *Antivir Ther*. 2004;9:S143 (Abstract 19). [http://www.aegis.com/conferences/13thHIVDrugResWkshop/Session\\_5.pdf](http://www.aegis.com/conferences/13thHIVDrugResWkshop/Session_5.pdf)
68. Lacey SF, Larder BA. Novel mutation (V75T) in HIV type 1 reverse transcriptase confers resistance to 2',3'-didehydro-2',3'- dideoxythymidine in cell culture. *Antimicrob Agents Chemother* 1994, 38:1428-1432. <http://amedeo.com/lit.php?id=7522429>
69. Lafeuillade A, Tardy JC. Stavudine in the face of cross-resistance between HIV-1 nucleoside reverse transcriptase inhibitors: a review. *AIDS Rev* 2003, 5:80-6. <http://amedeo.com/lit.php?id=12876897>
70. Landman R, Peytavin G, Descamps D, et al. Low genetic barrier to resistance is a possible cause of early virologic failures in once-daily regimen of abacavir, lamivudine, and tenofovir: the tonus study. Abstract 52, 11th CROI 2004, San Francisco, USA. <http://www.retroconference.org/2004/cd/Abstract/52.htm>
71. Lanier ER, Kubota M, Yau L, et al. Diverse effects of NRTI-associated mutations on resistance to abacavir, stavudine and zidovudine in the ZORRO trial. Abstract 1761, 41st ICAAC 2001, Chicago, USA. <http://hiv.net/link.php?id=27>



72. Lanier ER, Irlbeck D, Liao Q et al. Emergence of resistance-associated mutations over 96 weeks of therapy in subjects initiating ABC/3TC + d4T, EFV or APV/r. Abstract H-910, 43rd ICAAC 2003, Chicago, USA.
73. Larder B, de Vroey V, Dehertogh P, et al. Predicting HIV-1 phenotypic resistance from genotype using a large phenotype-genotype relational database. Abstract 106, 7th ECCATH 1999, Lisbon, Portugal.
74. Larder BA, Kemp SD. Multiple mutations in HIV-1 reverse transcriptase confer high-level resistance to zidovudine (AZT). *Science* 1989, 246:1155-1158. <http://amedeo.com/lit.php?id=2479983>
75. Larder BA, Bloor S. Analysis of clinical isolates and site-directed mutants reveals the genetic determinants of didanosine resistance. *Antivir Ther* 2001, 6:38.
76. Larder B, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. *AIDS* 2000; 14: 1943-8. <http://amedeo.com/lit.php?id=10997398>
77. Larder B, Revell A, Wang D, et al. Neural networks are more accurate predictors of virological response to HAART than rules-based genotype interpretation systems. Abstract PE3.4/13. 10<sup>th</sup> EACS, Dublin, Ireland.
78. Little SJ, Holle S, Routy JP, et al. Antiretroviral-drug resistance among patients recently infected with HIV. *N Engl J Med* 2002; 347:385-394. <http://content.nejm.org/cgi/content/short/347/6/385>
79. Loveday C, Devereux H, Hockett L, Johnson M. High prevalence of multiple drug resistance mutations in a UK HIV/AIDS patient population. *AIDS* 1999, 13: 627-628. <http://amedeo.com/lit.php?id=10203393>
80. Loutfy MR, Montaner JSG, Raboud JM, et al. Genotypic resistance assay for entire gp-41 sequence with identification of gp-41 polymorphisms in enfuvirtide-naïve patients and new gp-41 mutations in patients failing enfuvirtide. Abstract WeORB1292, 15th IAC 2004; Bangkok. [http://www.iasociety.org/ejias/show.asp?abstract\\_id=2173981](http://www.iasociety.org/ejias/show.asp?abstract_id=2173981)
81. Lu J, Sista P, Giguël F, Greenberg M, Kuritzkes DR. Relative replicative fitness of human immunodeficiency virus type 1 mutants resistant to enfuvirtide (T-20). *J Virol* 2004; 78: 4628-37. <http://amedeo.com/lit.php?id=15078945>
82. Maguire M, Shortino D, Klein A, et al. Emergence of resistance to protease inhibitor amprenavir in HIV type 1-infected patients: selection of four alternative viral protease genotypes and influence of viral susceptibility to coadministered reverse transcriptase nucleoside inhibitors. *Antimicrob Agents Chemother* 2002; 46:731-8. <http://aac.asm.org/cgi/content/full/46/3/731?view=full&pmid=11850255>
83. Marcelin AG, Lamotte C, Delaunay C, et al. Genotypic inhibitory quotient as predictor of virological response to ritonavir-amprenavir in HIV type 1 protease inhibitor-experienced patients. *Antimicrob Agents Chemother* 2003; 47: 594-600. <http://amedeo.com/lit.php?id=12543665>
84. Marcelin AG, Flandre P, Pavie J, et al. Clinically relevant genotype interpretation of resistance to didanosine. *Antimicrob Agents Chemother* 2005; 49: 1739-44. Abstract: <http://amedeo.com/lit.php?id=15855490>
85. Marcelin AG, Flandre P, de Mendoza C, et al. Interpretation of genotype for resistance to boosted saquinavir in HIV-1-infected PI-experienced patients. Abstract 54, 4th European HIV Drug Resistance Workshop 2006, Monte Carlo, Monaco.
86. Markowitz M, Mohri H, Mehandru S, et al. Infection with multidrug resistant, dual-tropic HIV-1 and rapid progression to AIDS: a case report. *Lancet* 2005; 365: 1031-8. Abstract: <http://amedeo.com/lit.php?id=15781098>
87. Martinez-Picado J, Savara AV, Sutton L, et al. Replicative fitness of protease inhibitor-resistant mutants of HIV type 1. *J Virol* 1999, 73:3744-3752. <http://amedeo.com/lit.php?id=10196268>
88. Masquelier B, Race E, Tamalet C, et al. Genotypic and phenotypic resistance patterns of HIV type 1 variants with insertions or deletions in the reverse transcriptase (RT): multicenter study of patients treated with RT inhibitors. *Antimicrob Agents Chemother* 2001, 45:1836-42. <http://amedeo.com/lit.php?id=11353634>
89. Mayers D, Leith J, Valdez H, et al. Impact of three or four protease mutations at codons 33, 82, 84 and 90 on 2 week virological responses to tipranavir, lopinavir, amprenavir and saquinavir all boosted by ritonavir in Phase 2B trial BI 1182.51. *Antivir Ther* 2004;9:S163.
90. McColl D, Parkin N.T., Miller M, Mertenskötter T. Charakterisierung von klinischen Virus-Isolaten mit L74V oder K65R in einer großen Resistenzdatenbank. Abstract P126, 10. Deutscher und 16. Österreichischer AIDS Kongress 2005, Vienna, Austria.
91. Metzner KJ, Rauch P, Walter H, et al. Detection of minor populations of drug-resistant HIV-1 in acute seroconverters. *AIDS* 2005; 19: 1819-25. Abstract: <http://amedeo.com/lit.php?id=16227789>
92. Meyer PR, Matsuura SE, Schinazi RF, So AG, Scott WA. Differential removal of thymidine nucleotide analogues from blocked DNA chains by HIV reverse transcriptase in the presence of physiological concentrations of 2'-deoxynucleoside triphosphates. *Antimicrob Agents Chemother* 2000, 44:3465-72. <http://amedeo.com/lit.php?id=11083661>

## 354 HIV Resistance Testing

93. Miller MD, Margot N, Lu B, et al. Genotypic and phenotypic predictors of the magnitude of response to tenofovir disoproxil fumarate treatment in antiretroviral-experienced patients. *J Infect Dis* 2004a; 189: 837-46. Epub 2004 Feb 10. Abstract: <http://amedeo.com/lit.php?id=14976601>
94. Miller MD. TAMs and Tenofovir. *AIDS Reviews* 2004b, 6:22-33. [http://www.aidsreviews.com/2004/rev01/art\\_03.html](http://www.aidsreviews.com/2004/rev01/art_03.html)
95. Miller MD, Margot NA, Hertogs K, Larder B, Miller V. Antiviral activity of tenofovir (PMPA) against nucleoside-resistant clinical HIV samples. *Nucleosides Nucleotides Nucleic Acids* 2001, 20:1025-8. <http://amedeo.com/lit.php?id=11562951>
96. Miller MD, White KL, Petropoulos CJ, et al. Decreased replication capacity of HIV-1 clinical isolates containing K65R or M184V RT mutations. Abstract 616, 10th CROI 2003, Boston, USA.
97. Mink M, Mosier SM, Janumpalli S, et al. Impact of HIV type 1 gp41 amino acid substitutions selected during enfuvirtide treatment on gp41 binding and antiviral potency of enfuvirtide in vitro. *J Virol* 2005, 79: 12447-12454. Abstract: <http://jvi.asm.org/cgi/content/abstract/79/19/12447>
98. Mo H, King MS, King K, et al. Selection of resistance in protease inhibitor-experienced, HIV type 1-infected subjects failing lopinavir- and ritonavir-based therapy: Mutation patterns and baseline correlates. *J. Virol.* 79: 3329-3338. Abstract: <http://jvi.asm.org/cgi/content/abstract/79/6/3329>
99. Monachetti A, Castagna A, Bagnarelli P. Genetic and phenotypic characteristics of enfuvirtide-resistant HIV-1 isolates evolved in vivo after long-term treatment. Abstract 660, 11th CROI 2004, San Francisco, USA. <http://64.251.206.31/2004/AbstractSearch/AbstractSearch.aspx>
100. Mueller SM, Daeumer M, Kaiser R, et al. Susceptibility to saquinavir and atazanavir in highly protease inhibitor (PI) resistant HIV-1 is caused by lopinavir-induced drug resistance mutation L76V. *Antiviral Therapy* 2004, 9:S44.
101. Naeger LK, Margot NA, Miller MD. Increased drug susceptibility of HIV-1 reverse transcriptase mutants containing M184V and zidovudine-associated mutations: analysis of enzyme processivity, chain-terminator removal and viral replication. *Antivir Ther* 2001, 6:115-26. <http://amedeo.com/lit.php?id=11491416>
102. Nijhuis M, Schuurman R, de Jong D, et al. Increased fitness of drug resistant HIV-1 protease as a result of acquisition of compensatory mutations during suboptimal therapy. *AIDS* 1999, 13:2349-59. <http://amedeo.com/lit.php?id=10597776>
103. Oette M, Kaiser R, Däumer M, et al. Epidemiology of primary HIV drug-resistance in Germany and efficacy of first-line antiretroviral therapy guided by resistance testing. Abstract V43, 10. Deutscher und 16. Österreichischer AIDS Kongress 2005, Vienna, Austria.
104. Parikh U, Koontz, Sluis-Cremer N, et al. K65R: a multinucleoside resistance mutation of increasing prevalence exhibits bi-directional phenotypic antagonism with TAM. Abstract 54, 11th CROI 2004; San Francisco. [http://www.retroconference.org/Search\\_Abstract\\_2004/AbstractSearch.aspx](http://www.retroconference.org/Search_Abstract_2004/AbstractSearch.aspx)
105. Parkin NT, Chappey C, Petropoulos CJ. Improving lopinavir genotype algorithm through phenotype correlations: novel mutation patterns and amprenavir cross-resistance. *AIDS* 2003, 17: 955-962. <http://amedeo.com/lit.php?id=14513419>
106. Perelson AS, Neumann AU, Markowitz M, et al. HIV-1 dynamics in vivo: virion clearance rate, infected cell life-span, and viral generation time. *Science* 1996, 271:1582-1586.
107. Petropoulos CJ, Parkin NT, Limoli KL, et al. A novel phenotypic drug susceptibility assay for HIV type 1. *Antimicrob Agents Chemother* 2000, 44:920-8. <http://amedeo.com/lit.php?id=10722492>
108. Prado JG, Wrin T, Beauchaine J, et al. Amprenavir-resistant HIV-1 exhibits lopinavir cross-resistance and reduced replication capacity. *AIDS* 2002; 16: 1009-17. 52. <http://amedeo.com/lit.php?id=11953467>
109. Riva C, Violin M, Cozzi-Lepri A, et al. Transmitted virus with substitutions at position 215 and risk of virological failure in antiretroviral-naïve patients starting highly active antiretroviral therapy. *Antivir Ther* 2002; 7:S103-S104.
110. Ross L, Parkin L, Chappey C, et al. HIV clinical isolates containing mutations representative of those selected after first line failure with unboosted GW433908 remain sensitive to other protease inhibitors. Abstract 19, XII Int HIV Drug Resist Workshop 2003, Los Cabos, Mexico.
111. Ross L, Lim M, Liao Q, et al. Prevalence of antiretroviral drug resistance and resistance mutations in antiretroviral therapy (ART) naïve HIV infected individuals. Abstract H-173, 44th ICAAC 2004, Washington, DC, USA.
112. Salzberger B, Marcus U, Vielhaber B, et al. German-Austrian recommendations for the antiretroviral therapy of HIV-infection. *Eur J Med Res* 2004, 9: 491-504. [http://www.daignet.de/media/Guidelines\\_ART.pdf](http://www.daignet.de/media/Guidelines_ART.pdf)
113. Sax PE, Islam R, Walensky RP, et al. Should resistance testing be performed for treatment-naïve HIV-infected patients? A cost-effectiveness analysis. *Clin Infect Dis* 2005; 41: 1316-23. Abstract: <http://amedeo.com/lit.php?id=16206108>
114. Schapiro J, Cahn P, Trottier B, et al. Effect of baseline genotype on response to tipranavir/ritonavir compared with standard-of-care comparator in treatment-experienced patients: The Phase 3 RESIST-1

- and -2 Trials. Abstract 104, 12th CROI 2005, Boston.  
<http://www.retroconference.org/2005/cd/Abstracts/25617.htm>
115. Schmidt B, Walter H, Marcus U, et al. Cross-resistance to amprenavir in PI-treated patients. Abstract 276, 7th CROI 2000, San Francisco, USA.
  116. Schnell T, Schmidt B, Moschik G, et al. Distinct cross-resistance profiles of the new protease inhibitors amprenavir, lopinavir, and atazanavir in a panel of clinical samples. *AIDS* 2003; 17:1258-61.  
<http://amedeo.com/lit.php?id=12819531>
  117. Schuurman R, Nijhuis M, van Leeuwen R, et al. Rapid changes in HIV type 1 RNA load and appearance of drug-resistant virus populations in persons treated with lamivudine (3TC). *J Infect Dis* 1995, 171:1411-1419. <http://amedeo.com/lit.php?id=7539472>
  118. Sharma PL, Crumpacker CS. Decreased processivity of HIV type 1 reverse transcriptase (RT) containing didanosine-selected mutation Leu74Val: a comparative analysis of RT variants Leu74Val and lamivudine-selected Met184Val. *J Virol* 1999, 73:8448-56. <http://amedeo.com/lit.php?id=10482597>
  119. Shafer RW, Iversen AK, Winters MA, et al. Drug resistance and heterogeneous long-term virologic responses of HIV type 1-infected subjects to zidovudine and didanosine combination therapy. *J Infect Dis* 1995, 172:70-78. <http://amedeo.com/lit.php?id=7541064>
  120. Shafer R. Stanford HIV RT and Protease Sequence Database 1998-2002a.  
<http://hiv.net/link.php?id=28>
  121. Shafer R. Stanford HIV RT and Protease Sequence Database 1998-2002b.  
<http://hiv.net/link.php?id=29>
  122. Shafer R. Stanford HIV RT and Protease Sequence Database 1998-2002c.  
<http://hiv.net/link.php?id=30>
  123. Shulman NS, Winters MA, Shafer RW, et al. Subtle changes in susceptibility to stavudine predict virologic response to stavudine monotherapy after zidovudine treatment. *Antiviral Ther* 2001, 6(Suppl 1):124. Abstract 124.
  124. Shulman NS, Hughes M, Winters MA, et al. d4T virtual phenotype can predict virological response to d4T monotherapy after AZT treatment, but not at the current cutoff. *Antiviral Therapy* 2004a; 9:S132, Abstract 118. [http://www.natap.org/2004/HIVDRW/hivdrw\\_16.htm](http://www.natap.org/2004/HIVDRW/hivdrw_16.htm)
  125. Shulman NS, Bosch RJ, Mellors JW, Albrecht MA, Katzenstein DA. Genetic correlates of efavirenz hypersusceptibility. *AIDS* 2004b; 18: 1781-5. Abstract: <http://amedeo.com/lit.php?id=15316338>
  126. Sugiura W, Matsuda Z, Yokomaku Y, et al. Interference between D30N and L90M in selection and development of protease inhibitor-resistant human immunodeficiency virus type 1. *Antimicrob Agents Chemother* 2002; 46:708-715. <http://amedeo.com/lit.php?id=11850252>
  127. Snowden W, Shortino D, Klein A, et al. Development of amprenavir resistance in NRTI-experienced patients: alternative mechanisms and correlation with baseline resistance to concomitant NRTIs. *Antiviral Ther* 2000, 5 (Supplement 3):84.
  128. Sista PR, Melby T, Davison D, et al. Characterization of determinants of genotypic and phenotypic resistance to enfuvirtide in baseline and on-treatment HIV-1 isolates. *AIDS* 2004; 18: 1787-94.  
<http://amedeo.com/lit.php?id=15316339>
  129. Tural C, Ruiz L, Holtzer C, et al. Utility of HIV genotyping and clinical expert advice - The Havana trial. Abstract 434, 8th CROI 2001, Chicago, USA.
  130. Tisdale M, Alnadaf T, Cousens D. Combination of mutations in HIV type 1 reverse transcriptase required for resistance to the carbocyclic nucleoside 1592U89. *Antimicrob Agents Chemother* 1997, 41:1094-1098. <http://amedeo.com/lit.php?id=9145875>
  131. Underwood M, St Clair M, Ross L, et al. Cross-resistance of clinical Samples with K65R, L74V, and M184V Mutations. Abstract 714, 12th CROI, Boston, MA, USA.  
<http://www.retroconference.org/2005/cd/Abstracts/25534.htm>
  132. US Department of Health and Human Services (DHHS). Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents. 2005. Available at:  
<http://aidsinfo.nih.gov/ContentFiles/AdultandAdolescentGL.pdf>
  133. Valer L, De Mendoza C, De Requena DG, et al. Impact of HIV genotyping and drug levels on the response to salvage therapy with saquinavir/ritonavir. *AIDS* 2002; 16:1964-6.
  134. Van der Horst C, Quinn JB, Hinkle J, et al. Predictors of virologic failure in HIV-infected adults on a stable lamivudine HAART regimen. Abstract H21050, 42nd ICAAC 2003, San Diego, USA.
  135. Van de Vijver DAMC, Wensing AMJ, Angarano G, et al. The calculated genetic barrier for drug resistance mutations in six different non-B subtypes and two CRFs in a large European dataset is largely similar to subtype B. *Antiviral Ther*. 2004;9:S98.  
<http://www.aegis.com/conferences/13thHIVDrugResWkshop/87.html>
  136. Vandamme AM, Van Laethem, de Clercq E. Managing resistance to anti-HIV drugs. *Drugs* 1999, 57:337-361. <http://amedeo.com/lit.php?id=10193687>

## 356 HIV Resistance Testing

137. Vingerhoets J, Azijn H, Fransen E, et al. TMC125 displays a high genetic barrier to the development of resistance: evidence from in vitro selection experiments. *J Virol* 2005; 79: 12773-82. Abstract: <http://amedeo.com/lit.php?id=16188980>
138. Weinheimer S, Discotto L, Friberg J, Yang H, Colonna R. Atazanavir signature I50L resistance substitution accounts for unique phenotype of increased susceptibility to other protease inhibitors in a variety of HIV type 1 genetic backbones. *Antimicrob Agents Chemother* 2005; 49: 3816-24. Abstract: <http://amedeo.com/lit.php?id=16127058>
139. Weinstein MC, Goldie SJ, Losina E, et al. Use of genotypic resistance testing to guide hiv therapy: clinical impact and cost-effectiveness. *Ann Intern Med* 2001; 134: 440-50. Abstract: <http://amedeo.com/lit.php?id=11255519>
140. Wensing AM, Boucher CA. Worldwide transmission of drug-resistant HIV. *AIDS Rev* 2003a; 5: 140-55. Abstract: <http://amedeo.com/lit.php?id=14598563>
141. Wensing AMJ, van der Vijver DAMC, Asjo B, et al. Analysis from more than 1600 newly diagnosed patients with HIV from 17 European countries shows that 10 % of the patients carry primary drug resistance: The Catch-study. Abstract LB1, 2nd IAS 2003b, Paris, France.
142. Wensing AM, van de Vijver DA, Angarano G, et al. Prevalence of drug-resistant HIV-1 variants in untreated individuals in Europe: implications for clinical management. *J Infect Dis* 2005; 192: 958-66. Abstract: <http://amedeo.com/lit.php?id=16107947>
143. Whitcomb J, Deeks S, Huang W, et al. Reduced susceptibility to NRTI is associated with NNRTI hypersensitivity in virus from HIV-1-infected patients. Abstract 234, 7th CROI 2000 San Francisco, USA.
144. White KL, Margot NA, Ly JK, et al. A combination of decreased NRTI incorporation and decreased excision determines the resistance profile of HIV-1 K65R RT. *AIDS* 2005; 19: 1751-60. Abstract: <http://amedeo.com/lit.php?id=16227782>
145. Wiese N, Müller H, Hingst K, et al. Primary resistance mutations and polymorphisms in gp41-sequences of HIV-1 B-and non-B subtypes from Fuzeon-naïve patients. Abstract P174, 10. Deutscher und 16. Österreichischer AIDS Kongress 2005, Vienna, Austria.
146. Wilson JW. Update on antiretroviral drug resistance testing: Combining laboratory technology with patient care. *AIDS Read* 2003, 13:25-38. <http://www.medscape.com/viewarticle/448717>
147. Winters MA, Shafer RW, Jellinger RA, et al. HIV type 1 reverse transcriptase genotype and drug susceptibility changes in infected individuals receiving dideoxyinosine monotherapy for 1 to 2 years. *Antimicrob Agents Chemother* 1997, 41:757-762. <http://amedeo.com/lit.php?id=9087484>
148. Winters B, Vermeiren H, Lecocq P, et al. The VirtualPhenotype™ analysis of an HIV-1 genotype provides an accurate prediction of the virus susceptibility to antiretroviral drugs. Abstract 7.14, 2nd European HIV Drug Resistance Workshop 2004, Rome, Italy.
149. Wirden M, Malet I, Derache A, et al. Clonal analyses of HIV quasispecies in patients harbouring plasma genotype with K65R mutation associated with thymidine analogue mutations or L74V substitution. *AIDS* 2005; 19: 630-2. Abstract: <http://amedeo.com/lit.php?id=15802984>
150. Xu L, Pozniak A, Wildfire A, et al. Emergence and evolution of enfuvirtide resistance following long-term therapy involves heptad repeat 2 mutations within gp41. *Antimicrob Agents Chemother* 2005; 49: 1113-9. Abstract: <http://amedeo.com/lit.php?id=15728911>
151. Yanchunas J Jr, Langley DR, Tao L, et al. Molecular basis for increased susceptibility of isolates with atazanavir resistance-conferring substitution I50L to other protease inhibitors. *Antimicrob Agents Chemother* 2005, 49: 3825-32. Abstract: <http://amedeo.com/lit.php?id=16127059>

## 10. Pregnancy and HIV

### Therapy for mothers and prevention for neonates

Mechthild Vocks-Hauck

Perinatal (vertical) HIV infection has become rare since the introduction of antiretroviral transmission prophylaxis and elective cesarean section. While the vertical HIV transmission rate ranged from 15 to 20 % in the United States and Europe at the beginning of the nineties, it now amounts to only a few percent (Connor 1994, European Collaborative Study 2001, Marcollet 2002, Hollwitz 2004). Postpartum HIV infections are avoidable provided that HIV-infected mothers do not breastfeed.

At the same time as transmission prophylaxis was introduced, the treatment of HIV infection changed too. Nowadays, pregnancy is no longer a contraindication for antiretroviral therapy as long as individual maternal circumstances are taken into consideration (Cooper 2002, Agangi 2005, CDC 2005 a)).

The following chapter summarizes the recommendations of different guidelines for HIV therapy in pregnancy and perinatal chemoprophylaxis.

Reference is made to the European (Coll 2002), German (DAIG), and Austrian AIDS societies (OEAG) (DAIG 2003) as well as American Guidelines (CDC 2005 a) and b)). In addition, detailed and continuously updated recommendations of the US guidelines are to be found on the HIVATIS website: <http://hiv.net/link.php?id=190>.

## HIV therapy in pregnancy

### Starting HIV therapy during pregnancy

The assessment of indications for therapy and drug selection is similar to that in non-pregnant patients (chapter ART 2005). Since the CD4 T-lymphocyte count decreases physiologically by approximately 10-20 % in pregnant patients, the threshold values should be corrected accordingly before treatment is started. Following the recommendations of the German/Austrian guidelines and the CDC, antiretroviral therapy in symptom-free patients should begin

- when CD4+ T-cell count is below 200–350/μl and/or
- with a viral load of > 50,000–100,000 copies/ml HIV RNA (by RT-PCR or 3.0 version b-DNA).

Before initiating therapy with one of the common combination regimens, a resistance test should be carried out (see chapter on Resistance).

When setting up a treatment plan, it is important that:

- 1) AZT (Retrovir™) should be one component of the combination – if the result of the resistance test is favorable; and
- 2) Efavirenz (Sustiva™, Stocrin™) should be avoided because of possible teratogenic effects in the first trimester, and

3) The combination ddI (Videx™) + d4T (Zerit™) should **not** be used because of possible severe mitochondriopathies (Bristol-Myers 2001).

Even if maximum suppression of viral activity is achieved during pregnancy, this is no guarantee for the prevention of HIV transmission. Therefore, prophylaxis to reduce perinatal HIV transmission is also recommended in sufficiently treated pregnant patients (see below in the section Antiretroviral transmission prophylaxis).

Table 1: Special features of anti-HIV therapy in pregnancy

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Explanation of risk: Only AZT is approved for perinatal transmission prophylaxis
HIV resistance testing
No efavirenz (Sustiva™) in the first trimester (teratogenicity)
No hydroxyurea (teratogenicity)
No d4T+ddI (Zerit™+Videx™) because of mitochondriopathies
Nevirapine related hepatotoxicity in women with CD4+ T-cell counts > 250/μl
Raised toxicity through combination therapy, therefore monthly controls of lactate, hepatic transaminase levels, viral load, CD4+ T-cell count
Therapeutic plasma drug level measurement (TDM) and possible dose adaptation

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## Continuation of treatment during pregnancy

More and more HIV-infected women, in whom pregnancy has been diagnosed, have been pretreated with antiretroviral agents.

As a rule, if pregnancy is diagnosed **after** the first trimester, the antiretroviral therapy should be continued. Interruption of treatment might give rise to an increase in viral load and a possible deterioration of immune function causing the danger of disease progression and, ultimately, of reduction of the immune status of mother and fetus. AZT should be administered as a component of a combination regimen starting at 32 weeks of gestation at the latest.

Women in whom pregnancy is diagnosed **during** the first trimester should be informed about the benefits and risks of treatment in this period. In cases of reduced immune status, in particular, antiretroviral therapy could be continued even in the first trimester under careful laboratory and ultrasonic controls. However, substances that can have a toxic effect on the embryo should not be administered during early pregnancy (Table 1).

## Interruption of treatment

Women who have to discontinue antiretroviral treatment during pregnancy, e.g. because of hyperemesis, should only restart therapy when drug tolerance can be expected. In this case, as in all others, the rule is: withdraw all drugs simultaneously and re-administer them simultaneously, but avoid functional monotherapy if drugs have a long plasma half-life.

In other cases – especially if pregnancy is diagnosed very early – the fear of possible embryotoxic effects may lead to an interruption of antiretroviral therapy until the end of the first trimester or 13 weeks of gestation. At present, however, there is not enough data available to give an unambiguous recommendation for each individual case. The clinical, immunological and virological situation of the patient

(Bucerri 2003) and the known or expected effects on the fetus must be considered before making a decision. A continuously updated summary of the current state of knowledge about antiretroviral drugs in pregnancy can be found on the internet at the web address <http://hiv.net/link.php?id=189>.

If treatment is interrupted, all drugs (NRTIs and PIs) should be withdrawn and re-administered simultaneously in order to prevent development of resistance. As it is usually not possible to determine pregnancy duration exactly, the restart is mostly initiated at the gestational age of 13 weeks. Functional monotherapy after discontinuation regimens with NNRTIs should be avoided. Pharmacokinetic data demonstrate that detectable drug levels may persist up to three weeks after discontinuation of nevirapine. It is recommended either to continue the dual nucleoside analog components for a period of time after nevirapine discontinuation (Chaix 2005), or to replace nevirapine by a (boosted) PI, or continue the NNRTI including regimen. In case of conception under nevirapine, the therapy is usually continued during early pregnancy because of the complicated interruption strategy.

## **Combination therapy for the duration of pregnancy**

The suggestion of offering a combination therapy to pregnant patients with a plasma HIV RNA level > 1,000–10,000 copies/ml from the second trimester (CDC 2005a) onward or 32 weeks of gestation, e.g. in Germany, is increasingly the subject of discussion in specialized medical literature. Combination therapy is offered to the patient as a means of “better” prevention, even if it is not indicated on the basis of the immunological and virological situation. This approach is based on the assumption that a decrease in viral load translates into a lowering of the transmission risk.

Furthermore, the possibility that a very low viral load might make vaginal deliveries possible is being discussed. With a viral load of less than 1,000 HIV RNA copies/ml, the advantage of cesarean section compared with vaginal delivery can no longer be verified in women receiving HAART (Shapiro 2004). For this reason, in the USA as well as in some European countries such as France and Switzerland, vaginal delivery is considered an option for women on antiretroviral combination therapy whose HIV status at the time of delivery is less than 1,000 copies/ml and/or undetectable and in whom no obstetric complications are expected. Since the study data are not yet definitive and C-section is still accepted as being safer (ECS 2005), countries such as Germany still prefer to use this mode of delivery.

## **Treatment monitoring**

In addition to measuring the hemoglobin concentration to exclude an AZT-associated anemia, transaminases for potential hepatic toxicity, and lactate level to detect lactic acidosis early, the CD4+ T-cell number and viral load should be monitored at monthly intervals. If PIs are part of the treatment, it is of particular importance to monitor the blood glucose level closely (Watts 2004).

## **Coinfections**

The diagnosis and therapy of genital infections are essential. Chlamydia infection, trichomoniasis, and bacterial vaginosis correlate with premature delivery. The latter

increases the transmission risk, as do premature rupture of membranes and amniotic infection syndrome.

Hepatitis B infection of the mother can be passed on during delivery and calls for simultaneous vaccination (active and passive) of the newborn. Perinatal transfer of hepatitis C infection is promoted by HIV infection – just as the hepatitis C infection may promote the transfer of HIV (Schuval 2004). In this constellation, C-section is of particular significance (Mok 2005, Schackman 2004). CMV infection is passed on to the child intrauterinely and perinatally and may also promote intrauterine infection with HIV. Cytomegaloviruses in HIV-infected women receiving AZT or nevirapine prophylaxis could be detected in the amniotic fluid (Mohlala 2005). 30 % of children infected with HIV perinatally, who have an early manifestation of AIDS due to PCP, are co-infected with CMV.

## Special aspects of HIV therapy in pregnancy

Because embryotoxicity cannot be excluded and hepatic metabolism is altered in pregnancy, some basic rules must be taken into consideration (CDC 2005 a) (Table 2). It is important to understand that a detectable plasma viral load always necessitates a resistance test. AZT resistance was verified, for example, in the United States in approximately 17 % of the women during pregnancy (Palumbo 2001), and infected children seem to have an unfavorable prognosis in these cases (The Italian Register for HIV Infection in Children 1999).

Table 2: Antiretroviral agents in pregnancy

Preferred NRTIs (full placenta transfer)	AZT + 3TC AZT + ddI	AZT is metabolized in the placenta; mitochondrialopathy risk: ddC > ddI > d4T > AZT > 3TC > ABC > TDF
Alternative NRTIs (full placenta transfer)	d4T + 3TC Abacavir Tenofovir Emtricitabine	No side-effects for PACTG 332 Only little published experience No published data in humans Alternative to 3TC, barely any experience
NNRTIs (full placenta transfer)	Nevirapine	General use in perinatal prophylaxis; Hepatic toxicity ↑ in pregnancy; enzyme induction, resistance mutation rate about 20 % even when administered once/twice
PIs (minimal placenta transfer)	Nelfinavir Indinavir Ritonavir Lopinavir/r Saquinavir SGC Amprenavir/ Fosamprenavir Atazanavir	Frequent use; often replaced by boosted PIs Hyperbilirubinemia, nephrotoxicity Poor tolerance, only as booster Some experience Low plasma levels, only boosted Few data No experience No experience; indir. hyperbilirubinemia
Entry Inhibitors	T-20	Only case reports



## Antiretroviral agents in pregnancy

### Nucleoside reverse transcriptase inhibitors (NRTIs)

Nucleoside analogs cross the placenta (Chappuy 2004) and can cause toxic damage not only to the mother but also to the child. The main problems are anemia and, when using combination therapy, lactate acidosis.

On the basis of pregnancies observed to date, it can be maintained that frequently used nucleoside analogs such as AZT, 3TC and d4T, do not increase teratogenicity by more than twofold (Antiretroviral Pregnancy Registry 2004). Most of our experience is related to AZT administration. Follow-ups of more than 20,000 children who had received AZT prophylaxis did not show any serious side effects. An analysis of the causes of death of 223 children, who died within the first five years of life, ruled out drug-related causes (The Perinatal Safety Review Working Group 2000). In other studies, no damage to mitochondrial DNA could be detected (Noguera 2004, Poirier 2004, Viganò 2004).

In contrast to these findings, in a prospective study by Barret et al. (2003) on 2,644 ART-exposed non-infected children, neurological symptoms with persistent mitochondrial dysfunction were reported in 0.26 %. Retardation of auditory evoked potentials (Poblano 2004), as well as nonspecific changes in cerebral MRTs in children perinatally exposed to AZT (plus 3TC) (Tardieu 2005) have been interpreted as a sign of neurotoxicity. 24 months after combined nucleoside exposure, raised lactate values as well as impairment of hematopoiesis can still be demonstrated in children (Alimenti 2003, Mofenson 2004). Even after eight years, neutrophil granulocytes were reduced in perinatally NRTI-exposed children (ECS 2004). So far, severe mitochondriopathies have been observed at least twice in pregnant women taking a combination therapy of the nucleoside analogues d4T+ddI plus nelfinavir or nevirapine (Sarner 2002). For this reason, the combination d4T+ddI is contraindicated in pregnancy (Bristol-Myers 2001). Hepatic toxicity with hyperbilirubinemia was described under AZT+3TC+efavirenz therapy. Following the administration of AZT+3TC+nelfinavir, one pregnant woman died of sudden acute liver failure (Hill 2001). Tenofovir did not show any maternal toxicity in animal experiments, but did cause a fetal growth retardation of 13 % as well as a slight decrease in the bone mineral density (Tarantal 2002).

### Non-nucleoside reverse transcriptase inhibitors (NNRTIs)

In perinatal prevention, nevirapine has been employed successfully, particularly in combination with AZT. Because of enhanced risk of liver toxicity during the first 18 weeks of treatment in women with a CD4+ T-cell count more than 250/ $\mu$ l, treatment should be monitored closely and at short intervals, especially in the time of dose escalation. Nevirapine in pregnant women is only recommended following very careful assessment of the benefit-risk ratio (CDC 2005a).

Perinatal single and two-dose prophylaxis has resulted in the development of drug resistance (Jackson 2000, Flys 2005). If a mother gives birth less than two hours following nevirapine administration, or has not received any prior nevirapine at all, the newborn should receive a dose of nevirapine immediately after birth and a further dose after 48-72 hours (Stringer 2003, Jackson 2006). Because of embryonic toxicity in the rhesus monkey and also in humans (neural tube impairments, Bristol-

Myers Squibb 2004) efavirenz is not used during the first trimester of pregnancy and only after the second in cases with no alternative treatment option providing reliable contraception is practiced after delivery (CDC 2005 a) and b)).

### **Protease inhibitors (PIs)**

The use of protease inhibitors must be monitored carefully, especially in the later stages of pregnancy, due to a possible diabetogenic effect (Beitune 2005) and hepatic toxicity. Presently, most experience relates to nelfinavir (Bryson 2002). However, in combination therapies, toxic side effects have also been described (Morris 2005) (see above). Indinavir can lead to hyperbilirubinemia and nephrolithiasis; the plasma levels can be lowered (Kosel 2003). As with indinavir, saquinavir should also be boosted with ritonavir in pregnancy (Acosta 2004). Ritonavir and lopinavir plasma levels are also lowered during pregnancy (Scott 2002, Stek 2004).

A Swiss research group suspected that the use of combination therapy might cause an increase in premature birth rate and a higher rate of malformations. Malformations appear to be rather unlikely due to the minimal placental transfer of PIs (Marzolini 2002) and have not been confirmed by other studies either. With regard to the premature birth rate, the available data is inconsistent (increases were reported by the European Collaborative Study 2003, Thorne 2004, Bekerman 2004; no increases were reported by Mandelbrot 2001 and Tuomala 2002).

The serum levels of HCG and estrogens were not reduced in women on PI-therapy (Einstein 2004).

### **FDA classification for drugs in pregnancy**

The FDA has classified the potential toxicity of drugs in pregnancy into the categories A-D. All HIV virustatic agents belong to the categories B-D, since "harmlessness through studies on the human being" (= category A) does not apply to any of these drugs.

FDA category B is defined as follows: "Animal studies have revealed no evidence of harm to the fetus; however, there are no adequate and well-controlled studies in pregnant women". The FDA category B includes ddI, emtricitabine, tenofovir, atazanavir, saquinavir, ritonavir, nelfinavir and enfuvirtide (T-20).

FDA category C is defined as follows: "Animal studies have shown an adverse effect and there are no adequate and well-controlled studies in pregnant women. Use in pregnancy should occur only after careful benefit/risk appraisal." All other drugs that were not mentioned in category B fall into the FDA category C. Efavirenz falls into category D because of neural tube defects in humans after first trimester exposure.

FDA category D (Efavirenz) is defined as follows: "Adequate well-controlled or observational studies in pregnant women have demonstrated a risk for the fetus. Nevertheless, the benefits of therapy may outweigh the potential risk." For example, the drug may be acceptable if it is needed in a life-threatening situation or serious disease for which safer drugs cannot be used or are ineffective.

### **Prevention of perinatal HIV infection**

In approximately 75 % of cases, HIV is transmitted prior to, or during the last weeks prior to birth. About 10 % of vertical HIV infections occur before the third trimester, and 10-15 % are caused by breastfeeding.

The probability of HIV transmission to a neonate correlates with the viral load. This also seems to apply to women who are being treated with antiretroviral drugs (Table 3). If the viral load is undetectable using currently available tests, the probability of transmission is indeed extremely low; however, infections have also been described under such circumstances (Ioannidis 2001). Likewise, premature births and premature rupture of membranes are associated with an increased infection risk for the child.

For this reason, reduction in the level of plasma viremia and improvement in the immune status of pregnant women are vital prophylactic measures. If a mother is treated with antiretrovirals, these drugs should continue to be taken, if possible, during delivery at the usual scheduled intervals in order to achieve the maximum effect and to minimize the risk of developing resistance.

Table 3: Known risk factors for perinatal HIV transmission

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High maternal viral load
Low CD4+ T-cell count
AIDS in the mother
Vaginal delivery
Premature rupture of membranes of > 4 h
Pre-term infants (< 37 weeks of gestation)
Breastfeeding

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For the general prevention of mother-to-child transmission of HIV, pregnant women should be warned not to use intravenous drugs or to have unprotected sex because of the increased risk of HIV transfer in these cases.

In addition to the indicated or optional antiretroviral therapy of the mother, the following rules should be observed regarding chemoprophylaxis

- Antiretroviral prophylaxis before and during delivery
- Elective cesarean section before onset of labor, because vaginal delivery with a viral load of > 1,000 HIV-RNA copies/ml increases the transmission risk
- Postnatal chemoprophylaxis of the infants (post-exposure prophylaxis)
- No breastfeeding

## Antiretroviral transmission prophylaxis

### Combination prophylaxis

Standard combination antiretroviral regimens for the treatment of HIV infection should be discussed and offered to all pregnant women with HIV regardless of the viral load. They are clearly recommended if the viral load is > 10,000 copies/ml. Combination prophylaxis should be introduced temporarily from 32+0 weeks gestation until immediately after birth (Table 4).

The combination of AZT+3TC is problematic because of the possible development of resistance in the M184 codon (Mandelbrot 2001). Therefore, HAART prophylaxis is increasingly being used.

Table 4: Combination prophylaxis with combination therapy containing AZT in cases with a viral load > 10,000 RNA copies/ml, but otherwise only standard risk

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*After resistance testing starting at 32 + 0 weeks gestation:*

2 x 250-300 mg AZT

+ a second NRTI

+ plus NNRTI or (boosted) PI (a third NRTI is rarely used)

During delivery (elective cesarean section from 37+0 weeks gestation to week 37 + 6):

IV infusions of AZT as standard prophylaxis:

2 mg/kg i.v. as a "loading dose" for 1 h to approx. 3 h preoperatively

1 mg/kg i.v. intraoperatively until delivery of the infant

In neonates AZT monoprophyllaxis:

2 mg/kg orally every 6 hours *within 6 hours* post partum for 2-4 weeks or

1.5 mg/kg i.v. every 6 hours *within 6 hours* post partum for 10 days

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### Prophylaxis in ART-pretreated pregnant women

In pregnant women who have already been pretreated with ART, AZT should be integrated into the combination therapy starting at 32+0 weeks gestation. When using combinations containing d4T, this agent should be substituted by another active component because of AZT antagonism.

### Procedure in cases with additional pregnancy risks

The pregnancy risks mentioned in Table 5 require an intensified prophylaxis.

Table 5: Risk adapted prophylaxis in the case of complications during pregnancy and delivery

<b>Increased risk</b>	
Multigravidity	Mother: AZT monoprophyllaxis, or combination therapy, e.g. AZT + 3TC + nevirapine or AZT + 3TC + nelfinavir/(boosted) PI from 29+0 weeks gestation Children: 4 weeks AZT (Table 7)
Early onset of labor	Mother: combination therapy, e.g. AZT + 3TC + nevirapine or AZT + 3TC + nelfinavir/(boosted) PI
Premature infants from 33+0 to 36+6 weeks of gestation or AZT-prophylaxis of < 4 weeks	Mother: in addition to AZT or a combination therapy: nevirapine* Child: dual combination therapy in the neonate (Table 7)
<b>Highly increased risk</b>	
Premature infants < 33+0 weeks of gestation Premature rupture of membranes > 4 h or Amniotic infection syndrome or Rise of the viral load towards the end of pregnancy	Mother: In addition to AZT or a combination therapy: nevirapine Child: triple combination prophylaxis (Table 7)
Incision injury of the child or Ingestion of hemorrhagic amniotic fluid or HIV infection diagnosed only post partum	Child: triple combination prophylaxis (Table 7)

\* In the case of preceding nevirapine therapy during pregnancy: reduced plasma half-life, therefore: increase nevirapine dose or alternative extension of therapy; after nevirapine monoprophyllaxis 20 % resistant strains in the mother. Thus, combination, where appropriate, with 2 NRTIs over 1-3 weeks (for example ddl, AZT+ddl or d4T+ddl; not 3TC because of rapid resistance development) or combination with (boosted) PI is advised.

### Intrapartum prophylaxis without antepartum regimens

If the diagnosis of HIV infection is only established at the time of delivery, mother and newborn receive a dual or triple combination prophylaxis with AZT (plus 3TC and/or nevirapine) in cases of highly increased risk (high viral load and/or medical complications during delivery).

### Simple prophylaxis

Starting at 32 weeks gestation with a time-limited monoprophyllaxis with AZT might be an appropriate option for women with HIV-RNA levels well below

10,000 copies/ml (DAIG 2005), and preferably in those with < 1,000 copies/ml (CDC 2005 a)) who wish to restrict exposure of their fetus to antiretroviral drugs (CDC 2005a)). This regimen is, however, controversial, not only because AZT-resistant viruses have been increasingly identified, but also because the risk of resistance formation under monotherapy cannot be neglected. The use of AZT alone during pregnancy is mentioned for the sake of completeness; in practice, it is now out-dated and hardly ever used.

Table 6: AZT monoprohylaxis in the case of low virus load (clearly less than 10,000 copies/ml), asymptomatic HIV infection and uncomplicated pregnancy course (out-dated because of the risk of development of resistance)

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*After resistance testing* starting at 32 + 0 weeks gestation  
2 x 250-300 mg AZT per os

During delivery (elective cesarean section from 37+0 up to 37+6 weeks gestation):  
2 mg/kg AZT i.v. as "loading dose" over 1 h to approx. 3 h preoperatively  
1 mg/kg AZT i.v. intraoperatively until the delivery of the child

In neonates AZT monoprohylaxis:  
2 mg/kg AZT orally every 6 hours *within 6 hours* postpartum for 2-4 weeks or  
1.5 mg/kg AZT i.v. every 6 hours *within 6 hours* postpartum for 10 days

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## Treatment during delivery

### Elective cesarean section in cases of uncomplicated course of pregnancy

Cesarean section is carried out swiftly by experienced obstetricians prior to the onset of labor from 37+0 up to 37+6 weeks of gestation using the Misgav-Ladach technique, which reduces bleeding. Blunt preparation and the delivery of the child within the intact amniotic sac are considered ideal (Schäfer 2001). A vaginal delivery in women under HAART with undetectable viral load appears to be possible, because no increased vertical transmission rates are found compared to elective cesarean section in pregnant women with a viral load under 1,000 HIV RNA copies/ml (Shapiro 2004, ECS 2005). In some European countries such as France and Switzerland and in the United States, women falling into this category can now deliver a child vaginally. In Europe, the percentage of vaginal births increased from 12 % in 1999 to 24 % in 2002 (Thorne 2004).

### High-risk pregnancy

Cesarean section in cases of multigravidity should be carried out using the same technique as for a cesarean section in a single pregnancy. In this context, the skill and experience of the operating surgeon are especially important. Cesarean sections in cases of premature infants are also important to avoid hypoxia in the neonate; the special aspects of chemoprophylaxis have been described above.

In cases with a premature rupture of membranes of less than four hours duration, a section is expedient for prophylactic reasons, providing the clinical situation at that stage of delivery still permits. If the rupture of membranes has lasted more than

four hours, the advantage of cesarean section compared to vaginal delivery is no longer expected. Nevertheless, vaginal delivery should occur as swiftly as possible, since the HIV transmission risk increases by about 2 % per hour. The extension of the prophylactic scheme (Table 5 and 7) is important.

### **Unknown HIV status in cases of known risk**

If, at the time of delivery, the HIV status is unknown and the existence of a risk is known, an HIV test can still be offered to the patient (Bulterys 2004). Although specificity is high, it is still considered inadequate. Thus, the combined use of two rapid tests from different manufacturers is ideal. If one of the two tests is negative, there is probably no infection.

## **Therapy of neonates**

### **Postnatal standard prophylaxis**

The postnatal transmission prophylaxis should begin, if possible, within the first 6 hours following birth with oral or – in the case of gastrointestinal symptoms – intravenous AZT prophylaxis. In Germany, the duration of the oral standard prophylaxis has been shortened from six to two (to four) weeks (Voeks-Hauck 2001).

### **Prophylaxis in cases of increased risk (multiple neonates, premature infants)**

In multiple-birth neonates without further risk, AZT prophylaxis of four weeks duration is recommended. In addition, premature infants receive nevirapine, which is given either once to the mother before delivery and once to the premature infant, or twice postnatally. If maternal nevirapine administration occurs less than an hour before delivery, then the newborn receives its first dose within the first 48 hours (Stringer 2003). If nevirapine was a part of the combination therapy for the mother, the dose is doubled to 4 mg/kg in newborns because of possible enzyme induction. In addition, newborns receive an extended AZT prophylaxis according to the regimen proposed for premature infants (see below) for the duration of four to six weeks.

### **Prophylaxis in cases of highly increased transmission risk**

In neonates with additional transmission risks, a combination prophylaxis with AZT+3TC is recommended. A strongly increased risk exists, for example, after premature rupture of membranes, in cases of amniotic infection syndrome, high viral load prior to delivery, lacking transmission prophylaxis and incision injury of the child during cesarean section, as well as in cases where the amniotic fluid sucked from the gastrointestinal or respiratory tract of the newborn is hemorrhagic.

Table 7: Postnatal antiretroviral prophylaxis/treatment for infants of HIV-positive mothers

Standard risk	Drug	Side effect
Uncomplicated pregnancy and delivery with complete pre- and intrapartal transmission prophylaxis	AZT, within 6 h after birth: 4 x 2 mg/kg orally for 2-4 weeks or 4 x 1.5 mg/kg i.v. for 10 days	Anemia, neutropenia; gastrointestinal irritation
<b>Increased risk</b>		
Multiple birth	AZT orally or i.v., within 6 h after delivery: (where appropriate, switch to oral administration after 10 days i.v.)  4 x 2 mg/kg orally for 4 weeks	see above
Premature labor Pre-term infants 33+0 up to 36+6 weeks of gestation * Early labor Therapy < 4 weeks in cases of low viral load and without obstetric risks	AZT, within 6 h after birth (see above): 4 x 2 mg/kg orally for 4-6 weeks  <b>plus</b> Single dose of nevirapine of 2 mg/kg after 48-72 hrs. **  AZT dosage in premature infants < 35 weeks of gestation: AZT 2 x 2 mg/kg orally or 2 x 1.5 mg/kg i.v., from 15 <sup>th</sup> day: 3 x 2 mg/kg orally, in infant < 30 weeks of gestation starting from day 29	AZT: see above, particularly anemia  Nevirapine: hepatotoxicity, rash
<b>Highly increased risk</b>		
Premature infants < 33 + 0 weeks of gestation**	AZT (dosage see above) for 4-6 weeks	AZT: As above, in combination with 3TC: gastrointestinal SE, mitochondrialopathy (lactate)
Prematurely ruptured membranes	<b>plus</b> 3TC* 2 x 2 mg/kg for 4-6 weeks	Nevirapine: hepatotoxicity, exanthema (not to be expected after two doses)
Amniotic infection	<b>plus</b>	
Elevated viral load at the end of pregnancy, also if no prophylaxis	Nevirapine** 2mg/kg as SD within 2h until 48h. If no prenatal nevirapine or later <2hrs, one additional dose 48-72h pp. If prenatal nevirapine, then only one dose after 48-72hrs.	
Incision injury of neonate		
Ingestion of hemorrhagic amniotic fluid		
HIV infection diagnosed at birth		

\*in premature infants, a triple combination prophylaxis is also possible, but use 3TC cautiously, \*\*Nevirapine: if no prenatal administration was possible, first adm. immediately and second adm. within 48-72 hrs postpartum. Dosage adaptation if possible enzyme induction in case of previous maternal NVP therapy; administration of the 1<sup>st</sup> dose < 2 hrs prepartal 2<sup>nd</sup> dose immediately after birth and 3<sup>rd</sup> dose after 48-72 hrs. AF = amniotic fluid; NN = neonate; pp = postpartum; SE = side effect



Table 8: Studies on antiretroviral prophylaxis in neonates

Drug	Average daily dose	Most frequent side effects	Study
AZT Zidovudine Retrovir™	8 mg/kg in 4 SD; 4 mg/kg in 2 SD in PI* < 35 GW, from 15 <sup>th</sup> day; 6 mg/kg* in 3 SD, in PI < 30 GW from 29 <sup>th</sup> day	Anemia, neutropenia Mitochondriopathy in combination with 3TC	(P)ACTG's 076, 316, 321, 353, 354, 358; HIVNET 012 III PACTG 331(PI)
3TC Lamivudine EpiVir™	4 mg/kg in 2 SD in neo- nates (< 30 days)	GI SE, vomiting, Mitochondriopathy in combination Incompatibility in pre- mature infants	PACTG 358
ddl Didanosine Videx™	100 mg/m <sup>2</sup> in 2 SD from 14 <sup>th</sup> day	Diarrhea, pancreatitis, mitochondriopathy in combination	PACTG 239, 249; HIV-NAT
d4T Stavudine Zerit™	1 mg/kg in 2 SD from birth to 13 days, 2 mg/kg in 2 SD from 14 <sup>th</sup> day	Mitochondriopathy in combination	PACTG 332, 356; HIV-NAT
ABC Abacavir Ziagen™	Up to 4 mg/kg in 2 SD; > 1 month 16 mg/kg in 2 SD (Study)	Hypersensitivity reaction (no restart), mitochon- driopathy, lactic acidosis	PACTG 321
NVP Nevirapine Viramune™	2-4 mg/kg as SD or 120 mg/m <sup>2</sup> for 14 days, thereafter 7-8 mg/kg or 240 mg/m <sup>2</sup> in 2 SD, maximal 400 mg/m <sup>2</sup>	Rash, hepatotoxicity, no restart after symptomatic hepatic event	PACTG 316,356, HIVNET 012
NFV Nelfinavir Viracept™	80 mg/kg in 2 SD (Study) from 1 week and 6 weeks; 110-150 mg/kg in 2 or 3 SD at 2 months	GI SE: particularly diar- rhea	PACTG 353, 356 PENTA 7
RTV Ritonavir Norvir™	350 mg/m <sup>2</sup> as SD or 700 mg/m <sup>2</sup> in 2 SD for 4 weeks (Study)	Hyperbilirubinemia, gastrointestinal SE	PACTG 354

I=infant; PI = premature infant; MI = mature born infant; SD = single dose; (P)ACTG = (Pedi-  
atric) AIDS Clinical Trial Group; HIV-NAT = HIV-Netherlands Australia Thailand Research  
Collaboration; NN = neonate; GI SE = Gastrointestinal side effect; GW = gestation week

Reference: Except for AZT in mature born infants, the dosage is taken from the studies.  
Antiretroviral substances that are not approved, should be used in neonates only in the con-  
text of studies, if possible.

### Procedure in cases of no pre- and intranatal prophylaxis

Combination prophylaxis of AZT+3TC should start within the first 6 to 12 hours after delivery. In addition, a perinatal nevirapine prophylaxis with two-fold administration is recommended.

If HIV infection is discovered only after birth, a combination prophylaxis, begun within 48 hours, seems to be far more effective than a prophylaxis, which is initiated only after 3 days (transmission rates 9.2 % vs. 18.4 %, Wade 1998). However, even then, a certain positive effect of AZT prophylaxis as opposed to no prophylaxis can still be verified (18.4 % vs. 26.6 %) (Table 7).

### Further studies for HIV prevention in neonates

A survey of studies about the pharmacokinetics in pregnancy and neonates is given in Table 8 (Ronkavilit 2001 & 2002, Wade 2004, Kovacs 2005, Mirochnik 2005, Best 2006).

### Studies

In order to continuously improve HIV therapy during pregnancy and the chemoprophylaxis of perinatal HIV infection, a thorough documentation of clinical data is necessary. In the US, the "Antiretroviral Pregnancy Registry" is an extensive therapy register that helps to evaluate the potential teratogenicity of antiretrovirals on the basis of "case reports" on HIV-exposed neonates:

Antiretroviral Pregnancy Registry, Research Park, 1011 Ashes Drive, Wilmington NC 28405; Kontakt: <http://www.apregistry.com/contact.htm>.

### References

1. Acosta EP, Bardeguet A, Zorrilla C et al. Pharmacokinetics of Saquinavir plus low dose ritonavir in human immunodeficiency virus-infected pregnant women. *Antimicrob Agents Chemother* 2004; 48: 430-6.
2. Agangi A, Thorne C, Newell ML: European Collaborative Study. Increasing likelihood of further live births in HIV-infected women in recent years. *BJOG* 2005; 112:881-7. <http://hiv.net/link.php?id=15957987>
3. Alimenti A, Burdge DR, Ogilvie GS et al. Lactic acidemia in HIV-uninfected infants exposed to perinatal antiretroviral therapy. *Pediatr Infect Dis* 2003; 22: 782-9. <http://hiv.net/link.php?id=14506368>
4. Barret B, Tardieu M, Rustin P et al. Persistent mitochondrial dysfunction in HIV-1-exposed but uninfected infants: clinical screening in large prospective cohort. *AIDS* 2003; 17: 1769-85. <http://hiv.net/link.php?id=12891063>
5. Beitune PE, Duarte G, Foss MC et al. Effect of antiretroviral agents on carbohydrate metabolism in HIV-1 infected pregnant women. *Diabetes Metab Res Rev* 2005. <http://hiv.net/link.php?id=16021650>
6. Bekerman K, Covington D, Garcia P et al. Association between antiretroviral therapy during pregnancy and prematurity/low birth weight. 11<sup>th</sup> CROI 2004, San Francisco.
7. Best BM, Mirochnik M, Caparelli EV et al. Impact of pregnancy on abacavir pharmacokinetics. *AIGS* 2006;20:553-60. <http://hiv.net/link.php?id=16470119>
8. Bristol-Myers warns of AIDS drugs use. *AIDS Read.* 2001; 11: 82.
9. Bristol-Myers Squibb company: Efavirenz drug label, revised December 2004 .
10. Bryson Y, Stek A, Mirochnik M et al. Pharmacokinetics, antiviral activity and safety of nelfinavir (NFV) in combination with ZDV/3TC in pregnant HIV-infected women and their infants: PACTG 353 cohort 2. Abstract 795, 9<sup>th</sup> CROI 2002, Seattle.
11. Bucceri AM, Somigliana E, Matrone R et al. Discontinuing combination antiretroviral therapy during the first trimester of pregnancy: insights from plasma HIV-1 RNA viral load and CD4 cell count. *Am J Obstet Gynecol*; 189: 545-51. <http://hiv.net/link.php?id=14520232>
12. Bulterys M, Jamieson DJ, O'Sullivan MJ et al. Rapid HIV-1 testing during labor: a multicenter Study. *JAMA* 2004; 292: 269-71.

13. Capparelli E, Mirochnick M, Dankner WM et al. Zidovudine pharmacokinetics in premature infants exposed to HIV. *J Pediatr* 2003; 142: 47-52.
14. Centers for Disease Control (CDC). Recommendations for use of antiretroviral drugs in pregnant HIV-1-infected women for maternal health and interventions to reduce perinatal HIV-1 transmission in the United States. February 24, 2005 a). <http://www.aidsinfo.nih.gov>
15. Centers for Disease Control (CDC). Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Recommendations of the panel on clinical practices for treatment of HIV. *MMWR* 2002; 51 (RR-7): 1-55. Update April 07, 2005 b). <http://www.aidsinfo.nih.gov>
16. Chaix ML, Dabis F, Ekouev D et al. Addition of 3 days of ZDV+3TC postpartum to a short course of ZDV+3TC and single-dose NVP provides low rate of NVP resistance mutations and high efficacy in preventing peri-partum HIV-1-transmission ANRS DITRAME Plus, Abidjan, Cote Divoire. Abstract 72LB, 12<sup>th</sup> CROI Boston 2005.
17. Chappuy H, Treluyer JM, Julien V, et al. Maternal-fetal transfer and amniotic fluid accumulation of nucleoside analogue reverse transcriptase inhibitors in HIV-infected pregnant women. *Antimicrob Agents Chemother* 2004;48: 4332-6. <http://hiv.net/link.php?id=15504861>
18. Coll O, Fiore S, Floridia M et al. Pregnancy and HIV-infection: a European consensus on management. *AIDS* 2002; 16 Suppl 2: 1-18. <http://hiv.net/link.php?id=12479261>
19. Connor EM, Sperling RS, Gelber R, et al. Reduction of maternal-infant transmission of HIV type 1 with zidovudine treatment. *N Engl J Med* 1994; 331:1173-80. <http://hiv.net/link.php?id=7935654>
20. Cooper ER, Charutat M, Mofenson L, et al. Combination antiretroviral strategies for the treatment of pregnant HIV-1-infected women and prevention of perinatal HIV-1-transmission. *J Acquir Immune Defic Syndr* 2002; 29: 484-94. <http://hiv.net/link.php?id=11981365>
21. Deutsche AIDS-Gesellschaft (DAIG), Österreichische AIDS-Gesellschaft (ÖAG), Robert Koch Institut et al. Deutsch-Österreichische Empfehlungen zur HIV-Therapie in der Schwangerschaft. Stand Juni 2005. [http://www.rki.de/INFEKT/AIDS\\_STD/BR\\_LINIE/BR\\_LINIE.HTM](http://www.rki.de/INFEKT/AIDS_STD/BR_LINIE/BR_LINIE.HTM)
22. Einstein FH, Wright RL, Trentacoste R et al. The impact of protease inhibitors on maternal serum screening analyte levels in pregnant women who are HIV- positive. *Am J Obstet Gynecol* 2004, 191:1004-1008.<http://hiv.net/link.php?id=15467580>
23. European Collaborative Study. HIV-infected pregnant women and vertical transmission in Europe since 1986. *AIDS* 2001; 15: 761-70. <http://hiv.net/link.php?id=11371691>
24. European Collaborative Study. Exposure to antiretroviral therapy in utero or early life: the health of uninfected children born to HIV-infected women. *J Acquir Immune Defic Syndr* 2003; 32: 380-7 <http://hiv.net/link.php?id=12640195>
25. European Collaborative Study. Levels and patterns of neutrophil cell counts over the first 8 years of life in children of HIV-infected mothers. *AIDS* 2004; 18: 2009-2017. <http://hiv.net/link.php?id=15577622>
26. European Collaborative Study. Mother- to- child transmission of HIV infection in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2005; 40: 458-65. <http://hiv.net/link.php?id=15668871>
27. Flys T, Nissley DV, Claassen CW et al. Sensitive drug-resistance assays reveal long-term persistence of HIV-1 variants with K103N nevirapine (NVP) resistance mutation in some women and infants after the administration of single-dose nevirapine. *J Infect Dis* 2005; 192: 24-9. <http://hiv.net/link.php?id=15942890>
28. Jackson JB, Parsons T Musoke P , et al. Association of Cord blood nevirapine concentration with reported timing of dose and HIV-1 transmission. *AIDS* 2006; 20: 212-17. <http://hiv.net/link.php?id=16511414>
29. Hill JB, Sheffield JS, Zeeman GG, Wendel GD. Hepatotoxicity with antiretroviral treatment of pregnant women. *Obstet Gynecol* 2001; 98: 909-11. <http://hiv.net/link.php?id=11704198>
30. Hollwitz B, Gingelmaier A, Gröger S et al. Course of pregnancy and fetal outcome of 594 HIV-exposed pregnancies in German reference centers 1999-2003. Abstract ThPeE7973, XV World AIDS Conference, Bangkok, 2004.
31. Ioannidis JP, Abrams EJ, Ammann A, et al. Perinatal transmission of HIV type I by pregnant women with RNA virus loads < 1000 copies/ml. *J Infect Dis* 2001; 183: 539-45. <http://hiv.net/link.php?id=11170978>
32. Jackson JB, Mrcanz M, Guay L, et al. Identification of the K103N resistance mutation in Ugandan women receiving nevirapine to prevent HIV-1 vertical transmission. *AIDS* 2000; 14: 111-5. <http://hiv.net/link.php?id=10983633>
33. Kovacs A, Cowles MK, Britto P et al. Pharmacokinetics of didanosine and drug resistance mutation in infants exposed to zidovudine during gestation or postnatally and treated with didanosine or zidovudine in the first three months of life. *Pediatr Infect Dis J* 2005; 24: 503-9. <http://hiv.net/link.php?id=15933559>
34. Kosel BW, Beckerman KP, Hayashi S, et al. Pharmacokinetics of nelfinavir and indinavir in HIV-1-infected pregnant women. *AIDS* 2003; 17: 1195-9. <http://hiv.net/link.php?id=1281952>

## 372 Pregnancy and HIV

35. Mandelbrot L, Landreau-Mascaro A, Rekacewicz C, et al. Lamivudine-zidovudine combination for prevention of maternal-infant transmission of HIV-1. *JAMA* 2001; 285: 2083-93. <http://hiv.net/link.php?id=11311097>
36. Marcollet A, Goffinet F, Firtion G, et al. Differences in postpartum morbidity in women who are infected with the HIV after elective cesarean delivery, emergency cesarean delivery, or vaginal delivery. *Am J Obstet Gynecol* 2002; 186:784-9. <http://hiv.net/link.php?id=11967508>
37. Marzolini C, Rudin C, Decostered LA, et al. Transplacental passage of protease inhibitors at delivery. *AIDS* 2002; 18: 889-93. <http://hiv.net/link.php?id=11919490>
38. Mirochnick M, Caparelli. Pharmacokinetics of antiretrovirals in pregnant women. *Clin Pharmacokin* 2004; 43:1071-87 <http://hiv.net/link.php?id=15568888>
39. Mirochnick M, Stek A, Acevedo M et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr* 2005; 39. <http://hiv.net/link.php?id=15905735>
40. Mofenson LM, Lu M, Pacheco S, et al. Perinatal antiretroviral (ARV) exposure and effect on hematopoiesis in HIV-exposed, uninfected children: the women and infants transmission study (WITS). 15<sup>th</sup> World AIDS Conference 2004, Bangkok, Abstract ThPeB7024.
41. Mohlala BK, Tucker TJ, Besser MR et al. Investigation of HIV in amniotic fluid from HIV-infected pregnant women at full term. *J Infect Dis* 2005 192:488-91. <http://hiv.net/link.php?id=15995963>
42. Mok J, Pembrey I, Tovo PA, Newell M; for the European Paediatric Hepatitis C Virus Network. When does mother to child transmission of hepatitis C virus occur? *Obstet Gynecol Surv* 2005; 60: 572-574. <http://hiv.net/link.php?id=16121099>
43. Morris AB, Dobles AR, Cu-Uvin S et al. Protease inhibitor use in 233 pregnancies. *J Acquir Immune Defic Syndr* 2005; 40: 30-33. <http://hiv.net/link.php?id=16123678>
44. Noguera A, Fortuny A, Munoz-Almagro C et al. Hyperlactatemia in human immunodeficiency virus-infected infants who are exposed to antiretrovirals. *Pediatrics* 2004; 114: e598-603. <http://hiv.net/link.php?id=15492359>
45. Palumbo P, Holland B, Dobbs T et al. Antiretrovirals resistance mutations among pregnant HIV type-I-infected women and their newborns in the United States: Vertical transmission and clades. *J Infect Dis* 2001; 184: 1120-6. <http://hiv.net/link.php?id=11598834>
46. Poblano A, Figueroa I, Figueroa-Damian, Schnaas I. Effects of prenatal exposure to Zidovudine and Lamivudine on brainstem auditory evoked potentials in infants from HIV-infected women. *Proc West Pharmacol Soc* 2004; 47: 46-9. <http://hiv.net/link.php?id=15633610>
47. Poirier MC, Olivero OA, Walker DM, Walker VE. Perinatal genotoxicity and carcinogenicity of antiretroviral nucleoside analog drugs. *Toxicol Appl Pharmacol* 2004; 199: 151-61. <http://hiv.net/link.php?id=15313587>
48. Rongkavilit C, Thaitumyanon P, Chuenyam T, et al. Pharmacokinetics of stavudine and didanosine coadministered with nelfinavir in HIV-exposed neonates. *Antimicrob Agents Chemother* 2001; 45: 3585-90. <http://hiv.net/link.php?id=11709344>
49. Rongkavilit C, van Heeswijk RP, Limpongsanurak S, et al. Dose-escalation study of the safety and pharmacokinetics of nelfinavir in HIV-exposed neonates. *J Acquir Immune Defic Syndr* 2002; 29:455-63. <http://hiv.net/link.php?id=11981361>
50. Sarner L, Fakoya A. Acute onset lactic acidosis and pancreatitis in the third trimester of pregnancy in HIV-1 positive women taking antiretroviral medication. *Sex Transm Infect* 2002; 78: 58-9. <http://hiv.net/link.php?id=11872862>
51. Schackman BR, Oneda K, Goldie SJ. The cost-effectiveness of elective Cesarean delivery to prevent hepatitis C transmission in HIV-coinfected women. *AIDS* 2004; 18: 1827-34. <http://hiv.net/link.php?id=15316344>
52. Schäfer A. HIV und Schwangerschaft. L'Age-Stehr J, Helm EB (Hrsg). *AIDS und die Vorstadien. Ein Leitfaden für Praxis und Klinik*. In Springer Verlag 2001; Bd 1: 1-18.
53. Schuval S, Van Dyke RB, Lindsey JC et al. Hepatitis C prevalence in children with perinatal human immunodeficiency virus infection enrolled in a long-term follow up protocol. *Arch Pediatr Adolesc Med* 2004; 158: 1007-13. <http://hiv.net/link.php?id=15466691>
54. Scott GB, Rodman JH, Scot WA, et al. Pharmacokinetics and virologic response to ritonavir (RTV) in combination with zidovudine (ZDV) and lamivudine (3TC) in HIV-1-infected pregnant women and their infants. Abstract 794, 9<sup>th</sup> CROI 2002, Seattle.
55. Shapiro D, Tuomola R, Pollack H, et al. Mother-to-child transmission risk according to antiretrovirals, mode of delivery, and viral load in 2895 U.S. women (PACTG 367). Abstract 99, 11<sup>th</sup> CROI 2004, San Francisco.
56. Stek A, Mirochnick M, Capparelli E, et al. Reduced lopinavir exposure during pregnancy. Preliminary pharmacokinetic results from PACTG 1026. Abstract ThPeE7981, 15<sup>th</sup> World AIDS Conference 2004, Bangkok.

57. Stringer JS, Sinkala M, Chapman V, et al. Timing of the maternal drug dose and risk of perinatal HIV transmission in the setting of intrapartum and neonatal single dose nevirapine. *AIDS* 2003; 17: 1165-69. <http://hiv.net/link.php?id=14654326>
58. Tarantal AF, Castillo O, Ekert JE, et al. Fetal and maternal outcome after administration of tenofovir to gravid rhesus monkeys (*Macaca mulatta*). *J Acquir Immune Defic Syndr* 2002; 29: 207-20. <http://hiv.net/link.php?id=11873070>
59. Tardieu M, Brunelle F, Raybaud C et al. Cerebral MR imaging in uninfected children born to HIV-seropositive mothers and perinatally exposed to zidovudine. *AJNR Am J Neuroradiol* 2005; 26: 695-701. <http://hiv.net/link.php?id=15814907>
60. The Italian Register for HIV Infection in Children. Rapid disease progression in perinatally Infected children born to mothers receiving zidovudine monotherapy during pregnancy. *AIDS* 1999; 13: 927-33. <http://hiv.net/link.php?id=10371173>
61. The Perinatal Safety Review Working Group. Nucleoside exposure in the children of HIV-infected women receiving antiviral drugs: absence of clear evidence for mitochondrial disease in children who died before 5 years of age in five united states cohorts. *J Acquir Immune Defic Syndr Hum Retrovirol* 2000; 15: 261-8. <http://hiv.net/link.php?id=11115957>
62. Thorne C, Patel D, Newell M.. Increased risk of adverse pregnancy outcomes in HIV-infected women with highly active antiretroviral therapy in Europe. *AIDS* 2004; 19:2337-9. <http://hiv.net/link.php?id=15577551>
63. Timmermans S, Tempelman C, Godfried MH et al. Nelfinavir and nevirapine side effects during pregnancy. *AIDS* 2005; 19: 795-9. <http://hiv.net/link.php?id=15867493>
64. Tuomala RE, Watts DH, Li d, et al. Improved obstetric outcomes and few maternal toxicities are associated with antiretroviral therapy, including highly active antiretroviral therapy during pregnancy. *J Acquir Immune Defic Syndr*. 2005: 1-38. <http://hiv.net/link.php?id=15764963>
65. Vigano A, Bianchi R, Schneider L, et al. Lack of hyperlactataemia and impaired mitochondrial DNA content in CD4+ cells of HIV-uninfected infants exposed to perinatal antiretroviral therapy. Abstract 942, 11<sup>th</sup> CROI 2004, San Francisco
66. Vocks-Hauck M. HIV-Infektion und AIDS bei Neugeborenen, Kindern und Jugendlichen. In L'Age-Stehr J, Helm EB (Hrsg). *AIDS und die Vorstadien. Ein Leitfaden für Klinik und Praxis*. Springer Verlag 2001; Bd 1: 1-49.
67. Wade NA, Bearhead GS, Warren BL, et al. Abbreviated regimens of zidovudine prophylaxis and perinatal transmission of the HIV. *N Engl J Med* 1998; 339: 1409-14. <http://hiv.net/link.php?id=9811915>
68. Wade NA, Unadkad JD, Huang S, et al. Pharmacokinetics and safety of stavudine in HIV-infected pregnant women and their infants: Pediatric AIDS Clinical Trials Group protocol 332. *J Infect Dis* 2004; 190: 2167-74. <http://hiv.net/link.php?id=15551216>
69. Watts DH, Balasubramanian R, Maupin RT, et al. Maternal toxicity and pregnancy complications in human immunodeficiency virus-infected women receiving antiretroviral therapy: PACTG 316. *Am J Obstet Gynecol* 2004; 190: 506-16. <http://hiv.net/link.php?id=15551216>



# 11. Antiretroviral Therapy in Children

Tim Niehues and Hermione Lyall

## Characteristics of HIV infection in childhood

Children are not small adults. The HIV infection in childhood is different from the infection in adults with regard to transmission, the natural course of viral dynamics, maturity of the immune system and clinical manifestations. Several factors have to be considered when giving antiretroviral drugs to children: children may already have been exposed to AZT and other drugs in utero, the pharmacokinetics of the drugs are age-dependent and children require special attention to help with adherence.

More than 95 % of children are infected by perinatal transmission of the virus from the mother to the child (vertical infection). Transmission by transfusion, sexual transmission and drug abuse are much less prevalent. In most cases (75-90 %) HIV is transmitted peri- or intrapartum. Only a small proportion of children are infected in utero (10-25 %). Transmission by breastfeeding is important in resource-poor settings, but plays a minor role in developed countries, where breastfeeding by known HIV-infected mothers is strongly discouraged. The increasing knowledge about how HIV is vertically transmitted has led to a highly effective transmission prophylaxis and significant reduction of the transmission rate to less than 2 %. However, new infections in HIV-exposed children still occur

- if the HIV status of the mother is unknown
- if transmission prophylaxis is incomplete
- if the mother doesn't have access to transmission prophylaxis during pregnancy

Without antiretroviral therapy there is a bimodal natural course of vertical HIV infection: in 10-25 % of the children, rapid progression with AIDS-defining symptoms and lethal complications is observed within the first year of life. In 75-90 % there is a much slower disease course with a mean duration of more than 8 years until AIDS-defining symptoms occur. At present, disease progression is mainly influenced by the efficacy of antiretroviral therapy.

At birth, viral load is usually low (< 10,000 copies/ml) and then slowly rises within the first 2 months of life to values above 100,000 copies/ml and only slowly decreases after the age of 4-5 years. These viral dynamics are significantly different from the rapid increase and decrease of the viral load seen in untreated adults within a few months following the acute HIV infection (figure 1).

In children, the higher viral load is associated with the somatic growth of the lymphatic system and the inability of the immature immune system in children to mount an HIV-specific response. When assessing the immune system in infants and children, it is very important to compare the child's CD4+ T-cell count with the age-appropriate values (e.g. the mean CD4+ T-cell count for a 6-month-old baby being 3.000  $\mu$ l). Lymphocyte counts are very high in infancy and decline to adult levels beyond 6 years of age (table 1).

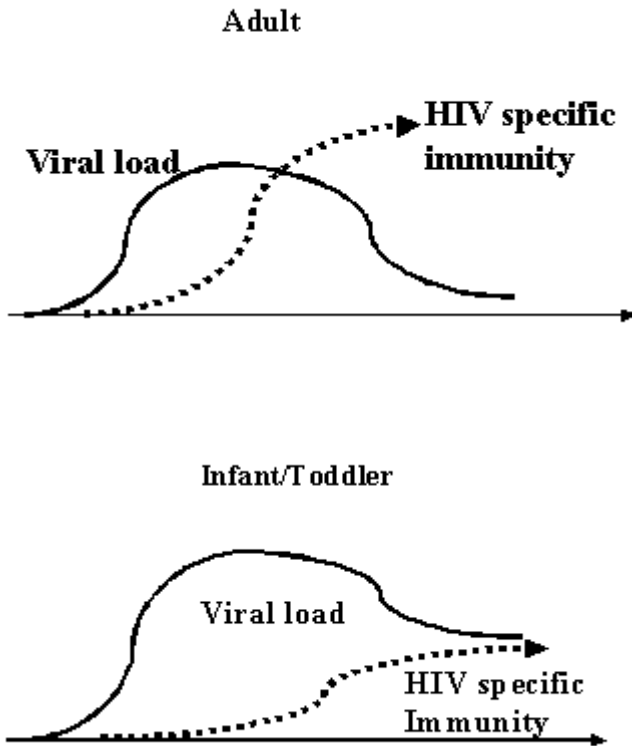


Figure 1: Differences in the natural course of viral load and anti-HIV immunity between adults and infants/toddlers

The spectrum of clinical manifestations in HIV-infected children is different from that of adults. In adults, typical manifestations of the acute HIV seroconversion illness are: fever, sore throat, lymphadenopathy and a mononucleosis-like disease. HIV seroconversion illness has not been described in perinatally-infected children. Symptomatic disease presenting in childhood has been classified according to severity of symptoms (table 2). Very recently a new WHO staging has been proposed (<http://www.who.int/hiv/pub/guidelines/en/index.html>). If antiretroviral therapy in children is effective, opportunistic infections (OIs) become a rarity. However, in children who newly present with HIV (e.g. if HIV status in the mother is unknown and there was no transmission prophylaxis), OIs can still be observed.



Table 1. 1994 Revised Human Immunodeficiency Virus Pediatric Classification System: Immune Categories Based on Age-Specific CD4+ T-cell Count and Percentage\*

Immune category*	< 12 months		1-5 yrs		6-12 yrs	
	cells/ $\mu$ l	(%)	cells/ $\mu$ l	(%)	cells/ $\mu$ l	(%)
Category 1: No suppression	$\geq 1,500$	( $\geq 25$ )	$\geq 1,000$	( $\geq 25$ )	$\geq 500$	( $\geq 25$ )
Category 2: Moderate suppression	750-1,499	(15-24)	500-999	(15-24)	200-499	(15-24)
Category 3: Severe suppression	< 750	(< 15)	< 500	(< 15)	< 200	(< 15)

\* Modified from: CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR* 1994; 43 (No. RR-12): p. 1-10.

Table 2. 1994 Revised HIV Pediatric Classification System: Clinical Categories

**Category N: Not Symptomatic**

Children who have no signs or symptoms considered to be the result of HIV infection or who have only one of the conditions listed in category A.

**Category A: Mildly Symptomatic**

Children with 2 or more of the following conditions but none of the conditions listed in categories B and C:

- Lymphadenopathy (> 0.5 cm at more than two sites; bilateral = one site)
- Hepatomegaly
- Splenomegaly
- Dermatitis
- Parotitis
- Recurrent or persistent upper respiratory infection, sinusitis, or otitis media

**Category B: Moderately Symptomatic**

Children who have symptomatic conditions, other than those listed for category A or category C, that are attributed to HIV infection. Examples of conditions in clinical category B include but are not limited to the following:

- Anemia (< 8 g/dl), neutropenia (< 1,000 cells/ $\mu$ l), or thrombocytopenia (< 100,000 cells/ $\mu$ l) persisting > 30 days
- Bacterial meningitis, pneumonia, or sepsis (single episode)
- Candidiasis, oropharyngeal (thrush) persisting for > 2 months in children aged > 6 months
- Cardiomyopathy
- Cytomegalovirus infection with onset before the age of one month
- Diarrhea, recurrent or chronic
- Hepatitis
- Herpes simplex virus (HSV) stomatitis, recurrent (i.e., more than two episodes within 1 year)

- HSV bronchitis, pneumonitis, or esophagitis with onset before age of 1 month
- Herpes zoster (i.e., shingles) involving at least two distinct episodes or more than one dermatome
- Leiomyosarcoma
- Lymphoid interstitial pneumonia (LIP) or pulmonary lymphoid hyperplasia complex
- Nephropathy
- Nocardiosis
- Fever lasting > 1 month
- Toxoplasmosis with onset before the age of 1 month
- Varicella, disseminated (i.e., complicated chickenpox)

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### Category C: Severely Symptomatic

Children who have any condition listed in the 1987 surveillance case definition for AIDS, with the exception of LIP (which is a category B condition).

- Serious bacterial infections, multiple or recurrent (i.e., any combination of at least 2 culture-confirmed infections within a 2-year period), of the following types: septicemia, pneumonia, meningitis, bone or joint infection, or abscess of an internal organ or body cavity (excluding otitis media, superficial skin or mucosal abscesses, and indwelling catheter-related infections)
- Candidiasis, esophageal or pulmonary (bronchi, trachea, lungs)
- Coccidioidomycosis, disseminated (at site other than or in addition to lungs or cervical or hilar lymph nodes)
- Cryptococcosis, extrapulmonary
- Cryptosporidiosis or isosporiasis with diarrhea persisting > 1 month
- Cytomegalovirus disease with onset of symptoms at age > 1 month (at a site other than liver, spleen, or lymph nodes)
- Encephalopathy (at least one of the following progressive findings present for at least 2 months in the absence of a concurrent illness other than HIV infection that could explain the findings): a) failure to attain or loss of developmental milestones or loss of intellectual ability, verified by standard developmental scale or neuropsychological tests; b) impaired brain growth or acquired microcephaly demonstrated by head circumference measurements, or brain atrophy demonstrated by computerized tomography or magnetic resonance imaging (serial imaging is required for children < 2 years of age); c) acquired symmetric motor deficit manifested by two or more of the following: paresis, pathologic reflexes, ataxia, or gait disturbance
- Herpes simplex virus infection causing a mucocutaneous ulcer that persists for > 1 month; or bronchitis, pneumonitis, or esophagitis for any duration affecting a child > 1 month of age
- Histoplasmosis, disseminated (at a site other than or in addition to lungs or cervical or hilar lymph nodes)
- Kaposi's sarcoma
- Lymphoma, primary, in brain
- Lymphoma, small, non-cleaved cell (Burkitt's), or immunoblastic or large cell
- Lymphoma of B-cell or unknown immunologic phenotype
- Mycobacterium tuberculosis, disseminated or extrapulmonary
- Mycobacterium, other species or unidentified species, disseminated (at a site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)

- Mycobacterium avium complex or Mycobacterium kansasii, disseminated (at site other than or in addition to lungs, skin, or cervical or hilar lymph nodes)
- Pneumocystis carinii pneumonia
- Progressive multifocal leukoencephalopathy
- Salmonella (non-typhoid) septicemia, recurrent
- Toxoplasmosis of the brain with onset at > 1 month of age
- Wasting syndrome in the absence of a concurrent illness other than HIV infection that could explain the following findings: a) persistent weight loss > 10 % of baseline, OR b) downward crossing of at least two of the following percentile lines on the weight-for-age chart (e.g., 95th, 75th, 50th, 25th, 5th) in a child  $\geq$  1 year of age OR c) < 5th percentile on weight-for-height chart on two consecutive measurements,  $\geq$  30 days apart PLUS a) chronic diarrhea (i.e., at least two loose stools per day for > 30 days) OR b) documented fever (for  $\geq$  30 days, intermittent or constant)

<sup>†</sup>CDC. 1994 Revised classification system for human immunodeficiency virus infection in children less than 13 years of age. *MMWR*, 1994. 43 (No. RR-12): p. 1-10.

## Diagnosis of HIV infection < 18 months of age

The detection of anti-HIV antibodies does not prove an infection in infants. High titers of anti-HIV IgG are transferred transplacentally from mother to child. Maternal antibodies can be detected in children up to the age of 18 months. Therefore a direct method of detecting HIV is necessary. Identification by PCR is highly sensitive and specific. Detection of HIV can be achieved within the first 48 hours after birth in 38 % of infected children, and within the first 2 weeks in 93 % of children (Dunn 1995). Once a positive HIV PCR is found, a second independent blood sample should soon be taken for repeat PCR analysis. As diverse subtypes of HIV exist, it is advised to test paired samples from mother and infant by HIV DNA PCR. If the mothers virus is not amplified by the primer set used, then another set or another test can be used to avoid a false negative result in the infant. Cord blood is not useful for the diagnosis because maternal cells may be present and may cause a false positive test result. In general, the disappearance of maternal IgG antibodies to HIV needs to be documented before HIV infection can be definitely excluded in the HIV-exposed child. There is a new WHO draft for diagnosing HIV in infants aimed at the developing world (<http://www.who.int/hiv/paediatric/infantdiagnosis.pdf>)

## Diagnosis of HIV infection > 18 months of age

HIV infection is diagnosed analogous to adults (see chapter “HIV Testing”).

## When to initiate antiretroviral therapy

Keep the following facts in mind before starting antiretroviral therapy in children:

- Treatment of HIV-infected children is usually not an emergency
- Take as much time as needed to decide whether to start with HAART or not

Commencing ART too early risks possible long-term side effects and early exhaustion of the limited supply of antiretroviral drugs that can be safely used in children. Therefore, many experts defer treatment in asymptomatic children with a low viral

load and without immunodeficiency. The indication for treatment is based on CD4+ T-cell count, viral load and clinical criteria. There are new WHO guidelines for resource-poor settings (<http://www.who.int/hiv/pub/guidelines/art/en/index.html>)

Table 3. PENTA recommendations on when to start antiretroviral therapy  
<http://www.ctu.mrc.ac.uk/penta/guidelines.htm>

Infants
<ol style="list-style-type: none"> <li>1. Clinical           <ul style="list-style-type: none"> <li>Start all infants with CDC stage B or C (AIDS) disease.</li> </ul> </li> <li>2. Surrogate marker           <ul style="list-style-type: none"> <li>Start in all infants with CD4+ T-cell % &lt; 25–35 %.</li> <li>Strongly consider starting with a VL &gt; 1 million copies/ml.</li> <li>Many experts treat all infants, whether symptomatic or not (with the aim of preventing HIV encephalopathy).</li> </ul> </li> </ol>
Children aged 1–3 years
<ol style="list-style-type: none"> <li>1. Clinical           <ul style="list-style-type: none"> <li>Start all children with stage C disease.</li> </ul> </li> <li>2. Surrogate marker           <ul style="list-style-type: none"> <li>Start all children with a CD4+ T-cell % &lt; 20 %.</li> <li>Strongly consider starting with a VL &gt; 250,000 copies/ml.</li> </ul> </li> </ol>
Children aged 4–8 years
<ol style="list-style-type: none"> <li>1. Clinical           <ul style="list-style-type: none"> <li>Start all children with stage C disease.</li> </ul> </li> <li>2. Surrogate marker data           <ul style="list-style-type: none"> <li>Start all children with a CD4+ T-cell % &lt; 15 %.</li> <li>Strongly consider starting with a VL &gt; 250,000 copies/ml.</li> </ul> </li> </ol>
Children aged 9–12 years
<ol style="list-style-type: none"> <li>1. Clinical           <ul style="list-style-type: none"> <li>Start all children with stage C disease.</li> </ul> </li> <li>2. Surrogate marker data           <ul style="list-style-type: none"> <li>Start all children with CD4+ T-cell &lt; 15 %, but with less urgency than in a younger child.</li> <li>Strongly consider starting with a VL &gt; 250,000 copies/ml.</li> </ul> </li> </ol>
Adolescents aged 13–17 years
<ol style="list-style-type: none"> <li>1. Clinical           <ul style="list-style-type: none"> <li>Start all adolescents with stage C disease.</li> </ul> </li> <li>2. Surrogate marker data           <ul style="list-style-type: none"> <li>Start all adolescents with an absolute CD4+ T-cell count between 200 and 350 cells/<math>\mu</math>l</li> </ul> </li> </ol>

In a meta analysis of 17 studies with 3,941 children who received no therapy or AZT monotherapy, viral load and CD4+ T-cell counts proved to be independent prognostic markers for the end stage, AIDS or death (Dunn 2003). From this large cohort of children, a computer program has been generated which can be used to give the risk of progression to AIDS or death within 6/12 months according to the age and either CD4+ T-cell count or viral load in the child (“PENTA Calculator” <http://www.ctu.mrc.ac.uk/penta/hppmcs/calcProb.htm>). Updated guidelines for treatment from Europe and the United States were published in 2004 (PENTA 2004

<http://www.ctu.mrc.ac.uk/penta/>; <http://aidsinfo.nih.gov/guidelines/>). The PENTA guidelines use the HPPMC cohort data to optimize timing of starting treatment at different ages, according to CD4+ T-cell count/viral load, in order to maintain the 1-year risk of progression to AIDS at < 10 % and death at < 5 %. (tables 3, 4).

Table 4. US Guidelines for the Use of Antiretroviral Agents in Pediatric HIV Infection (<http://aidsinfo.nih.gov/guidelines/>);

A. Indications for Initiation of antiretroviral therapy in children < 12 months of age

Clinical Category	CD4+ T-cell Percentage	Plasma HIV RNA Copy Number <sup>1</sup>	Recommendation
Symptomatic (Clinical category A, OR B, or C)	< 25 % (Immune category 2 or 3)	Any Value	Treat
Asymptomatic (Clinical category N) AND	≥ 25 % (Immune category 1)	Any Value	Consider Treatment <sup>2</sup>

<sup>1</sup> Plasma HIV RNA levels are higher in HIV-infected infants than older infected children and adults. Because overall HIV RNA levels are high and overlap between infants who have and those who do not have rapid disease progression, HIV RNA levels may be difficult to interpret in infants < 12 months of age.

<sup>2</sup> Because HIV infection progresses more rapidly in infants than older children or adults, some experts would treat all HIV-infected infants < 6 months or < 12 months of age, regardless of clinical, immunologic or virologic parameters.

B. Indications for Initiation of Antiretroviral Therapy in Children ≥ 1 Year of Age

Clinical Category	CD4+ T-cell Percentage	Plasma HIV RNA Copy Number	Recommendation
AIDS (C) OR	< 15 % (Immune Category 3)	Any value	Treat
Mild-Moderate Symptoms (A or B) OR	15-25 % <sup>1</sup> (Immune Category 2)	OR ≥ 100,000 copies/ml <sup>2</sup>	Consider treatment
Asymptomatic (N) AND	> 25 % (Immune Category 1)	AND < 100,000 copies/ml <sup>2</sup>	Many experts would defer therapy and closely monitor clinical, immune, and viral parameters

<sup>1</sup> Many experts would initiate therapy if CD4+ T-cell percentage is between 15 to 20 %, and defer therapy with increased monitoring frequency in children with 21 % to 25 %.

<sup>2</sup> There is controversy among pediatric HIV experts regarding the plasma HIV RNA threshold warranting consideration of therapy in children in the absence of clinical or immune abnormalities; some experts would consider initiation of therapy in asymptomatic children if plasma HIV RNA levels were between 50,000 to 100,000 copies/ml.

## General considerations for treatment of HIV-infected children

The treatment of children with antiretroviral drugs is becoming increasingly complex. A successful treatment requires an interdisciplinary approach to the children and their families.

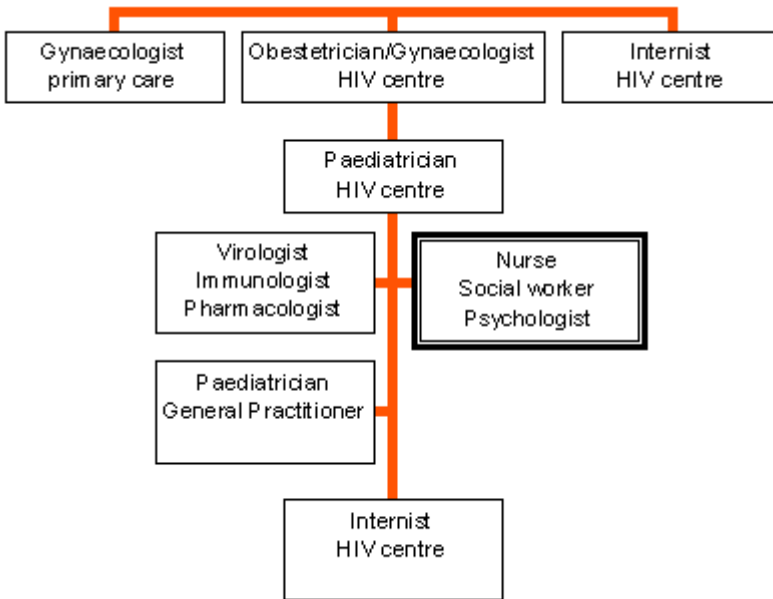


Figure 2: Interdisciplinary care for children and families who are affected by HIV

Antiretroviral therapy cannot be successful without good adherence to treatment. In the prospective PACTG 377, trial adherence was defined as having not missed a single medication dose over the last 3 days. According to this definition, only 70 % of children were found to be adherent (125 children within an observation period of 48 weeks; Van Dyke 2002). These data show that continuous motivation of children and their care providers is of high importance. The modalities of the daily intake of the medication need to be discussed in detail and adjusted to the daily and weekly routines of the family activities. Clear treatment goals need to be set, e.g. 90 % of the prescribed doses. Education of the patient and the family regarding the antiretroviral drugs is necessary. Sometimes a brief period of hospitalization at the start of antiretroviral therapy is useful to educate the patient and assess the tolerability of the treatment regimen. Adherence is particularly problematic in adolescence. In this age group, adherence often needs a close follow up including other health care professions such as psychologists and social workers. Peer support may also be helpful for young people. Sometimes periods off ART, despite the risk of ill health, have to be accepted in this group of patients until the young person is ready to restart therapy themselves. Underdosing has been shown to be a problem in day to day practice (Menson 2006). Dosing by weight instead of body surface area (given as an alter-

native in some old guidelines) may result in underdosing and simply ongoing growth may not be adjusted for. Plasma levels of NNRTIs and PIs can be measured (pharmacologic drug monitoring) to detect interindividual differences in drug metabolism, lack of adherence to exclude dosage that is too low and to prevent toxicity.

Obviously, regular physical examination and laboratory tests are necessary to monitor antiretroviral therapy in HIV-infected children. Only a physician who is experienced in the care of HIV-infected children and in the use of ART will be able to provide adequate care. Before medication is initiated or changed, the decision should always be based on at least 2 independent blood samples. Infections and vaccinations may influence viral load and CD4+ T-cell count. Therefore, it is not recommended to base decisions on data that have been gathered within 14 days of an infection or vaccination.

## Strategy

At present, eradication of HIV cannot be achieved by the existing therapy. In some children, viral load remains below detection level for years and subsequently there are no more HIV-specific antibodies detectable in these children. Even in these children, ultra-sensitive assays can still detect HIV (Persaud 2004). Therefore risks and benefits of antiretroviral therapy have to be balanced in each child. Interruption or incomplete adherence may cause more harm than deferring the therapy. The decision to start antiretroviral therapy has fundamental consequences for the children and families. From this point on, it usually means that children need to take the medication for life. Structured treatment interruptions have not been tested in childhood and adolescence in controlled studies. A retrospective analysis of unplanned treatment interruptions in children demonstrated a significant decline of CD4+ T-cell percentages by 6.6 % per year (Gibb 2004). PENTA (Pediatric European Network for Treatment of AIDS) is currently offering a paediatric study for CD4 guided treatment interruptions (PENTA11).

Table 5 shows the current treatment concept for choosing antiretroviral drug combinations. In the American PACTG 338-study on 297 children, it has been shown that a PI-containing combination is more effective than a dual combination of 2 NRTIs. It appears useful to start with a combination that includes two substance classes (2 NRTIs + PI or 2 NRTIs + NNRTI) in order to spare one or two substance classes for future change of antiretroviral therapy. If there is not full viral suppression on treatment, development of cross-resistance to NNRTIs and PIs is very likely. Therefore, sparing substance classes may be useful for a better long-term efficacy. However, in the recent PACTG 256 study, an aggressive approach with inclusion of 3 substance classes (NRTI + NNRTI + PI) led to a highly effective and long-lasting virus load reduction (72 % of patients over 4 years), especially if therapy was started at an early age (< 3 months) (Luzuriaga 2004). Because of small patient numbers in childhood and adolescence it is highly recommended to include all children who receive antiretroviral therapy in multicenter clinical trials (e. g. PENTA (Pediatric European Network for Treatment of AIDS), <http://www.pentatrials.org>, Tel. Dr. Diana Gibb ++ 44 20 7670 4709; Lynda Harper ++ 44 20 7670 4791). The PENPACT 1 study with participation both of the PENTA and the PACTG group has recruited 266 children and will answer the

question whether initial therapy in children is more effective with 2 NRTIs + PI or with 2 NRTIs + NNRTI.

Table 5. Treatment concept in HIV-infected children

Regime	Recommendation
NRTI 1 + NRTI 2 + PI or NRTI 1 + NRTI 2 + NNRTI	Include children in multicenter clinical trials (e.g. PENPACT 1)

Nucleoside Reverse Transcriptase Inhibitors: AZT, ddl, 3TC, d4T, ABC, FTC, TDF. Some NRTI combinations not recommended (AZT+d4T, FTC+3TC, d4T+ddl)

Protease Inhibitors: NFV, LPV/RTV, ATV, IDV, APV. Ritonavir as booster drug.

Non-nucleoside Reverse Transcriptase Inhibitors: NVP, EFV.

In the placebo-controlled CNA3006 study on children who had already received antiretroviral therapy, a triple NRTI therapy was shown to be more effective than 2 NRTIs (Saez-Llorens 2001). However, this study was carried out on children who were already on ART and were not treatment naive. Data in adults suggest that a triple NRTI strategy is less effective than a therapy including a PI or NNRTI. At present there are no data on triple NRTI therapy as initial therapy for children.

## Classes of antiretrovirals

In the following paragraphs the different antiretroviral classes that are currently used in children are introduced with emphasis on pediatric issues and in particular daily dosage, relation to food intake (unless the drug can be taken independent of meals) and side effects. All drugs can lead to nausea, vomiting, fever, headache, diarrhea, rash and anorexia.

### Nucleos(t)ide analog reverse transcriptase inhibitors

NRTIs have been used for over 15 years in the treatment of HIV-infected children. The combination of 2 NRTIs as part of HAART is effective and well tolerated. Severe side effects are rare but potentially life-threatening, such as lactic acidosis and hepatic steatosis. Other side effects are neuromuscular dysfunction, cardiomyopathy, pancytopenia, pancreatitis and neuropathy. All of these effects are probably related to mitochondrial toxicity caused by NRTIs. Due to pharmacologic and antiviral antagonism as well as synergistic neurotoxicity, the following combinations are not recommended: AZT+d4T, ddI+d4T (not first line), FTC+3TC. The less mitochondrially toxic NRTIs include 3TC, ABC, FTC and TDF.

**Zidovudine** (ZDV, AZT, Retrovir™) is available as syrup, capsules, tablets and concentrate for injection or intravenous infusion. Dosage is 180 mg/m<sup>2</sup> orally every 12 hours. Maximum dosage is 300 mg every 12 hours.

**Lamivudine** (3TC, Epivir™) is available as oral solution and tablets. Dosage is 4 mg/kg every 12 hours, maximum dosage is 150 mg every 12 hours. In older children and adolescents (> 35 kg body weight) combination with AZT (Combivir™) can be used and daily pill burden reduced. In adults, 3TC shows antiviral activity against hepatitis B virus. Therefore, it is useful to include 3TC in the HAART



regimen for children with chronic hepatitis B. A once-daily regimen in combination with abacavir has been shown to be as effective as twice daily (PENTA 13 Trial).

**Stavudine** (d4T, Zerit™) is available as oral solution and capsules. Dosage is 1 mg/kg every 12 hours. Maximum dosage is 40 mg every 12 hours. d4T is not recommended for first-line therapy as it has a high risk of causing lipoatrophy (see below).

**Didanosine** (ddI, Videx™) is available as oral solution and tablets. Dosage is 200 mg/m<sup>2</sup> once daily. Maximum dosage is 400 mg (body weight ≥ 60 kg) or 250 mg (body weight < 60 kg). It should be taken on an empty stomach.

**Abacavir** (ABC, Ziagen™) is available as oral solution and tablets. Dosage is 8 mg/kg every 12 hours, maximum dosage is 300 mg twice daily or 600 mg once daily. In the PENTA 5 trial, ABC-containing regimens showed a better efficacy regarding viral load suppression than combinations containing AZT and 3TC. There is a potential risk of a fatal hypersensitivity reaction. If ABC hypersensitivity occurs and the drug is stopped, it should not be restarted as, rarely, deaths have occurred in adults upon rechallenge. HLA B57 appears to be associated with hypersensitivity and HLA testing before starting ABC may be useful, as one may consider an alternative NRTI in HLA B57 positive children. In the PENTA 15 study the pharmacokinetics, feasibility and acceptability of dosing ABC or ABC in combination with 3TC once daily in children aged 3 months to 36 months will be assessed.

**Emtricitabine** (FTC, Emtriva™) is available as capsules and oral solution. Dosage is 6 mg/kg. The administration of capsules results in a 20 % higher plasma level. FTC can be given once daily. Maximum dosage is 200 mg once daily.

**Tenofovir** (TDF, Viread™) is only available as tablets (300 mg). In 18 children and adolescents between 6 and 16 years of age, a dosage of 200 mg/m<sup>2</sup> once daily was well tolerated (Hazra 2004). TDF should be taken with meals. There are no controlled trials regarding its efficacy in children. TDF has been shown to have renal and bone side effects which may be significant for children and should be monitored closely.

## Non nucleoside reverse transcriptase inhibitors

NNRTIs have a low genetic barrier to resistance. Within a few weeks suboptimal dosing or adherence can lead to cross-class resistance mutations affecting all available NNRTIs. NNRTIs exist in palatable liquid preparations which are easier for children to tolerate than the liquid PI solutions.

**Efavirenz** (EFV, Sustiva™ or Stocrin™) is available as capsules and oral solution. Dosage is 200 mg (body weight 10-15 kg), 250 mg (15-20 kg), 300 mg (20-25 kg), 350 mg (25-33 kg), 400 mg (33-40 kg), 600 mg (> 40 kg) once daily. Maximum dosage is 600 mg once daily. When using the solution, a 20 % higher dosage than for capsules is necessary. Central nervous system symptoms (somnolence, insomnia, abnormal dreams, confusion, abnormal thinking, concentration, amnesia, agitation, depersonalization, hallucinations, euphoria) appear to be more common in adults than in children. Skin rash is observed in < 10 %. It is rarely severe and usually disappears within days despite continuation of efavirenz. Efavirenz causes raised lipids in some patients.

**Nevirapine** (NVP, Viramune™) is available as tablets and suspension. Dosage is 150 mg/m<sup>2</sup> once daily for 14 days, followed by 150 mg/m<sup>2</sup> every 12 hours, if liver function tests are normal. In a retrospective analysis, once-daily application – 300 mg/m<sup>2</sup> after week 2 – was as effective as twice-daily (Verweel 2003). The most common side effect of nevirapine is a skin rash. Rash occurs in up to 16 % of children during the first weeks of treatment and may be quite severe (8 %) and require hospitalization. Life-threatening complications (Steven Johnson Syndrome, toxic epidermal necrolysis) are rare. Hepatotoxicity may also occur, and fatal cases have been reported in adults, but this appears to be less common in children.

## Protease inhibitors

All PIs can be used in combination with 2 NRTIs. PIs differ from each other in respect to their tolerability and side effects. As with adults, dyslipidemia is associated with PI use (Lainka 2002). It includes elevated total cholesterol, triglycerides (TG), and low density lipoprotein cholesterol (LDL-c) and decreases in high density lipoprotein cholesterol (HDL-c). In lipodystrophy, there is a loss of subcutaneous fat (lipoatrophy) and/or a deposition of fat tissue subcutaneously or in visceral stores (lipohypertrophy) including the presence of dorsocervical fat accumulation ("buffalo hump") and increased waist-to-hip ratio. Lipoatrophy is marked by thinning of subcutaneous fat in the face, buttocks, and extremities associated with a prominent appearance of peripheral veins. The body habitus changes usually occur gradually over months to years. The exact prevalence of lipodystrophy in children is unknown and there are no clear diagnostic criteria. Lipodystrophy and dyslipidemia coexist, their interconnection is unclear. Other substance classes such as NRTIs (e.g. d4T) and NNRTIs (efavirenz, not nevirapine) may also play a role in the pathogenesis of lipodystrophy. Insulin resistance is another side effect which may present with or without fasting hyperglycemia, with new onset diabetes mellitus and exacerbations of pre-existing diabetes. Moreover, PIs may influence bone mineral density and metabolism (Mora 2004). Taken together, the long-term consequences of PI-containing ART for growth and development of the child are currently not known.

**Lopinavir/Ritonavir** (LPV/r, Kaletra™) is a coformulation of lopinavir and ritonavir, in which ritonavir acts as a pharmacokinetic enhancer (booster). It is available as capsules, tablets and oral solution. In therapy-naïve and -experienced children, the combination of LPV/r and NRTI or NNRTI has high efficacy (Saez-Llorens 2003, Fraaij 2004). The dosage is 13 mg/kg lopinavir plus 3.25 mg/kg ritonavir twice daily (bodyweight 7 - < 15 kg), 11 mg/2.75 mg (15-50 kg), 533 mg/133 mg (> 50 kg). It should be taken with meals. The dosage of LPV/r may need to be increased by up to 30 % when combined with a NNRTI. A therapeutic drug monitoring is useful in this situation.

**Nelfinavir** (NFV, Viracept™) is available as tablets and powder. It is well tolerated in most children. The dosage is 55 mg/kg every 12 hours, but in infants < 3 months 75 mg/kg every 12 hours is required. Maximum dosage is 1,250 mg every 12 hours. Some older children require 1,500 mg every 12 hours, more than the adult dose. Therapeutic drug monitoring is useful. In the PENTA 7 trial in newborns and infants below the age of 3 months, combination of nelfinavir with d4T and ddI was poorly absorbed with poor plasma levels and consequently poor viral load suppression (Aboulker 2004). It should be taken with meals. The most common side effect

is diarrhea, which rarely causes discontinuation of the drug. To facilitate the administration of nelfinavir, the tablets can be crushed or readily dissolved in water. In the PENTA 5 study, nelfinavir powder was only poorly tolerated.

**Amprenavir** (APV, Agenerase™) is not recommended for children < 4 years of age. It is available as capsules and oral solution. Capsule dosage is 20 mg/kg every 12 hours, for the oral solution 22.5 mg/kg every 12 hours. The maximum dosage is 1,200 mg every 12 hours. The dosage of amprenavir needs to be increased by 30 % in case of combination with NNRTI. In 5 children, who were intensively pretreated, amprenavir in combination with delavirdine showed good efficacy (Engelhorn 2004). The most common side effects are nausea, vomiting, diarrhea and headaches. The prodrug of amprenavir is fosamprenavir, which is currently used for antiretroviral therapy in adults at a dosage of 1,400 mg twice daily (without ritonavir) or 1,400 mg + ritonavir 200 mg once daily. It should be taken with meals. There is no pediatric dose. The drug is currently under investigation for use in HIV-infected children.

**Ritonavir** (RTV, Norvir™) is available as oral solution or capsules. However, most children do not tolerate the taste of the oral solution. The dosage is 350-400 mg/m<sup>2</sup> every 12 hours, maximum dosage 600 mg every 12 hours. It should be taken with meals. Today, ritonavir is almost exclusively used as a drug to boost other protease inhibitors, and for this purpose, the dosage is 75 mg/m<sup>2</sup> every 12 hours.

**Indinavir** (IDV, Crixivan™) is available as capsules. Dosage is 500 mg/m<sup>2</sup> every 12 hours in combination with ritonavir 750 mg/m<sup>2</sup> every 12 hours. It should be taken on an empty stomach. Side effects include nephrolithiasis, especially at high plasma levels.

**Saquinavir** (SQV, Invirase™ tablets). Dosage in children is unknown. There is very limited experience with 50 mg/kg every 12 hours. Saquinavir should only be used in combination with ritonavir because of poor bioavailability. It should be taken with meals.

**Atazanavir** (ATV, Reyataz™) is available as capsules. It should be taken with meals. Atazanavir could be an interesting drug for use in children in the future, because of its once-daily application and lower incidence of dyslipidemia. At present, there is no approved dosage for children. Phase I and II studies are underway. Some patients develop jaundice. Better ATV levels are obtained with ritonavir boosting.

**Tipranavir** (TPV, Aptivus™) is available as 250 mg soft gel capsules. It should be taken with meals. At present, there is no approved dosage for children and it has been associated with significant hepatotoxicity in adults. Phase I and II studies in children are being conducted.

## Fusion inhibitors

Fusion inhibitors represent a new antiretroviral class (see HAART chapter). In adults, randomized studies have proven an effect of T-20 (the first drug of this substance class) within salvage treatment protocols.

**Enfuvirtide** (T-20, Fuzeon™) can be used in children older than 6 years of age. The drug is injected subcutaneously at a dosage of 2 mg/kg every 12 hours. A study with 14 children showed no severe side effects, but after a 2-year treatment duration only 6 out of 14 children stayed on this therapy (Church 2004). Reasons for treat-

ment discontinuations were aversion to injections, local injection site reactions, inefficient viral load suppression, thrombocytopenia and edema. There are no controlled studies on the use of T-20 in children.

## Drug interaction

There is a great number of interactions, which may complicate antiretroviral therapy when it is co-administered with other drugs. In particular, tuberculosis and atypical mycobacterial treatment may interact with ART, so close monitoring and expert advice should be sought.

## Monitoring of therapy efficacy and therapy failure

A good treatment response is documented by a permanent suppression of the viral load below the detection limit. Not all children achieve complete viral suppression, and development of resistance is not uncommon due to the selection pressure of the anti-HIV immune response as well as antiretroviral therapy. There is no commonly used definition of treatment failure in children treated with antiretroviral drugs. Therefore, it is also not certain when to change antiretroviral therapy. In the PENPACT 1 study, this important question is being addressed: children are randomized to change a failing treatment at either low or high viral rebound ( $> 1,000$  or  $> 30,000$  copies/ml) Alternatively, therapy failure can be defined by a decrease in CD4+ T-cell counts, e.g. a decrease by at least a third of the absolute CD4+ T-cell number in less than 6 months. In children with relatively low CD4+ T-cell percentages of less than 15 %, a decrease by more than 5 % may already be significant for therapy failure. The use of clinical criteria, such as toxicity of the drugs, a progression within the CDC classification, an increased susceptibility to infections, encephalopathy and failure to thrive, may all indicate treatment failure.

Many children with multi-disciplinary support do now manage to maintain longterm ( $> 5$  years) viral suppression on first line therapy, and the longer this can be maintained on first line therapy the better. Indeed over the last few years as more treatments have become available for children they have been increasingly successful with treatment. The most common cause of treatment failure is insufficient adherence, which can be found in up to 25-30 % of children. Assessment of adherence may be difficult as questionnaires may not be reliable. Determination of plasma levels and resistance tests (e.g. reoccurrence of wild type) are other options to assess adherence and monitor antiretroviral therapy more effectively.

## Change of therapy

There are no systematic data on how and when to change therapy in HIV-infected children. The suppression of viral load that can be reached by a second or third regimen depends on the preceding therapy and the resistance status. The longer and more intensive pretreatment has been, the lower the viral load reduction that can be expected. When a new antiretroviral drug combination is introduced, the age of the child, the availability of appropriate formulations (e.g. solution for infants), side effects and interactions with other drugs are all taken into account. At present, it is unclear whether dyslipidemia and lipodystrophy can be influenced by a change

from a PI-containing regimen to an NNRTI-containing HAART (McComsey 2003). In adults, randomized and prospective trials have shown that a change of antiretroviral therapy guided by resistance tests leads to a better response. In children there is a smaller prospective study (Englund 2004). Usually, the initial treatment regimen contains a double NRTI backbone (e.g. AZT+3TC or ABC+3TC). When changing therapy, it appears useful to introduce a backbone with two new NRTIs and one new substance class into the treatment combination. A mega-HAART therapy combining five to six antiretroviral drugs has not been systematically investigated in children. In single cases, it may be useful to introduce up to five drugs if treatment failure has occurred despite multiple different drug regimens.

## Supportive therapy and prophylaxis

Opportunistic infections have become rare in perinatally infected children who experience immune reconstitution with HAART. In most of these HIV infected children respiratory and other infections are not more common than in healthy children. HIV infected children who are treated with HAART and who are clinically stable can even be given live varicella virus vaccine and show a specific response, which is an impressive sign of successful immune reconstitution (Armeninan, 2006). In most of these children treatment with i.v. immunoglobulins and PCP prophylaxis is no longer required (Nachman 2005b).

However, there are still life-threatening infections and deaths from HIV, if perinatal HIV infection is unrecognized or HAART has not yet led to immune reconstitution. A description of such infections in adults is given in other chapters of this book. An excellent and detailed guide for treatment of children with OIs can be found at <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5314a1.htm>.

## Conclusion

In many aspects, HIV infection in children is different from HIV infection in adults. The ongoing growth and development of children, their viral dynamics and immaturity of the immune system result in a different response to HIV in children compared to adults. This has important consequences for diagnosis and treatment of HIV in children. The aim of the therapy is to reach maximum efficacy while avoiding long-term side effects. Sustained success in the treatment of children with HIV infection can be achieved by:

- a multidisciplinary approach;
- standardized treatment protocols;
- participation in multicenter trials;
- development of new drugs and strategies for children.

In developed countries, the clinical picture of HIV infection in children has now changed from an often fatal to a treatable chronic infection. This picture is entirely different in developing countries, where the majority of children do not have access to HAART. According to the WHO, more than 500,000 children died from HIV infection or its sequelae in the year 2004.

## References

1. Aboulker JP, Babiker A, Chaix ML, et al. Highly active antiretroviral therapy started in infants under 3 months of age: 72-week follow-up for CD4 cell count, viral load and drug resistance outcome. *AIDS* 2004; 18:237-45. <http://amedeo.com/lit.php?id=15075541>
2. Brambilla P, Bricalli D, Sala N, et al. Highly active antiretroviral-treated HIV-infected children show fat distribution changes even in absence of lipodystrophy. *AIDS* 2001; 15:2415-22. <http://amedeo.com/lit.php?id=11740192>
3. Buseyne F, Blanche S, Schmitt D, et al. Detection of HIV-specific cell-mediated cytotoxicity in the peripheral blood from infected children. *J Immunol.* 1993;150:3569-81. <http://amedeo.com/lit.php?id=8096852>
4. Church JA, Hughes M, Chen J, et al. Long term tolerability and safety of enfuvirtide for human immunodeficiency virus 1-infected children. *Pediatr Infect Dis J* 2004;23:713-8. <http://amedeo.com/lit.php?id=15295220>
5. Dunn DT, Brandt CD, Krivine A, et al. The sensitivity of HIV-1 DNA polymerase chain reaction in the neonatal period and the relative contributions of intra-uterine and intra-partum transmission. *AIDS* 1995; 9:F7-11. <http://amedeo.com/lit.php?id=8527070>
6. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet* 2003; 362:1605-11 <http://amedeo.com/lit.php?id=14630440>
7. Engelhorn C, Hoffmann F, Kurowski M, et al. Long-term pharmacokinetics of amprenavir in combination with delavirdine in HIV-infected children. *AIDS.* 2004;18:1473-5. <http://amedeo.com/lit.php?id=15199327>
8. Englund JA, Raskino C, Vavro C, et al. Mutations linked to drug resistance, HIV type 1 biologic phenotype and their association with disease progression in children receiving NRTIs. *Pediatr Infect Dis J* 2004; 23:15-22. <http://amedeo.com/lit.php?id=14743040>
9. Fraaij PL, Neubert J, Bergshoeff AS, et al. Safety and efficacy of a NRTI-sparing HAART regimen of efavirenz and lopinavir/ritonavir in HIV-1-infected children. *Antivir Ther* 2004;9:297-9. <http://amedeo.com/lit.php?id=15134193>
10. Galli L, de Martino M, Tovo PA, et al. Onset of clinical signs in children with HIV-1 perinatal infection. Italian Register for HIV Infection in Children. *AIDS* 1995;9:455-61. <http://amedeo.com/lit.php?id=7639970>
11. Gibb DM, Duong T, Leclézio VA, et al. Immunologic changes during unplanned treatment interruptions of highly active antiretroviral therapy in children with HIV type 1 infection. *Pediatr Infect Dis J* 2004;23:446-50. <http://amedeo.com/lit.php?id=15131469>
12. Gotch F, Hardy G. The immune system: our best antiretroviral. *Curr Opin Infect Dis* 2000;13:13-17. <http://amedeo.com/lit.php?id=11964767>
13. Grosch-Wörner I, Schäfer A, Obladen M, et al. An effective and safe protocol involving zidovudine and caesarean section to reduce vertical transmission of HIV-1 infection. *AIDS* 2000; 14:2903-11. <http://amedeo.com/lit.php?id=11153672>
14. Hazra R, Balis FM, Tullio AN, et al. Single-dose and steady-state pharmacokinetics of tenofovir disoproxil fumarate in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2004;48:124-9. <http://amedeo.com/lit.php?id=1469352>
15. Lainka E, Oezbek S, Falck M, Ndagijimana J, Niehues T. Marked dyslipidemia in HIV-infected children on protease inhibitor-containing antiretroviral therapy. *Pediatrics* 2002; 110:e56. <http://amedeo.com/lit.php?id=12415062>
16. Luzuriaga K, McManus M, Mofenson L, et al.; PACTG 356 Investigators. A trial of three antiretroviral regimens in HIV-1-infected children. *N Engl J Med.* 2004; 350:2471-80. <http://amedeo.com/lit.php?id=15190139>
17. McComsey G, Bhumbra N, Ma JF, et al. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics* 2003;111:e275-81. <http://amedeo.com/lit.php?id=12612284>
18. Mora S, Zamproni I, Beccio S, et al. Longitudinal changes of bone mineral density and metabolism in antiretroviral-treated human immunodeficiency virus-infected children. *J Clin Endocrinol Metab* 2004;89:24-8. <http://amedeo.com/lit.php?id=4715822>
19. Nachman SA, Stanley K, Yogev R, et al. Nucleoside analogs plus ritonavir in stable antiretroviral therapy-experienced HIV-infected children: a randomized controlled trial. *JAMA* 2000; 283:492-8. <http://amedeo.com/lit.php?id=11579244>
20. Niehues T, Wintergerst U, Funk M, für die Konsensusgruppe der Pädiatrischen Arbeitsgemeinschaft AIDS (PAAD). Empfehlungen zur antiretroviralen Therapie bei HIV-infizierten Kindern - Vollständig überarbeitetes und aktualisiertes Konsensus-Statement der PAAD und der Deutschen Gesellschaft für Pädiatrische Infektiologie (DGPI) *Monatsschr Kinderheilkd* 2001; 149:1372-82.

21. Paediatric European Network for Treatment of AIDS (PENTA). Comparison of dual nucleoside-analogue reverse-transcriptase inhibitor regimens with and without nelfinavir in children with HIV-1 who have not previously been treated: the PENTA 5 randomised trial. *Lancet* 2002; 359:733-40. <http://amedeo.com/lit.php?id=11888583>
22. Persaud D, Siberry GK, Ahonkhai A, et al. Continued production of drug-sensitive human immunodeficiency virus type 1 in children on combination antiretroviral therapy who have undetectable viral loads. *J Virol* 2004;78:968-79. <http://amedeo.com/lit.php?id=14694128>
23. Saez-Llorens X, Nelson RP Jr, Emmanuel P, et al. A randomized, double-blind study of triple nucleoside therapy of abacavir, lamivudine, and zidovudine versus lamivudine and zidovudine in previously treated HIV type 1-infected children. The CNA3006 Study Team. *Pediatrics* 2001, 107:E4. <http://amedeo.com/lit.php?id=11134468>
24. Saez-Llorens X, Violari A, Deetz CO, et al. Forty-eight-week evaluation of lopinavir/ritonavir, a new protease inhibitor, in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2003, 22:216-24. <http://amedeo.com/lit.php?id=12634581>
25. Van Dyke RB, Lee S, Johnson GM, et al. Reported adherence as a determinant of response to highly active antiretroviral therapy in children who have HIV infection. *Pediatrics* 2002;109:e61. <http://amedeo.com/lit.php?id=11927734>
26. van Rossum AM, Fraaij PL, de Groot R. Efficacy of highly active antiretroviral therapy in HIV-1 infected children. *Lancet Infect Dis* 2002; 2:93-102 <http://amedeo.com/lit.php?id=11901656>
27. Verweel G, Sharland M, Lyall H, et al. Nevirapine use in HIV-1-infected children. *AIDS* 2003, 17:1639-47. <http://amedeo.com/lit.php?id=12853746>
28. Wang LH, Wiznia AA, Rathore MH, et al. Pharmacokinetics and safety of single oral doses of emtricitabine in human immunodeficiency virus-infected children. *Antimicrob Agents Chemother* 2004;48:183-91. <http://amedeo.com/lit.php?id=4693538>
29. Working Group on Antiretroviral Therapy and Medical Management of HIV Infected Children, National Pediatric and Family Resource Center (NPHRC), Health Resources and Services Administration (HRSA) and National Institutes of Health (NIH). Guidelines for the use of antiretroviral agents in pediatric HIV infection, January 2004, <http://www.aidsinfo.nih.gov/guidelines>





Part 3

AIDS



## 12. Opportunistic Infections (OIs)

Christian Hoffmann

### OIs in the HAART era

In Western industrialized countries, many OIs have become rare today. This is particularly true for those infections that are associated with severe immunodeficiency, such as CMV and MAC disease. The incidence of these OIs has now been reduced to less than one tenth of their frequency in the pre-HAART era. However, HAART has not only lowered the incidence, but also changed the course of OIs quite considerably. While survival times after the first AIDS illness were previously two to three years at most, many patients now live with AIDS for ten years and longer. Our own study of around 150 patients with cerebral toxoplasmosis demonstrates this: while 5-year survival after the toxoplasmosis episode was at 8 % in the years 1990-1993, it had climbed to 30 % by 1994-1996. This rate has risen to approximately 80 % since 1997.

Most patients who develop AIDS or severe opportunistic infections today are unaware of their HIV infection status. Since the year 2000, around 50 % of patients who presented with AIDS at our outpatient clinic were unaware of their HIV infection at the time. Another 35 % of patients had not been treated with antiretroviral drugs until AIDS was diagnosed. These patients often present late, usually in a very serious condition. AIDS remains life threatening, and a severe PCP does not become less critical because of the overall improvement in long-term survival. The acute danger remains. Therefore, every HIV clinician should be familiar with the diagnosis and therapy of OIs, even today.

Although much has improved in recent years, many problems remain. There is still no adequate treatment available for diseases such as PML or cryptosporidiosis, and resistance will become an increasing problem with other infections. HAART does not always lead to immediate improvement, and may even complicate things because of the atypical course of disease under HAART, as well as with immune reconstitution. For this reason, we have included a separate sub-chapter on immune reconstitution syndrome (IRIS). There are still no guidelines for OI prophylaxis in many countries, and the US recommendations, last published in December 2004 (Benson 2004), cannot always be adopted elsewhere, as seroprevalence rates often differ. In addition, it is becoming clear that nearly every type of prophylaxis or maintenance therapy can be discontinued when a sufficient level of immune reconstitution has been reached.

In many places, diagnostic problems recur again and again for many OIs, perhaps with the exception of larger HIV centers. Those unfamiliar with the pathogens will not recognize them! Therefore, we urgently recommend that after an initial consultation any specimens be sent to specialized reference laboratories. Further advice, if needed, can also be sought from a specialized clinician or a clinical HIV center.

The most important rule remains true even today for nearly all OIs: the poorer the immune status of the patient, the earlier the invasive diagnostic procedures should begin! The primary aim should not be to spare patients extensive diagnostic testing

involving unpleasant procedures. If nothing can be found the first time around, diagnostic tests must be repeated. Treatment should be initiated as rapidly as possible. The second rule: in many cases, a number of OIs can largely be excluded if the immune status and viral load are known. Knowledge of the current status is therefore very important! Table 1 shows cut-offs for CD4+ T-cells, below which certain infections can be expected. The occurrence of OIs above the respective cut-off values is usually the exception.

Table 1. Important cut-offs for CD4+ T-cells, above which particular AIDS illnesses are improbable. These CD4 counts are only reference values; exceptions are always possible.

No cut-off	Kaposi's sarcoma, pulmonary tuberculosis, HZV, bacterial pneumonia, lymphoma
< 250/ $\mu$ l	PCP, esophageal candidiasis, PML, HSV
< 100/ $\mu$ l	Cerebral toxoplasmosis, HIV encephalopathy, cryptococcosis, miliary tuberculosis
< 50/ $\mu$ l	CMV retinitis, atypical mycobacteriosis

The third rule: if not already in place, antiretroviral therapy should be started as quickly as possible in the presence of an OI. Immune reconstitution is the best protection against relapses. It will also protect against further OIs. However, the optimal start for HAART is still not clear. In many cases it may be better to wait for a few days or even weeks with acute OI therapies which are mainly toxic and highly interactive. This applies, for example, to PCP, CMV retinitis, or toxoplasmosis. On the other hand, treatment of esophageal candidiasis or a herpes infection is usually no reason to delay HAART. For some OIs, such as PML or cryptosporidiosis, which have no specific therapy, starting HAART is the only hope. In these cases in particular, there is no time to lose.

The following is intended as a relevant practical overview, and will not include clinical rarities. The literature cited refers to interesting reviews and almost exclusively to controlled and, if possible, randomized studies.

## OI reviews

1. Brodt HR, Kamps BS, Gute P, Knupp B, Staszewski S, Helm EB. Changing incidence of AIDS-defining illnesses in the era of antiretroviral combination therapy. *AIDS* 1997, 11:1731-8. <http://amedeo.com/lit.php?id=9386808>
2. Jacobson MA, French M. Altered natural history of AIDS-related opportunistic infections in the era of potent combination antiretroviral therapy. *AIDS* 1998, Suppl A:S157-63. <http://amedeo.com/lit.php?id=9632998>
3. Kaplan JE, Masur H, Holmes KK. Guidelines for preventing opportunistic infections among HIV-infected persons 2002. Recommendations of the US Public Health Service and the IDSA. *MMWR* 2002, 51(RR-8):1-52. <http://amedeo.com/lit.php?id=12081007>
4. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med* 2002, 137:239-50. <http://amedeo.com/lit.php?id=12186514>
5. Ledergerber B, Egger M, Erard V, et al. AIDS-related opportunistic illnesses occurring after initiation of potent antiretroviral therapy: the Swiss HIV Cohort Study. *JAMA* 1999, 282: 2220-6. <http://amedeo.com/lit.php?id=10605973>

6. Lundgren J, Masur H. New approaches to managing opportunistic infections. *AIDS* 1999, 13 Suppl A:S227-34.
7. McNaghten AD, Hanson DL, Jones JL, Dworkin MS, Ward JW. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. *AIDS* 1999, 13:1687-95. <http://amedeo.com/lit.php?id=10509570>
8. Sepkowitz KA. Effect of HAART on natural history of AIDS-related opportunistic disorders. *Lancet* 1998, 351: 228-230.

## Pneumocystis pneumonia (PCP)

PCP is still one of the most frequent OIs. This interstitial pneumonia, from which most patients died in the early years of the HIV epidemic, is caused by pneumocysts. In the last 20 years, there has been significant progress in the knowledge about this organism, especially through DNA analysis (detailed review in: Thomas 2004). Although *Pneumocystis* was previously classified as a protozoan, it was established in 1988 that it is in fact an unusual type of fungus (Edman 1988). In the 1990s, it was recognized that every host, whether rat, mouse, monkey or human, has its own specific pneumocysts. It also became clear that *Pneumocystis carinii*, first described in 1910, does not occur in humans at all, but only in rats. The *Pneumocystis* species that affects humans is referred to as *Pneumocystis jirovecii*, not *P. carinii* - and “*carinii*” has now been taken out of the name for the pneumonia, although the abbreviation remains the same (Stringer 2002).

The majority of patients diagnosed with PCP are not pre-treated with antiretroviral drugs, even today, and many of these do not know of their HIV infection status (or do not want to). PCP is a life-threatening disease, which should be treated by an HIV specialist. It often requires mechanical ventilation and still continues to have a high fatality rate. Older patients have a particularly high mortality risk (Benfield 2001). The relapses that were frequently seen in the past have become rare, thanks to HAART and prophylaxis. Scar tissue formation may result in susceptibility to recurring pneumothoraces. PCP may also rarely occur in relation to an immune reconstitution syndrome (see below).

### Signs and symptoms

Every clinician should be familiar with the classic triad of PCP symptoms: dry cough, subfebrile temperatures and gradual onset of dyspnea on exertion (Ask patients specifically! Measure respiratory rate!). A subacute course is typical. This almost always allows differentiation from bacterial pneumonia (Productive cough! Acutely high fever! Pain! Dyspnea less likely!). Often there is significant oral thrush. Weight loss of several kilograms in the weeks before is also common. Symptoms may be subtler in cases with suboptimal prophylaxis (rare).

Often, weeks or sometimes even months may go by before the diagnosis of PCP is made. It is important to note that decompensation – as with all interstitial pneumonias – often occurs much more quickly than expected. It is not rare that a patient suddenly requires ventilation after weeks of antibiotic therapy (even broad spectrum antibiotics don't help!) prescribed by the primary health care provider. A patient with significant exertional dyspnea or even resting dyspnea must be sent to hospital immediately!

### Diagnosis

If there is clinical suspicion of PCP, physical examination (Respiratory rate? Usually nothing is heard on auscultation, but oral thrush is often a further clinical finding) should be followed without delay by a chest x-ray and, if possible, high resolution computed tomography (HRCT) of the lungs. The chest x-ray often shows relatively characteristic findings with a butterfly-shaped (perihilar) interstitial infiltrate.

In the early stages, the focus is on the mid and lower fields. Cystic changes may also occur (Fätkenheuer 1997). Indistinct, diffuse changes are more easily visible on HRCT than on chest x-ray. A CT scan also allows a fairly certain distinction from other pulmonary infections (Hidalgo 2003).

However, if nothing pathological is visible on CT (experience of radiologist?), which does occur, rapid initiation of treatment is justified even without a definitive diagnosis – particularly in the presence of the classic triad of symptoms, low CD4 T cell count and no previous prophylaxis. There is almost always partial respiratory insufficiency, which should be confirmed by arterial blood gas analysis. Lactate dehydrogenase (LDH) is often elevated and may have limited use as a parameter for the course of disease. A high LDH is an unfavorable sign and reflects, even if not precisely, the severity of the PCP. In contrast, CRP is usually normal, provided there are no other concurrent infections.

Sputum specimens are generally not useful (review of various methods: Cruciani 2002), so that a bronchoalveolar lavage (BAL) is usually necessary. This can lead to detection of pneumocysts even after several days of treatment; therefore it is not essential to wait for the BAL to start treatment. However, HIV-inexperienced microbiologists may easily overlook *Pneumocystis*, so that an additional specimen should always be sent to an experienced laboratory. The laboratory should be specifically alerted to the suspicion of PCP. Performing the BAL as soon as possible also allows for the timely diagnosis of co-infections (CMV, pneumococci). It should be noted that respiratory insufficiency can deteriorate with BAL. Full blood count, transaminases and kidney function must be monitored during treatment and baseline values should be determined at this point.

Newer diagnostic approaches include antibody testing (Bishop 2003) and measurement of S-adenosylmethionine, a substance that pneumocysts require but cannot produce. S-adenosylmethionine levels are significantly reduced in patients with PCP (Skelly 2003). It is currently not foreseeable, whether these tests, which spare patients the discomfort of bronchoscopy, will be available for routine diagnostic testing in the future.

## Treatment

### General

Treatment should be initiated immediately if there is clinical suspicion. In cases of mild PCP (BGA:  $PO_2 > 70-80$  mm Hg), ambulatory treatment can be attempted; oral medication can even be administered in very mild forms. This may well be possible in cooperation with a competent HIV nursing service. If such monitoring is not possible, if respiratory deterioration occurs, and in every case with resting dyspnea, immediate hospitalization is advised. If ventilation becomes necessary, patients have a poor prognosis, even today. Non-invasive methods (like CPAP) may be beneficial if used from an early stage. This helps particularly in prevention of pneumothoraces (Confalonieri 2002).

In Germany, initiation of HAART is usually postponed in ART-naïve patients until the PCP has resolved. In other countries, treatments are usually administered concurrently. A general recommendation cannot be given at present. A recent retrospective study showed improved survival in patients who began HAART while

hospitalized (Morris 2003). Disadvantages of this approach include possible cumulative toxicities and allergies, which may necessitate discontinuation of both PCP and HIV treatment (Watson 2002).

## Drugs

Acute therapy should last for 21 days. The drug of choice is co-trimoxazole. The dose of three 960 mg tablets three times daily is only possible in milder cases. However, these higher oral doses are also associated with poor gastrointestinal tolerability. All severe cases should be treated intravenously in hospital. Due to possible clinical deterioration, which is probably a result of the bursting of pneumocysts in the alveoli, 20-40 mg prednisone bid should always be simultaneously co-administered with the PCP therapy for 5-10 days. There should be no hesitation to use steroids especially with worsening blood gases. On steroids, significantly less patients need intubation (Briel 2005). Important: clinical deterioration during the first week of treatment is still not uncommon. Initial treatment should be re-evaluated after one week at the earliest, and only after exclusion of co-infections such as CMV.

The high doses of co-trimoxazole require monitoring of full blood count, electrolytes, renal function parameters and transaminases at least three times weekly. The main problems in addition to myelotoxicity, liver and kidney problems include a rash that usually occurs after the middle of the second week of treatment, often accompanied by drug fever. Patients should be checked daily for skin changes. If such an exanthema occurs, one can attempt to interrupt treatment for one or two days, and then continue with half the dose under antihistamines and steroids. Otherwise, co-trimoxazole must be discontinued and replaced with alternative treatments.

All alternatives to co-trimoxazole are less effective. In cases of intolerability or history of sulfonamide allergy, intravenous pentamidine is recommended as the drug of second choice. An induction therapy is administered over the first few days (200-300 mg in 500 ml 5 % glucose or 0.9 % NaCl), and half the dose can then be given from day 6. This treatment is very toxic, which is why we have not used it for many years. Severe decompensations of electrolyte and blood glucose levels (both hyper- and hypoglycemia) are possible, as well as pancreatitis, arrhythmia and renal failure. Initially, daily monitoring of blood glucose, electrolytes and renal parameters is necessary.

In very mild cases of PCP, inhalative treatment with daily pentamidine inhalations (300-600 mg daily for three weeks) can be attempted (Arasteh 1990, Montgomery 1995). However, the experiences have not all been positive (Conte 1990, Soo 1990), and the current US-guidelines advise against inhalatory acute therapy (Benson 2004). Instead of pentamidine, treatment with atovaquone suspension (better than the tablets used in the past) or a combination of clindamycin and primaquine is possible. However, data on these alternative therapies is only available for mild to moderately severe cases of PCP (Hughes 1993, Dohn 1994, Toma 1998). Primaquine is no longer licensed in Germany, although it can be supplied through international pharmacies.

In the past few years, we have only used these alternative substances (intravenous pentamidine, atovaquone, clindamycin, primaquine) in exceptional cases. Instead, we have changed to treating with high dose co-trimoxazole for as long as possible



(motto: every day with co-trimoxazole is a good day!). A 10-day initial therapy is achievable in almost all patients, most of whom are then already significantly better. If exanthema or toxicity forces the interruption of co-trimoxazole between day 10 and 14, daily pentamidine inhalation is called into question in the third and last week of acute therapy. As this is not toxic, it can usually be started in parallel to HAART. However, a study on this strategy has not yet been published.

### Prophylaxis

Patients with less than 200 CD4<sup>+</sup> T-cells/ $\mu$ l (<14 %) are at risk: above these values, the occurrence of PCP is rare. Therefore, these patients are treated prophylactically, ideally with co-trimoxazole. Daily dosing may be slightly more effective than giving the dose three times weekly (El Sadr 1999). Gradual lead-in dosing over 14 days is supposed to prevent allergic reactions, but is cumbersome (Para 2000).

In cases of mild or moderate allergy to co-trimoxazole, desensitization after several weeks is possible (Leoung 2001), and should definitely be attempted. Although dapsone and pentamidine inhalations are almost equally effective (Bozzette 1995, Bucher 1997), co-trimoxazole prophylaxis is better for preventing bacterial infections such as enteritis, sinusitis and pneumonia (DiRienzo 2002). More importantly, co-trimoxazole simultaneously provides reliable protection for cerebral toxoplasmosis.

Pediatric co-trimoxazole suspension can be used for desensitization, by slowly increasing exposure within six days from 12.5, 25, 37.5, 50 and 75 to 100 % of the dose in the 480 mg tablet. In a study of almost 200 patients, no cases of severe allergy occurred, and there was a reduction of fever and headaches. Approximately three quarters of all patients are thus able to tolerate co-trimoxazole again. However, re-exposure should only be attempted after an interval of eight weeks (Leoung 2001).

Monthly inhalation of pentamidine is a well-tolerated alternative. Coughing may occur, asthma attacks are rare, and pneumothoraces even rarer. A suitable inhalation system should be used, after administration of a beta-sympathomimetic to dilate the bronchi. The loading dose (300 mg tid for the first 5 days) frequently used in the past is no longer a universal standard. In patients with severe pulmonary disease, inhalation is probably less effective.

**Treatment/Prophylaxis of PCP**

(daily doses, if not specified otherwise)

<b>Acute therapy</b>		Duration: always at least three weeks
Severe to moderately severe PCP	Co-trimoxazole	Co-trimoxazole 4-5 amp. à 480 mg tid <b>plus</b> prednisolone 2-2-0 tbl. à 20 mg (5-10 days)
Mild PCP	Co-trimoxazole	Co-trimoxazole 3 tbl. à 960 mg tid
Alternatives	Pentamidine	Pentamidine 200-300 mg i.v. for 5 days (4 mg/kg), then halve dose In very mild cases: daily inhalations with 300 mg
	Atovaquone	Atovaquone suspension 5-10 ml bid (750-1500 mg bid)
	Clindamycin + Primaquine	Clindamycin 1 amp. à 600 mg i.v. q 6-8 h plus primaquine 1 tbl à 30 mg qd
<b>Prophylaxis</b>		Below 200 CD4+ T-cells/ $\mu$ l; after PCP episode
First choice	Co-trimoxazole	Co-trimoxazole 1 tbl. à 480 mg qd or Co-trimoxazole 1 tbl. à 960 mg 3 x/week
Alternatives	Pentamidine	Pentamidine inhalation 300 mg 1-2 x/month
	Dapsone	Dapsone 2 tbl. à 50 mg qd
	Dapsone + Pyrimethamine	Dapsone 1 tbl. à 50 mg qd <b>plus</b> pyrimethamine 2 tbl. à 25 mg/week <b>plus</b> leucovorin 2 tbl. à 15 mg/week
	Atovaquone	Atovaquone suspension 5 ml bid (750 mg bid)

Further options are problematic. Dapsone has poor gastrointestinal tolerability, is quite myelotoxic and often leads to elevation of LDH. LDH, an important diagnostic parameter, can therefore not be utilized under treatment with dapsone (Ioannidis 1996). Atovaquone was proven to be of comparable efficacy to co-trimoxazole, dapsone and pentamidine in two multicenter studies (El-Sadr 1998, Chan 1999), and since then, is considered to be a good alternative for PCP prophylaxis. The oral suspension has better tolerability than the tablet formulation (Rosenberg 2001). A significant disadvantage of atovaquone for long-term prophylaxis is the disproportionately high cost (approximately 1,000 Euro/month – guaranteed to be queried by the health insurance).

PCP prophylaxis regimens can be discontinued fairly safely with sufficient immune reconstitution: more than 200 CD4+ T-cells/ $\mu$ l for three months (Schneider 1999, Weverling 1999, Lopez 2001, Ledergerber 2001). PCP has only rarely been described in cases with CD4+ T-cell counts greater than 200/ $\mu$ l after stopping prophylaxis (Degen 2002, Mussini 2003).

Stopping prophylaxis not only reduces side effects and costs, but also avoids other negative developments: the proportion of co-trimoxazole-resistant bacteria is constantly increasing among HIV patients (Martin 1999). The worldwide use of co-trimoxazole has also affected pneumocysts. Resistance analyses were previously difficult, as this organism, even almost 100 years after its discovery, can still not be cultured. However, it is now possible to sequence sections of the genome encoding for dihydropteroate synthetase (DHPS). DHPS is an important enzyme involved in the folate metabolism of many organisms, and is targeted by sulfonamides such as

sulfamethoxazole (SMX) and dapsone. The first mutations in the DHPS gene in pneumocysts were discovered in 1997. A further study showed DHPS mutations in 43 %, while the gene region for dihydrofolate reductase (DHFR), targeted by trimethoprim (TMP) and pyrimethamine, did not show a single relevant mutation. In contrast to SMX, there seems to be no selective pressure associated with TMP – a suspicion that has to be analyzed, that TMP is not effective against pneumocysts (Ma 1999). Recently, however, even DHFR-mutations have been proven (Nahimana 2004). In addition, studies in large groups of patients have demonstrated that the frequency of sulfa resistance mutations has in general significantly increased in recent years. Resistance correlated significantly with the duration of prior prophylaxis and its failure (Helweg-Larsen 1999, Kazanjian 2000, Nahimana 2003 + 2004).

### Current controversy in PCP research

It is presently not clear, whether DHPS mutations should affect decisions on PCP therapy or lead to a change in treatment (Stein 2004). In a Danish study on 144 PCP patients, DHPS mutations correlated with higher mortality rates (Helweg-Larsen 1999). In a further study, however, a trend was discovered (Crothers 2005). A working group in the US eventually observed mostly low-level resistance, which could be overcome with high sulfonamide doses (Kazanjian 2000). It should be stressed that resistance testing for pneumocysts is currently still in the experimental stages. Results are often poorly reproducible (Beard 2004).

The sequencing of the *Pneumocystis* genome has uncovered other possibly relevant findings: it seems highly likely that PCP is caused by a new infection, rather than the reactivation of an existing infection as previously assumed (Stringer 2002, Nahimana 2003, Wakefield 2003). Asymptomatic HIV patients with frequent detection of pneumocysts may be reservoirs (Wakefield 2003), in addition to HIV-negative patients on corticosteroid therapy (Maskell 2003) and of course patients with active PCP. However, other authors doubt patient-to-patient transmission (Wohl 2002), and isolation of PCP patients is still not generally recommended (Thomas 2004).

An Italian working group has repeatedly stressed in recent years that the effect of protease inhibitors on pneumocysts detectable *in vitro* has clinical relevance – patients with PI-containing HAART apparently have better protection from PCP than patients on NNRTIs (Atzori 2003). However, these effects have not yet been demonstrated in larger numbers of patients.

### References

1. Arasteh K, Heise W, L'age M. Treatment of mild to moderately severe pneumocystis carinii pneumonia with cotrimoxazole versus pentamidine aerosol. *Med Klin* 1990, 85 Suppl 2:260-3. <http://amedeo.com/lit.php?id=2197535>
2. Atzori C, Clerici M, Trabattini D, et al. Assessment of immune reconstitution to *Pneumocystis carinii* in HIV-1 patients under different highly active antiretroviral therapy regimens. *J Antimicrob Chemother* 2003, 52:276-81. <http://amedeo.com/lit.php?id=12837736>
3. Beard CB, Roux P, Nevez G, et al. Strain typing methods and molecular epidemiology of *Pneumocystis pneumonia*. *Emerg Infect Dis* 2004, 10:1729-35. <http://amedeo.com/lit.php?id=15504257>
4. Benfield TL, Helweg-Larsen J, Bang D, et al. Prognostic markers of short-term mortality in AIDS-associated *Pneumocystis carinii* pneumonia. *Chest* 2001, 119:844-851. <http://amedeo.com/lit.php?id=11243967>

5. Bishop LR, Kovacs JA. Quantitation of anti-Pneumocystis jiroveci antibodies in healthy persons and immunocompromised patients. *J Infect Dis* 2003, 187: 1844-8. <http://amedeo.com/lit.php?id=12792860>
6. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced HIV. *N Engl J Med* 1995, 332:693-9. <http://amedeo.com/lit.php?id=7854375>
7. Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against Pneumocystis carinii pneumonia and toxoplasma encephalitis in HIV-infected patients. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997, 15:104-14. <http://amedeo.com/lit.php?id=9241108>
8. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aero-solized pentamidine for prevention of Pneumocystis carinii pneumonia in HIV-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis* 1999, 180:369-76. <http://amedeo.com/lit.php?id=10395851>
9. Confalonieri M, Calderini E, Terraciano S, et al. Noninvasive ventilation for treating acute respiratory failure in AIDS patients with Pneumocystis carinii pneumonia. *Intensive Care Med* 2002, 28:1233-8. <http://amedeo.com/lit.php?id=12209270>
10. Cruciani M, Marcati P, Malena M, et al. Meta-analysis of diagnostic procedures for Pneumocystis carinii pneumonia in HIV-1-infected patients. *Eur Respir J* 2002, 20:982-9. <http://amedeo.com/lit.php?id=12412693>
11. Degen O, van Lunzen J, Horstkotte MA, Sobotta I, Stellbrink HJ. Pneumocystis carinii pneumonia after the discontinuation of secondary prophylaxis. *AIDS* 2002, 16:1433-4.
12. DiRienzo AG, van Der Horst C, Finkelstein DM, et al. Efficacy of trimethoprim-sulfamethoxazole for the prevention of bacterial infections in a randomized prophylaxis trial of patients with advanced HIV infection. *AIDS Res Hum Retroviruses* 2002, 18:89-94. <http://amedeo.com/lit.php?id=11839141>
13. Edman JC, Kovacs JA, Masur H, et al. Ribosomal RNA sequence shows Pneumocystis carinii to be a member of the fungi. *Nature* 1988, 334:519-522. <http://amedeo.com/lit.php?id=2970013>
14. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of Pneumocystis carinii pneumonia in HIV-infected persons. *Clin Infect Dis* 1999, 29:775-783. <http://amedeo.com/lit.php?id=10589887>
15. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of Pneumocystis carinii pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998, 339:1889-95. <http://amedeo.com/lit.php?id=9862944>
16. Fätkenheuer G, Franzen C, Hartmann P, et al. Cystic form of Pneumocystis carinii pneumonia. *Dtsch Med Wochenschr* 1997, 122:1441-6. <http://amedeo.com/lit.php?id=9424421>
17. Helweg-Larsen J, Benfield TL, Eugen-Olsen J, Lundgren JD, Lundgren B. Effects of mutations in Pneumocystis carinii dihydropteroate synthase gene on outcome of AIDS-associated PCP. *Lancet* 1999, 354:1347-51. <http://amedeo.com/lit.php?id=10533864>
18. Hidalgo A, Falco V, Mauleon S, et al. Accuracy of high-resolution CT in distinguishing between Pneumocystis carinii pneumonia and non-Pneumocystis carinii pneumonia in AIDS patients. *Eur Radiol* 2003, 13:1179-84. <http://amedeo.com/lit.php?id=12695843>
19. Ioannidis JP, Cappelleri JC, Skolnik PR, Lau J, Sacks HS. A meta-analysis of the relative efficacy and toxicity of Pneumocystis carinii prophylactic regimens. *Arch Intern Med* 1996, 156:177-88. <http://amedeo.com/lit.php?id=8546551>
20. Kazanjian P, Armstrong W, Hossler PA, et al. Pneumocystis carinii mutations are associated with duration of sulfa or sulfone prophylaxis exposure in AIDS patients. *J Infect Dis* 2000, 182:551-7. <http://amedeo.com/lit.php?id=10915088>
21. Ledergerber B, Mocroft A, Reiss P, et al. Discontinuation of secondary prophylaxis against Pneumocystis carinii pneumonia in patients with HIV infection who have a response to antiretroviral therapy. *N Engl J Med* 2001, 344:168-74. <http://amedeo.com/lit.php?id=11188837>
22. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for pneumocystis carinii pneumonia prophylaxis in HIV-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis* 2001, 184:992-7. <http://amedeo.com/lit.php?id=11574913>
23. Lopez Bernaldo de Quiros JC, Miro JM, Pena JM, et al. A randomized trial of the discontinuation of primary and secondary prophylaxis against Pneumocystis carinii pneumonia after HAART in patients with HIV infection. *N Engl J Med* 2001, 344:159-67. <http://amedeo.com/lit.php?id=11172138>
24. Ma L, Borio L, Masur H, Kovacs JA. Pneumocystis carinii dihydropteroate synthase but not dihydrofolate reductase gene mutations correlate with prior trimethoprim-sulfamethoxazole or dapsone use. *J Inf Dis* 1999, 180:1969-78. <http://amedeo.com/lit.php?id=10558954>
25. Martin JN, Rose DA, Hadley WK, et al. Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS Era. *J Infect Dis* 1999, 180:1809-18. <http://amedeo.com/lit.php?id=10558935>

26. Maskell NA, Waine DJ, Lindley A, et al. Asymptomatic carriage of *Pneumocystis jiroveci* in subjects undergoing bronchoscopy: a prospective study. *Thorax* 2003, 58:594-7. <http://amedeo.com/lit.php?id=12832674>
27. Morris A, Wachter RM, Luce J, Turner J, Huang L. Improved survival with highly active antiretroviral therapy in HIV-infected patients with severe *Pneumocystis carinii* pneumonia. *AIDS* 2003, 17:73-80. <http://amedeo.com/lit.php?id=12478071>
28. Mussini C, Pezzotti P, Antinori A, et al. Discontinuation of secondary prophylaxis for *Pneumocystis carinii* pneumonia in HIV-infected patients: a randomized trial by the CIOF Study Group. *Clin Infect Dis* 2003, 36:645-51. <http://amedeo.com/lit.php?id=12594647>
29. Nahimana A, Rabodonirina M, Zanetti G, et al. Association between a specific *Pneumocystis jiroveci* dihydropteroate synthase mutation and failure of pyrimethamine/sulfadoxine prophylaxis in HIV-positive and -negative patients. *J Infect Dis* 2003, 188:1017-23. <http://amedeo.com/lit.php?id=14513422>
30. Para MF, Finkelstein D, Becker S, et al. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia. *J AIDS* 2000, 24:337-43. <http://amedeo.com/lit.php?id=11015150>
31. Rosenberg DM, McCarthy W, Slavinsky J, et al. Atovaquone suspension for treatment of *Pneumocystis carinii* pneumonia in HIV-infected patients. *AIDS* 2001, 15:211-4. <http://amedeo.com/lit.php?id=11216929>
32. Schneider MM, Borleffs JC, Stolk RP, Jaspers CA, Hoepelman AI. Discontinuation of prophylaxis for *Pneumocystis carinii* pneumonia in HIV-1-infected patients treated with HAART. *Lancet* 1999, 353:201-3. <http://amedeo.com/lit.php?id=9923876>
33. Skelly M, Hoffman J, Fabbri M, et al. S-adenosylmethionine concentrations in diagnosis of *Pneumocystis carinii* pneumonia. *Lancet* 2003; 361:1267-8.
34. Stein CR, Poole C, Kazanjian P, Meshnick SR. Sulfa use, dihydropteroate synthase mutations, and *Pneumocystis jirovecii* pneumonia. *Emerg Infect Dis* 2004, 10:1760-5. <http://amedeo.com/lit.php?id=15504261>
35. Stringer JR, Beard CB, Miller RF, Wakefield AE. A new name (*Pneumocystis jiroveci*) for *Pneumocystis* from humans. *Emerg Infect Dis* 2002, 8:891-6. <http://amedeo.com/lit.php?id=12194762>
36. Thomas CF Jr, Limper AH. *Pneumocystis pneumonia*. *N Engl J Med* 2004, 350: 2487-98.
37. Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs. Trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). *Clin Infect Dis* 1998, 27:524-30. <http://amedeo.com/lit.php?id=9770152>
38. Wakefield AE, Lindley AR, Ambrose HE, Denis CM, Miller RF. Limited asymptomatic carriage of *Pneumocystis jiroveci* in HIV-infected patients. *J Infect Dis* 2003, 187: 901-8. <http://amedeo.com/lit.php?id=12660936>
39. Watson J. *Pneumocystis carinii*: where are we now? *J HIV Ther* 2002, 7:8-12. <http://amedeo.com/lit.php?id=11956498>
40. Weverling GJ, Mocroft A, Ledergerber B, Kirk O, et al. Discontinuation of *Pneumocystis carinii* pneumonia prophylaxis after start of HAART in HIV-1 infection. *Lancet* 1999, 353:1293-8. <http://amedeo.com/lit.php?id=10218526>
41. Wohl AR, Simon P, Hu YW, Duchin JS. The role of person-to-person transmission in an epidemiologic study of *Pneumocystis carinii* pneumonia. *AIDS* 2002, 16:1821-5. <http://amedeo.com/lit.php?id=12218395>

## Cerebral toxoplasmosis

Although the incidence in Europe has been reduced to a quarter as a result of HAART (Abgrall 2001), cerebral toxoplasmosis remains the most important neurological OI in HIV patients. Today, it is typically diagnosed in HIV patients with hitherto unknown HIV infection or in those not under regular routine care. Cerebral toxoplasmosis almost always results from the reactivation of a latent infection with *Toxoplasma gondii*, an intracellular parasite that infects birds, mammals and humans. Prevalence rates vary considerably worldwide (Porter 1992, Jones 1996). Whereas *Toxoplasma gondii* is relatively rare in the USA, prevalence rates in a few regions within central Europe are as high as 90 %. *Toxoplasma* has an affinity to the CNS. Extracerebral organ manifestations (heart, skeletal muscle, liver, intestine, lung) are extremely rare and often only detected at autopsy.

Cerebral toxoplasmosis is potentially life threatening, and treatment is complicated. In severe cases, there may be residual neurological syndromes with significant disabilities (hemiparesis!). It is not rare to see a remaining lifelong susceptibility to seizures as a result of defective healing. It should be noted that relapses may occur even after long periods of time due to intracerebral persistence.

### Signs and symptoms

Clinical symptoms depend on the localization of lesions, with acute or peracute onset within a few days. The major signs include focal neurological deficits such as paresis, speech problems or sensory loss (Porter 1992). A febrile psychosyndrome with confusion is also frequently an early sign. It is not unusual to see an epileptic seizure as the initial presentation, in the absence of other symptoms. Headaches with fever or subfebrile temperatures are always suspicious. Meningitic signs, however, are less typical. Atypical manifestations in patients with immune reconstitution under HAART have been described (Ghosn 2003).

A fairly rare, but important manifestation is *Toxoplasma* chorioretinitis. It causes impairment of vision, is an important differential diagnosis to CMV retinitis and may occur on its own (Rogers 1996).

*Toxoplasma* chorioretinitis should be treated in the same way as cerebral toxoplasmosis.

### Diagnosis

Cerebral toxoplasmosis seldomly occurs above a CD4+ T-cell count of 100 cells/ $\mu$ l; over 200 CD4+ T-cells/ $\mu$ l it is very rare (Bossi 1998). In contrast, it should always be expected below 100 CD4+ T-cells/ $\mu$ l. A CT or MRI scan of the head should be performed promptly (not a week later!) in every case of focal neurological deficit, but also if seizures occur in significantly immunocompromised patients. An MRI is superior to a CT scan and almost always shows more visible lesions. A third of cases have either solitary, several (2-5) or multiple lesions, respectively. In approximately nine out of ten cases, ring enhancement is found around the lesions, often accompanied by edema. Hemorrhage may occasionally occur.

For all radiologically detected lesions, the most likely diagnosis is cerebral toxoplasmosis. In addition, the most important differential diagnosis is an “atypical” cerebral toxoplasmosis. The more lesions there are, the more likely the diagnosis of toxoplasmosis! However, the distinction from a bacterial abscess or cerebral lymphoma is not always simple radiologically. Other rare differential diagnoses include PML, infarcts, tuberculomas and cryptococcomas. “HIV-unrelated” diseases such as brain tumors or vascular disease should also be considered.

A brain biopsy is not obligatory. Suspicion of toxoplasmosis always justifies a treatment attempt before it comes to this. Response to therapy then confirms the diagnosis. However, if the patient does not improve clinically within one week, or even worsens, stereotactical brain biopsy cannot be avoided, and in this case, should not be postponed.

The cerebrospinal fluid (CSF), which also does not necessarily have to be analyzed if there are clear radiological findings (several lesions with contrast enhancement), usually shows moderate pleocytosis and slightly elevated total protein. Our experience with *Toxoplasma* PCR from CSF has not been good. A negative result (frequent!) never excludes toxoplasmosis.

An updated serology should be available for every patient. Up to 97 % of patients with cerebral toxoplasmosis have IgG antibodies, and so a negative result, which should be repeated in another laboratory if there is any doubt, makes toxoplasmosis unlikely. Some clinicians use levels of IgG titers or increased titers as indicators (Derouin 1996), but this approach has not been properly validated. IgM is only rarely positive, and therefore usually does not help. PCR from the blood also has little relevance (review in: Bretagne 2003).

## Treatment

Treatment of cerebral toxoplasmosis is not simple. The most frequently used combinations are usually effective (resistance has not yet been convincingly described), but require modification in at least half the patients due to side effects – particularly allergies. Sulfadiazine and clindamycin are presumably equally effective in combination with pyrimethamine (Dannemann 1992). However, one large European study demonstrated a trend, though not significant, in favor of sulfadiazine (Katlama 1996). A loading dose for pyrimethamine during the first few days has been propagated since the first published study (Leport 1988). It has not yet been proven whether this is necessary. Even the doses used are variable: in the USA 200 mg is recommended for the first day (followed by 50-75 mg depending on the body weight); here, 100 mg is often given for three days, followed by 50 mg. It should be noted that, in contrast to clindamycin, pyrimethamine is also active in the presence of an intact blood brain barrier, and is sometimes therefore the only effective substance.

Due to the myelotoxicity of sulfonamides and pyrimethamine, which inhibits transformation of folic acid to folinic acid, it is important to substitute sufficiently with folinic acid (unfortunately expensive!) from the start. Folic acid (cheap!) itself is ineffective, as it cannot be converted in the presence of pyrimethamine (Luft 2000).

We recommend using sulfadiazine and pyrimethamine for an initial attempt as oral treatment. In cases of sulfonamide allergy, sulfadiazine should be substituted with

oral or intravenous clindamycin from the beginning. All disoriented patients should receive clindamycin infusions, at least for reasons of compliance. Because of the high rate of allergies under sulfadiazine, however, some clinicians completely oppose this treatment. We do not share this view, after all clindamycin is also allergenic and can be problematic – consider pseudomembranous colitis in cases of persistent diarrhea!

Good results are also reported with intravenous co-trimoxazole, with administration of the same dosages as for PCP (Canessa 1992). In at least two randomized studies on patients with ocular or cerebral toxoplasmosis, co-trimoxazole was as effective as sulfadiazine/pyrimethamine (Torre 1998, Soheilien 2005).

If allergies or intolerance to both sulfonamides and clindamycin occur, a combination of atovaquone and pyrimethamine is a possible alternative (Chirgwin 2002). A combination of azithromycin plus pyrimethamine could be another alternative (Bosch-Driessen 2002), however there is only very vague data available.

Acute therapy is of four to (better) six weeks duration, possibly even longer for the less effective reserve therapies. Treatment success can be assessed clinically in the first 14 days - often an improvement in the symptoms can be observed within a few days. A patient that has not improved at all after two weeks of therapy, or has even deteriorated, probably does not have toxoplasmosis! If this occurs, the diagnosis has to be reviewed and an urgent brain biopsy must be organized. Changing the toxoplasmosis therapy is not useful in such cases and just costs valuable time.

A control MRI is recommended for stable patients after two weeks at the earliest. Significant resolution of lesions is often only visible after four weeks. In cases of increased intracranial pressure or extensive edema, steroids are given (8 mg dexamethasone q 6-8 h). Administration of steroids should be for a limited duration, as there is otherwise a significantly increased risk of aspergillosis. All treatment combinations require initial monitoring of blood count, glucose, transaminases and renal parameters at least three times weekly. Maintenance therapy with the reduced dose should only be initiated if lesions have resolved by at least 75 %.

## Prophylaxis

IgG-negative patients can protect themselves from initial infection – they should avoid eating raw or only briefly cooked meat (lamb, beef, pork, game). However, it has not been proven, despite widespread opinion, that HIV patients can infect themselves by mere contact with cats, the definitive host of *Toxoplasma gondii*. The only study that has seriously investigated this to date could not prove endangerment as a result of proximity to cats (Wallace 1993). Nevertheless, stricter measures of hygiene should be followed (e.g. use gloves for the cat litter box! Details in: Kaplan 2002).

All IgG-positive patients with less than 100 CD4+ T-cells/ $\mu$ l require primary prophylaxis. The drug of choice is co-trimoxazole. In cases of co-trimoxazole allergy, desensitization may be considered (see PCP). An alternative is dapsone plus pyrimethamine or high-dose dapsone alone. All primary prophylaxes can be discontinued safely if CD4+ T-cells increase and are above 200/ $\mu$ l for at least three months.



**Treatment/prophylaxis of cerebral toxoplasmosis**  
(daily doses, if not specified otherwise)

<b>Acute therapy</b>		Duration: always at least four weeks
First choice	Sulfadiazine+ Pyrimethamine	Sulfadiazine 2-3 tbl. à 500 mg qid <b>plus</b> pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) <b>plus</b> leucovorin 3 x 1 tbl. à 15 mg/week
First choice	Clindamycin + Pyrimethamine	Clindamycin 1 amp. à 600 mg i.v. qid or 1 tbl. à 600 mg qid <b>plus</b> pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) <b>plus</b> leucovorin 3 x 1 tbl. à 15 mg/week
Alternative	Atovaquone + Pyrimethamine	Atovaquone suspension 10 ml bid (1500 mg bid) <b>plus</b> pyrimethamine 2 tbl. à 25 mg bid (for 3 days, then halve dose) <b>plus</b> leucovorin 3 x 1 tbl. à 15 mg/week
<b>Maintenance therapy</b>		
	As for acute therapy	As for acute therapy, but halve dose Discontinue if > 200 CD4+ T-cells/ $\mu$ l for > 6 months (if MRI is normal or without contrast enhancement)
possibly	Co-trimoxazole	Co-trimoxazole 1 tbl. à 960 mg qd
<b>Primary prophylaxis</b>		
Standard	Co-trimoxazole	Co-trimoxazole 1 tbl. à 480 mg qd
Alternative	Dapsone	Dapsone 2 tbl. à 50 mg qd
Alternative	Dapsone + Pyrimethamine	Dapsone 1 tbl. à 50 mg qd <b>plus</b> pyrimethamine 2 tbl. à 25 mg/week <b>plus</b> leucovorin 2 tbl. à 15 mg/week

In the absence of immune reconstitution, patients with cerebral toxoplasmosis require lifelong maintenance therapy or secondary prophylaxis, as there are otherwise recurrences in nearly all cases. It usually consists of half the dose of the acute therapy (Podzamczar 2000). However, clindamycin is presumably less suitable, as it cannot cross the intact blood-brain barrier (Luft 2000). Co-trimoxazole seems to be not as effective for secondary prophylaxis, but should be considered because it is simple. However, it definitely requires higher doses than those used to treat PCP (Ribera 1999, Duval 2004). With sufficient immune reconstitution (at least six months above 200 CD4+ T-cells/ $\mu$ l), even secondary prophylaxis can probably be stopped (Benson 2004).

If possible, an updated MRI scan should be available beforehand. If there is enhancement, it may mean that lesions have become active even after years – and there is a risk of a recurrence. We have seen a recurrence even after five years, despite CD4+ T-cells levels being around 200/ $\mu$ l.

This and other cases (Stout 2002, Ghosn 2003) have shown that quantitative measurement of CD4 T cells on HAART does not always reflect the quality of the Toxoplasma-specific immune response. As a result, there have been increasing efforts in recent years to improve the characterization of this specific immune response via ELISPOT. Studies have shown that the Toxoplasma-specific immune response remains poor in approximately 10-20 % of patients on HAART, despite good CD4 T cell counts (Fournier 2001, Miro 2003). In the future, ELISPOT test-

ing might allow identification of patients who are at risk of recurrence despite good CD4 counts and who should therefore continue with secondary prophylaxis.

## References

1. Abgrall S, Rabaud C, Costagliola D. Incidence and risk factors for toxoplasmic encephalitis in HIV-infected patients before and during the HAART era. *Clin Infect Dis* 2001, 33: 1747-55. <http://amedeo.com/lit.php?id=11595976>
2. Bosch-Driessen LH, Verbraak FD, Suttorp-Schulten MS. A prospective, randomized trial of pyrimethamine and azithromycin vs pyrimethamine and sulfadiazine for the treatment of ocular toxoplasmosis. *Am J Ophthalmol* 2002, 134:34-40. <http://amedeo.com/lit.php?id=12095805>
3. Bossi P, Caumes E, Astagneau P, et al. Epidemiologic characteristics of cerebral toxoplasmosis in 399 HIV-infected patients followed between 1983 and 1994. *Rev Med Interne* 1998, 19:313-7. <http://amedeo.com/lit.php?id=9775164>
4. Bretagne S. Molecular diagnostics in clinical parasitology and mycology: limits of the current polymerase chain reaction (PCR) assays and interest of the real-time PCR assays. *Clin Microbiol Infect* 2003, 9:505-11. <http://amedeo.com/lit.php?id=12848725>
5. Bucher HC, Griffith L, Guyatt GH, Opravil M. Meta-analysis of prophylactic treatments against pneumocystis carinii pneumonia and toxoplasma encephalitis in HIV-infected patients. *J Acquir Immune Defic Syndr Hum Retrovirol* 1997, 15:104-14. <http://amedeo.com/lit.php?id=9241108>
6. Canessa A, Del Bono V, De Leo P, Piersantelli N, Terragna A. Cotrimoxazole therapy of toxoplasma gondii encephalitis in AIDS patients. *Eur J Clin Microbiol Infect Dis* 1992, 11:125-30. <http://amedeo.com/lit.php?id=1396726>
7. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with AIDS: ACTG 237/ANRS 039 Study. *Clin Infect Dis* 2002, 34:1243-50. <http://amedeo.com/lit.php?id=11941551>
8. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992, 116:33-43. <http://amedeo.com/lit.php?id=1727093>
9. Derouin F, Leport C, Pueyo S, et al. Predictive value of *Toxoplasma gondii* antibody titres on the occurrence of toxoplasmic encephalitis in HIV-infected patients. *ANRS 005/ACTG 154 Trial Group. AIDS* 1996, 10:1521-7. <http://amedeo.com/lit.php?id=8931787>
10. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS* 2004, 18:1342-4. <http://amedeo.com/lit.php?id=15362670>
11. Fournier S, Rabian C, Alberti C, et al. Immune recovery under highly active antiretroviral therapy is associated with restoration of lymphocyte proliferation and interferon- $\gamma$  production in the presence of *Toxoplasma gondii* antigens. *J Inf Dis* 2001, 183:1586-1591. <http://amedeo.com/lit.php?id=11343206>
12. Ghosn J, Paris L, Ajzenberg D, et al. Atypical toxoplasmic manifestation after discontinuation of maintenance therapy in a HIV type 1-infected patient with immune recovery. *Clin Infect Dis* 2003, 37:112-114. <http://amedeo.com/lit.php?id=13130422>
13. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993, 328:1514-20. <http://amedeo.com/lit.php?id=8479488>
14. Jones JL, Hanson DL, Chu SY, et al. Toxoplasmic encephalitis in HIV-infected persons: risk factors and trends. *AIDS* 1996, 10:1393-9. <http://amedeo.com/lit.php?id=8902069>
15. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996, 22:268-75. <http://amedeo.com/lit.php?id=8838183>
16. Leport C, Raffi F, Matheron S, et al. Treatment of central nervous system toxoplasmosis with pyrimethamine/sulfadiazine combination in 35 patients with the AIDS. Efficacy of long-term continuous therapy. *Am J Med* 1988, 84:94-100. <http://amedeo.com/lit.php?id=3337134>
17. Luft BJ, Chua A. Central Nervous System Toxoplasmosis in HIV. *Pathogenesis, Diagnosis, and Therapy. Curr Infect Dis Rep* 2000, 2:358-362. <http://amedeo.com/lit.php?id=11095878>
18. Miro JM, Lejeune M, Claramonte X. Timing of reconstitution of *Toxoplasma gondii*-specific T-cell responses in AIDS patients with acute toxoplasmic encephalitis after starting HAART: A prospective multi-center longitudinal study. Abstract 796, 10th CROI 2003, Boston, USA.
19. Podzamczar D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2000, 19:89-95. <http://amedeo.com/lit.php?id=10746493>

20. Porter SB, Sande MA. Toxoplasmosis of the central nervous system in the AIDS. *N Engl J Med* 1992, 327:1643-8. <http://amedeo.com/lit.php?id=1359410>
21. Ribera E, Fernandez-Sola A, Juste C, et al. Comparison of high and low doses of Trimethoprim-Sulfamethoxazole for primary prevention of toxoplasmic encephalitis in HIV-infected patients. *Clin Infect Dis* 1999, 29:1461-6. <http://amedeo.com/lit.php?id=10585796>
22. Rodgers CA, Harris JR. Ocular toxoplasmosis in HIV infection. *Int J STD AIDS* 1996, 7:307-9. <http://amedeo.com/lit.php?id=8894817>
23. Ruf B, Schurmann D, Bergmann F, et al. Efficacy of pyrimethamine/sulfadoxine in the prevention of toxoplasmic encephalitis relapses and pneumocystis carinii pneumonia in HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 1993, 12:325-9. <http://amedeo.com/lit.php?id=8354297>
24. Stout JE, Lai JC, Giner J, Hamilton CD. Reactivation of retinal toxoplasmosis despite evidence of immune response to highly active antiretroviral therapy. *Clin Infect Dis* 2002, 35:37-39. <http://amedeo.com/lit.php?id=12145740>
25. Torres RA, Barr M, Thorn M, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of pneumocystis carinii pneumonia and toxoplasmic encephalitis. *Am J Med* 1993, 95:573-83. <http://amedeo.com/lit.php?id=8018144>
26. Wallace MR, Rossetti RJ, Olson PE. Cats and toxoplasmosis risk in HIV-infected adults. *JAMA* 1993, 269:76-7. <http://amedeo.com/lit.php?id=8416410>
27. Weigel HM, de Vries E, Regez RM, et al. Cotrimoxazole is effective as primary prophylaxis for toxoplasmic encephalitis in HIV-infected patients: a case control study. *Scand J Infect Dis* 1997, 29:499-502. <http://amedeo.com/lit.php?id=9435040>

## CMV retinitis

Infections with cytomegalovirus are widespread. In Germany, seroprevalence is around 50-70 %, and above 90 % in homosexual men. In severely immunocompromised individuals, (CD4+ T-cell count below 50/ $\mu$ l), reactivation of CMV infection can lead to retinitis. In the past, CMV retinitis was a common AIDS-associated illness, leading to blindness in up to 30 % of patients. It occurs mainly in untreated patients, who are often first diagnosed with HIV infection on presentation (Jacobson 2000). An inflammatory CMV retinitis, usually with severe vitritis, is also possible in the course of an immune reconstitution syndrome. If CMV retinitis is not diagnosed and treated promptly, the patient's sight is always at risk. Impairment of vision is almost always associated with lesions, which are no longer reversible even with adequate treatment. This is why CMV retinitis remains a dangerous illness even in the HAART era, although the prognosis has been significantly improved by HAART (Goldberg 2003, Salzberger 2005).

Other manifestations of disseminated CMV infection are rare (ca. 15 %), and can affect every organ. The lung (pneumonia), esophagus (ulcers), colon (colitis) and CNS (encephalitis) are most frequently involved. Sinusitis may also occur (Jutte 2001). The clinical signs of these CMV diseases depend on the organ affected. Diagnosis is often difficult and may only be possible on histology (Goodgame 1993). There is insufficient data on the treatment of these manifestations, so that systemic therapies are usually chosen in analogy to treatment for CMV retinitis (Whitley 1998).

## Signs and symptoms

Any visual impairment occurring peracutely or acutely, such as blurred vision or floaters – especially unilaterally – should prompt immediate ophthalmological examination of the patient. Today, not tomorrow! Symptomatic CMV retinitis is an emergency – once there is a black spot in the visual field, it will be permanent. All CMV treatment regimens can only prevent progression of lesions, not reverse them.

Eye pain, burning, increased production of tears and conjunctival irritation are not typical. Many patients suffer from systemic symptoms such as fever and weight loss.

## Diagnosis

Diagnosis is made by fundoscopy. Assessment of the usually peripheral, whitish exudates is dependent on the experience of the ophthalmologist. However, this can frequently be a problem, due to the rare occurrence of CMV retinitis today. Unfortunately, incorrect diagnoses that are ill fated due to the valuable time (and retina) lost are no exception. Therefore, if the ophthalmologist remains undecided: start with oral ganciclovir if necessary and transport the patient to a larger clinical center with ophthalmologists who are experienced in HIV! It is essential that they also receive information about the immune status. In cases of poor immune status and CD4+ T-cell count less than 100/ $\mu$ l, chorioretinitis caused by *Toxoplasma gondii* is the most important differential diagnosis. CMV retinitis can almost be excluded at CD4+ T-cell counts above 100/ $\mu$ l; other viral infections (HSV, VZV) or

even neurosyphilis should then be considered. CMV lesions may also be confused with cotton wool spots, which are not rare in HIV patients with high HIV viral load. Multiple small lesions without hemorrhage or exudates are almost always cotton wool spots, and almost never CMV retinitis! Bilateral involvement is also usually the exception. Vitritis is rare, except with immune reconstitution syndrome.

CMV serology (IgG almost always positive, IgM variable) is only seldomly helpful for diagnosis. CMV PCR or a blood test for pp65 antigen to detect antibodies against a CMV-specific phosphoprotein may be more useful. CMV retinitis or a recurrence is unlikely with a negative PCR or pp65 result. The higher the levels of CMV viremia, the higher the risk of CMV disease. Patients with positive CMV PCR have a 3-5-fold elevated risk (Casado 1999, Nokta 2002). Positive CMV PCR is also independently associated with a poor prognosis for the patient (Deayton 2004, Jabs 2005, Wohl 2005).

As with *Toxoplasma gondii*, there have been efforts to determine the antigen-specific immune response more precisely (Jacobsen 2004), although such testing is not yet routine.

## Treatment

CMV treatment should always be initiated promptly and strictly monitored by fundoscopy (once a week in the beginning; photodocumentation is advisable). Initially, an intensive induction therapy is administered for two to three weeks, until there is scar formation of the lesions. The HIV clinician and ophthalmologist should work closely together, particularly during the induction therapy, and if possible, should make contact several times a week. Induction therapy is followed by maintenance therapy at a reduced dose.

There have been significant developments for CMV treatment in the past few years. Several new drugs have been licensed. Most importantly, the introduction of oral valganciclovir has led to fundamental changes in treatment. This is the reason why many treatment approaches investigated in numerous studies, as well as subsequent recommendations developed with great effort only a few years ago, are no longer important.

HAART in particular has dramatically improved the prognosis of patients. All patients should therefore, if this has not already happened, start HAART as soon as possible. This can restore CMV-specific immune responses (Komandouri 1998), so that CMV viremia may disappear even without specific therapy after a few weeks (Deayton 1999, O'Sullivan 1999). However, if retinitis is present, CMV-specific treatment should nevertheless be started, as immune reconstitution may take several months.

### Systemic treatment

Valganciclovir, a prodrug of ganciclovir with good oral absorption, has led to a decisive improvement in the treatment of CMV. In a randomized study (Martin 2002) on 160 patients with retinitis, the results were impressive: valganciclovir tablets were just as effective as ganciclovir infusions. However, the toxicity profile of both substances was comparable. This means that on oral treatment the blood count has to be as frequently monitored as for infusions, and that the indication has to be equally carefully set. This is exactly where aspiring young doctors make many

mistakes. Treating a positive IgM serology (without any further diagnosis) with valganciclovir is not only expensive, but also usually an unnecessary risk!

Valganciclovir was licensed in Germany in June 2002. Our experience with the drug has been good so far. Not only intravenous ganciclovir, but also the other options for systemic treatment have become less important, and are only used in cases of recurrence. Oral ganciclovir has become obsolete as a monotherapy due to its poor bioavailability.

If there is intolerability or resistance to valganciclovir (Drew 1999), foscarnet, which for years has been an important and irreplaceable component in CMV medicine, remains an option. This, however, requires daily infusions. Further problems with this drug include nephrotoxicity, and very painful penile ulcers. Very intensive hydration of the patient is therefore necessary under all circumstances.

There are no direct comparative studies available for cidofovir, which due to its long half-life is also used occasionally (Berenguer 2000). Although a Phase I study showed a good effect of cidofovir in combination with oral ganciclovir (Jacobson 1999), the benefit of the long half-life (once weekly dosing possible) is outweighed by the considerable renal side effects of the drug (Plosker 1999). We observed creatinine elevations in every second patient treated, despite the fact that a strict infusion plan was closely followed (see Drugs section).

New drugs in CMV therapy, such as maribavir, will take a while to come onto the market. CMV retinitis has become rare in the field of HIV infection, and progress is slower in transplantation medicine, where the current need for new CMV drugs with improved tolerability might be greater (maribavir is undergoing Phase II studies at present).

In one analysis of three large studies, patients with CMV retinitis, who had received additional treatment with G-CSF (filgrastim) in the years 1990-1997, had improved survival rates. In particular, there was a reduction of bacterial infections. However, the reason for this positive effect remains unclear despite extensive analyses. Administration of filgrastim is presently not generally recommended (Davidson 2002).

### **Local treatment**

Several options for local treatment of CMV retinitis have been tested (review in: Smith 1998). Although such treatments can be safely administered by experienced ophthalmologists and are associated with few complications (infections, hemorrhage), disadvantages remain. Weekly intravitreal injections of ganciclovir or foscarnet, or pellet implantation (Vitrasert™, must be replaced every 6-9 months) do not protect from infection of the contralateral eye or from extraocular manifestations (Martin 1999). The same is true for fomivirsen (Vitravene™), an antisense-oligonucleotide for intravitreal injection, which is astonishingly effective even with multiresistant CMV strains (Perry 1999). These local treatments have become less important since HAART and valganciclovir, and some have been taken off the market.

### **Prophylaxis**

In the prospective studies that have been performed, no primary prophylaxis regimen has been convincing. There is also no effective vaccine. Therefore, the most

important method for prevention in patients with CD4+ T-cell counts less than 200 cells/ $\mu$ l is still funduscopy every three months. With good immune reconstitution, intervals between examinations can be extended. It is important to perform a funduscopy in severely immunocompromised patients prior to starting HAART. This allows detection of smaller lesions, which may later present with severe inflammation during the course of immune reconstitution.

After approximately three weeks of acute therapy, but at the earliest with scar formation of lesions, a reduced dose secondary prophylaxis (maintenance therapy) should begin, preferably with oral valganciclovir (Lalezari 2002). However, the drug is not only extremely expensive (three weeks of induction therapy cost around 4,500 Euro – the manufacturer demands a high price for the savings in nursing or hospital care), but also just as myelotoxic as ganciclovir infusions.

#### Treatment/prophylaxis of CMV retinitis

(daily doses, if not specified otherwise)

<b>Acute therapy</b>		Duration: always at least three weeks
Treatment of choice	Valganciclovir	Valganciclovir (Valcyte®) 2 tbl. à 450 mg bid
Alternative	Ganciclovir	Ganciclovir 5 mg/kg i.v. bid
Alternative	Foscarnet	Foscarnet 90 mg/kg i.v. bid
Alternative	Ganciclovir + Foscarnet	Half of the doses above
<b>Maintenance therapy</b>		Discontinue when > 100-150 CD4+ T-cells/ $\mu$ l > 6 mo
Treatment of choice	Valganciclovir	Valganciclovir (Valcyte®) 1 tbl. à 450 mg bid
Alternative	Foscarnet	Foscarnet 120 mg/kg i.v. qd on 5 days/week
Alternative	Cidofovir	Cidofovir 5 mg/kg i.v. qd every 14 days (plus probenecid hydration according to protocol, see Drugs section)
<b>Primary prophylaxis</b>		Not recommended

Discontinuation of secondary prophylaxis as quickly as possible, is therefore also desirable for this OI (MacDonald 1998, Tural 1998, Jouan 2001), but it also requires strict ophthalmologic monitoring. According to US guidelines, discontinuation should occur at the earliest after six months of maintenance therapy and with an immune reconstitution above 100-150 CD4+ T-cells/ $\mu$ l. However, we have even successfully stopped ganciclovir at lower CD4+ T-cell counts, if both HIV and CMV PCR in blood were below the level of detection. One study showed that stopping after 18 months of HAART/maintenance therapy can be safe above 75 CD4+ T-cells/ $\mu$ l (Jouan 2001).

The previously required life-long daily infusions of ganciclovir or foscarnet via port, pumps and nursing service are luckily now a thing of the past. If there are relapses under oral valganciclovir, we recommend re-induction and maintenance therapy with foscarnet or possibly with cidofovir.

## References

1. Berenguer J, Mallolas J, and the Spanish Cidofovir Study Group. Intravenous cidofovir for compassionate use in AIDS Patients with cytomegalovirus retinitis. *Clin Inf Dis* 2000, 30: 182-84. <http://amedeo.com/lit.php?id=10619750>
2. Casado JL, Arrizabalaga J, Montes M, et al. Incidence and risk factors for developing cytomegalovirus retinitis in HIV-infected patients receiving protease inhibitor therapy. *AIDS* 1999, 13:1497-1502. <http://amedeo.com/lit.php?id=10465073>
3. Davidson M, Min YI, Holbrook JT, et al. Use of filgrastim as adjuvant therapy in patients with AIDS-related cytomegalovirus retinitis. *AIDS* 2002; 16: 757-65. <http://amedeo.com/lit.php?id=11964532>
4. Deayton J, Mocroft A, Wilson P, et al. Loss of cytomegalovirus viraemia following HAART in the absence of specific anti-CMV therapy. *AIDS* 1999, 13:1203-6. <http://amedeo.com/lit.php?id=10416523>
5. Deayton JR, Prof Sabin CA, Johnson MA, et al. Importance of cytomegalovirus viraemia in risk of disease progression and death in HIV-infected patients receiving highly active antiretroviral therapy. *Lancet* 2004, 363:2116-21. <http://amedeo.com/lit.php?id=15220032>
6. Drew WL, Stempien MJ, Andrews J, et al. Cytomegalovirus (CMV) resistance in patients with CMV retinitis and AIDS treated with oral or intravenous ganciclovir. *J Infect Dis* 1999, 179:1352-5. <http://amedeo.com/lit.php?id=10228054>
7. Goldberg DE, Wang H, Azen SP, Freeman WR. Long term visual outcome of patients with cytomegalovirus retinitis treated with highly active antiretroviral therapy. *Br J Ophthalmol* 2003;87:853-5.
8. Goodgame RW. Gastrointestinal cytomegalovirus disease. *Ann Intern Med* 1993, 119:924-35. <http://amedeo.com/lit.php?id=8215005>
9. Jacobson MA, Stanley H, Holtzer C, et al. Natural history and outcome of new AIDS-related cytomegalovirus retinitis in the era of HAART. *Clin Inf Dis* 2000, 30:231-3. <http://amedeo.com/lit.php?id=10619774>
10. Jacobson MA, Maecker HT, Orr PL, et al. Results of a cytomegalovirus (CMV)-specific CD8+/interferon- gamma+ cytokine flow cytometry assay correlate with clinical evidence of protective immunity in patients with AIDS with CMV retinitis. *J Infect Dis* 2004, 189:1362-73. <http://amedeo.com/lit.php?id=15073672>
11. Jacobson MA, Wilson S, Stanley H, et al. Phase I study of combination therapy with intravenous cidofovir and oral ganciclovir for CMV retinitis in patients with AIDS. *Clin Infect Dis* 1999, 28:528-33. <http://amedeo.com/lit.php?id=10194072>
12. Jouan M, Saves M, Tubiana R, et al. Discontinuation of maintenance therapy for cytomegalovirus retinitis in HIV-infected patients receiving HAART. *AIDS* 2001, 15: 23-31. Abstract: <http://amedeo.com/lit.php?id=11192865>
13. Jutte A, Fätkenheuer G, Hell K, Salzberger B. CMV sinusitis as the initial manifestation of AIDS. *HIV Med* 2000, 1:123-4.
14. Komanduri KV, Viswanathan MH, Wieder ED, et al. Restoration of cytomegalovirus-specific CD4+ T-lymphocyte responses after ganciclovir and HAART in individuals infected with HIV-1. *Nature Med* 1998, 8:953-6. <http://amedeo.com/lit.php?id=9701250>
15. Lalezari J, Lindley J, Walmsley S, et al. A safety study of oral valganciclovir maintenance treatment of cytomegalovirus retinitis. *J Acquir Immune Defic Syndr* 2002, 30:392-400. <http://amedeo.com/lit.php?id=12138345>
16. Macdonald JC, Torriani FJ, Morse LS, et al. Lack of reactivation of CMV retinitis after stopping CMV maintenance therapy in AIDS patients with sustained elevations in CD4+ T cells in response to HAART. *J Infect Dis* 1998, 177:1182-7. <http://amedeo.com/lit.php?id=9593001>
17. Martin DF, Kuppermann BD, Wolitz RA, et al. Oral ganciclovir for patients with cytomegalovirus retinitis treated with a ganciclovir implant. *N Engl J Med* 1999, 340:1063-70. <http://amedeo.com/lit.php?id=10194235>
18. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *N Engl J Med* 2002, 346:1119-26. <http://amedeo.com/lit.php?id=11948271>
19. Foscarnet-Ganciclovir Cytomegalovirus Retinitis Trial: 5. Clinical features of cytomegalovirus retinitis at diagnosis. Studies of ocular complications of AIDS Research Group in collaboration with the ACTG. *Am J Ophthalmol* 1997,124:141-57. <http://amedeo.com/lit.php?id=9262538>
20. Nokta MA, Holland F, De Gruttola V, et al. Cytomegalovirus polymerase chain reaction profiles in individuals with advanced HIV infection: relationship to CMV disease. *J Infect Dis* 2002, 185:1717-22. <http://amedeo.com/lit.php?id=12085316>



21. O'Sullivan CE, Drew WL, McMullen DJ, et al. Decrease of cytomegalovirus replication in HIV infected-patients after treatment with HAART. *J Infect Dis* 1999, 180:847-9. <http://amedeo.com/lit.php?id=10438377>
22. Perry CM, Balfour JA. Fomivirsen. *Drugs* 1999, 57:375-80. <http://amedeo.com/lit.php?id=10193689>
23. Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. *Drugs* 1999, 58:325-45. <http://amedeo.com/lit.php?id=10473024>
24. Smith CL. Local therapy for cytomegalovirus retinitis. *Ann Pharmacother* 1998, 32:248-55. <http://amedeo.com/lit.php?id=9496411>
25. Tural C, Romeu J, Sirera G, et al. Long-lasting remission of cytomegalovirus retinitis without maintenance therapy in HIV-infected patients. *J Infect Dis* 1998, 177:1080-3. <http://amedeo.com/lit.php?id=9534987>
26. Whitley RJ, Jacobson MA, Friedberg DN, et al. Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: recommendations of an international panel. *Arch Intern Med* 1998, 158:957-69. <http://amedeo.com/lit.php?id=9588429>

## Candidiasis

Candidiasis is an infection with yeast-forming fungi. Of the 150 *Candida* species known to date, only approximately 20 cause disease. By far the most frequent species is *C. albicans*. Other species such as *C. tropicalis*, *C. glabrata* and *C. krusei* are rare, but may respond less readily to treatment with azoles. Although it is commonly assumed that azole resistance is a problem particularly with *albicans* strains, this has not been the case to date (Sanglard 2002).

Candidiasis is an important indicator of immunodeficiency and should be seen as a reason to consider starting HAART, even with a good immune status. Esophageal candidiasis and even oral thrush often occur following other OIs. Fever, which is not a classic symptom of candidiasis, is a particular indication to be on the alert. If immune status is good, it must be remembered that there are also other reasons for thrush – alcoholism and steroid treatment are only two of many possibilities. In addition to candidiasis of the oropharynx and esophagus, vaginitis is a frequent problem in women (also occurring in healthy individuals). Candidemia occurs only rarely in HIV-infected patients, even with severe immunodeficiency.

### Signs and symptoms

The oropharynx is usually affected, with taste disturbances and sometimes, a burning sensation on the tongue. White, non-adherent plaques on the buccal mucosa, tonsillar ring and tongue confirm the diagnosis. Involvement of the tongue alone is rare. Occasionally, there may be atrophic candidiasis, which presents only with an erythematous mucosa.

*Candida* esophagitis usually occurs with oropharyngeal involvement, but in about one third of cases there is no oral thrush. It often presents with dysphagia (“drinking is ok, but food can’t go down”) and retrosternal pain. Some patients complain of nausea, although vomiting occurs only rarely.

### Diagnosis

Diagnosis in the oropharynx can be made based on the clinical appearance. A swab is not usually required. Characterization by culture or even determination of drug susceptibility (beware laboratory uncertainty!) is only advised if one treatment attempt with fluconazole or itraconazole has failed. Oral candidiasis is not to be confused with oral hairy leukoplakia (OHL). In contrast to candidiasis, the whitish, hairy plaques of OHL, on the sides of the tongue, cannot be scraped off! OHL is not caused by fungi but by EBV, and is an important disease marker for HIV, even if it is harmless and does not require treatment.

*Candida* esophagitis can also initially be diagnosed clinically. Dysphagia, retrosternal pain and oral candidiasis make the diagnosis very probable. Empiric fluconazole therapy reduces costs (Wilcox 1996)! Upper GI endoscopy is only required if complaints about fluconazole persist. To distinguish fluconazole-resistant esophageal candidiasis from herpes or CMV esophagitis, samples of lesions should always be taken. In contrast, determination of serum antibodies or antigen is always unnecessary.

## Treatment

With relatively good immune status and presentation for the first time, treatment with topical antimycotics (gargle, rinse mouth and then swallow!) can be attempted. However, systemic treatment is usually necessary. This is more effective and prevents relapses for longer (Pons 1997). Fluconazole is the treatment of choice, and one week of oral treatment is usually sufficient (Sangeorzan 1994). If symptoms persist for more than a week, a swab should be taken and the fluconazole dose may be increased up to 800 mg for the second attempt.

Itraconazole should only be used if the second treatment attempt fails and non-albicans strains have been found. It will be effective in approximately two thirds of cases (Saag 1997). Although itraconazole suspension is as effective as fluconazole (Graybill 1998), we do not primarily use it as plasma levels are unreliable and there are problems with numerous interactions.

Several new and promising antimycotics have been developed in recent years. However, these should only be used in clear cases of fluconazole resistance. Vori-conazole is expected to be as effective as fluconazole, but is possibly not tolerated as well (Ruhnke 1997, Ally 2001). Like amphotericin B, it can be used for treatment of multi-azole resistant mycoses. Caspofungin or micafungin, two antimycotics belonging to the new class of echinocandins, also have good efficacy (Keating 2001, Villanueva 2001, Arathoon 2002, de Wet 2004). Both agents, which can only be administered intravenously, showed similar efficacy and tolerability to intravenous fluconazole for treatment of *Candida esophagitis* in randomized studies (Villanueva 2001, de Wet 2004).

An adequate HAART regimen should be initiated when such mycoses occur, particularly with multiresistant strains, as these usually disappear with sufficient immune reconstitution (Ruhnke 2000).

## Prophylaxis

No survival benefit has been demonstrated for any *Candida* prophylaxis to date (McKinsey 1999, Rex 2000, Goldmann 2005). In probably the largest randomized study on this theme, which was recently published, a reduction in oral candidiasis episodes as well as in invasive candidiasis was observed on long-term prophylaxis (Goldman 2005). The hypothesis (held until now) that long-term prophylaxis will lead to the selection of resistant non-albicans strains (Vazquez 2001) was not confirmed in this study, and where possible should be re-evaluated. Azol resistant candidas were not seen more frequently in the long-term therapy group. But: check the mouth of every immunocompromised patient at every visit!

## Treatment/prophylaxis of candidiasis (daily doses)

<b>Acute therapy</b>		Duration: 5-10 days
In mild cases	Topical	e.g. amphotericin B 1 lozenge qid or nystatin suspension 1 ml qid
Treatment of choice	Fluconazole	Diflucan™ or fluconazole CT/Stada 1 x 1 cap à 100 mg for oral candidiasis  Diflucan™ or fluconazole CT/Stada 1 x 1 cap à 200 mg for esophageal candidiasis  (twice the dose on the first day in each case)
Alternative	Itraconazole	Itraconazole 1-2 cap. à 100 mg bid or Itraconazole suspension 10-20 ml bid (1 ml = 10 mg)
<b>Prophylaxis</b>		Not recommended

## References

1. Ally R, Schurmann D, Kreisel W, et al. A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. *Clin Infect Dis* 2001, 33:1447-54. <http://amedeo.com/lit.php?id=11577374>
2. Arathoon EG, Gotuzzo E, Noriega LM, et al. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiasis. *Antimicrob Agents Chemother* 2002, 46:451-7. <http://amedeo.com/lit.php?id=11796357>
3. de Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. *Clin Infect Dis* 2004, 39:842-9. <http://amedeo.com/lit.php?id=15472817>
4. Graybill JR, Vazquez J, Darouiche RO, et al. Randomized trial of itraconazole oral solution for oropharyngeal candidiasis in HIV/AIDS patients. *Am J Med* 1998, 104:33-9. <http://amedeo.com/lit.php?id=9528717>
5. Keating GM, Jarvis B. Caspofungin. *Drugs* 2001, 61:1121-9; discussion 1130-1. <http://amedeo.com/lit.php?id=11465873>
6. McKinsey DS, Wheat LJ, Cloud GA, et al. Itraconazole prophylaxis for fungal infections in patients with advanced HIV infection: randomized, placebo-controlled, double-blind study. *Clin Infect Dis* 1999, 28:1049-56. <http://amedeo.com/lit.php?id=10452633>
7. Pons V, Greenspan D, Lozada-Nur F, et al. Oropharyngeal candidiasis in patients with AIDS: randomized comparison of fluconazole versus nystatin oral suspensions. *Clin Infect Dis* 1997, 24:1204-7. <http://amedeo.com/lit.php?id=9195083>
8. Rex JH, Walsh TJ, Sobel JD, et al. Practice guidelines for the treatment of candidiasis. *Clin Infect Dis* 2000, 30:662-78. <http://amedeo.com/lit.php?id=10770728>
9. Ruhnke M, Adler A, Muller FM. Clearance of a fluconazole-resistant *Candida albicans* strain after switching antifungal therapy and initiation of triple therapy for HIV infection. *Clin Microbiol Infect* 2000, 6:220-3.
10. Ruhnke M, Schmidt-Westhausen A, Trautmann M. In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with HIV infection. *Antimicrob Agents Chemother* 1997, 41:575-7. <http://amedeo.com/lit.php?id=9055995>
11. Saag MS, Fessel WJ, Kaufman CA, et al. Treatment of fluconazole-refractory oropharyngeal candidiasis with itraconazole oral solution in HIV-positive patients. *AIDS Res Hum Retroviruses* 1999, 15:1413-7. <http://amedeo.com/lit.php?id=10555103>
12. Sangeorzan JA, Bradley SF, He X, et al. Epidemiology of oral candidiasis in HIV-infected patients: colonization, infection, treatment, and emergence of fluconazole resistance. *Am J Med* 1994, 97:339-46. <http://amedeo.com/lit.php?id=7942935>
13. Sanglard D, Odds FC. Resistance of *Candida* species to antifungal agents: molecular mechanisms and clinical consequences. *Lancet Infect Dis* 2002, 2:73-85. <http://amedeo.com/lit.php?id=11901654>
14. Vazquez JA, Peng G, Sobel JD, et al. Evolution of antifungal susceptibility among *Candida* species isolates recovered from HIV-infected women receiving fluconazole prophylaxis. *Clin Infect Dis* 2001, 33:1069-75. <http://amedeo.com/lit.php?id=11528582>

15. Villanueva A, Arathoon EG, Gotuzzo E, et al. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. *Clin Infect Dis* 2001, 33:1529-35. <http://amedeo.com/lit.php?id=11588698>
16. Walsh TJ, Gonzalez CE, Piscitelli S, et al. Correlation between in vitro and in vivo antifungal activities in experimental fluconazole-resistant oropharyngeal and esophageal candidiasis. *J Clin Microbiol* 2000, 38:2369-73. <http://amedeo.com/lit.php?id=10835005>
17. Wilcox CM, Alexander LN, Clark WS, Thompson SE 3rd. Fluconazole compared with endoscopy for HIV-infected patients with esophageal symptoms. *Gastroenterology* 1996, 110:1803-9. <http://amedeo.com/lit.php?id=8964406>

## Tuberculosis

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Tuberculosis has a greater impact worldwide on morbidity and mortality in HIV-1-infected individuals than all other opportunistic infections (OI) (Unaids 2006). In fact, the rising incidence of tuberculosis in many regions of the world is closely related to the HIV epidemic (Corbett 2003). Approximately 1/3 of the 40 million people infected with HIV-1 are co-infected with *Mycobacterium tuberculosis* (*M. tuberculosis*, *M. africanum*, *M. bovis*, *M. canetti* or *M. microti* – MTB). The prevalence of HIV in tuberculosis patients in Africa has been reported to be around 40 percent (Corbett 2003) and the incidence of HIV is more than 8 times higher in HIV-positive than in HIV-negative people (Corbett 2006). Recently, co-infection of the two pathogens has become more noticeable in Eastern Europe and in Asia (Field 2004, Sonnenberg 2004, Steinbrook 2004, Surendran 2004). In addition, there is increasing concern that HIV-1 will enhance the spread of multidrug resistant MTB in these regions (Kruuner 2001), as MDR-TB is approximately 10 times more prevalent in Eastern Europe than in Africa (Dye 2002, Morozova 2003).

Despite a steadily increasing prevalence of HIV-1 infection in Western Europe and North America in recent years, the incidence of tuberculosis has continuously declined in countries where antiretroviral therapies (ART) against HIV-1 are available (Kirk 2000, Girardi 2000). However, treatment of co-infected patients with ART and antituberculous medications simultaneously is complicated, due to a wide spectrum of pharmacological interactions and side effects.

## Interaction of HIV and MTB

The influence of HIV and MTB on immunoregulation by the host is bidirectional. The incidences of post-primary tuberculosis and reactivation tuberculosis are increased in HIV-infected patients in comparison to HIV-seronegative individuals (Havlir 1999, Badri 2001). For example, the incidence of post-primary TB is increased from 5 % to 30 % in HIV-1 infected subjects. Further, it is likely that tuberculosis enhances immunodeficiency in patients with chronic HIV infection (Toossi 2003). Despite adequate therapy of tuberculosis, the subsequent morbidity and mortality is increased in patients with HIV infection in comparison to HIV-seronegative patients with tuberculosis (Manas 2004, Whalen 2000). While most opportunistic infections, including all other mycobacterial diseases, occur in the advanced stages of HIV infection, patients can develop tuberculosis at any stage, regardless of the levels of circulating CD4+ T-cells (Ackah 1995). More than 50 percent of cases with pulmonary tuberculosis occur in patients with CD4 counts of more than 200 cells/ $\mu$ l in the peripheral blood (Badri 2001). However, the incidence of disseminated tuberculosis is much higher in patients with advanced immunodeficiency (Wood 2000). Recently, it was shown that the risk of developing tuberculosis is already significantly increased in the first year following HIV-antibody seroconversion, (Sonnenberg 2005). The factors that lead to tuberculosis reactivation in HIV infection have not been determined in detail.

## Clinical manifestations

The risk of developing tuberculosis in patients with latent MTB infection (LTBI) is approximately 8 percent per year in HIV-infected patients compared with a lifetime risk of 5 to 10 percent in HIV-seronegative individuals (UNAIDS 2006). The pathogenesis of tuberculosis is dependent on the stage of immunodeficiency. When LTBI is reactivated in the early stages of HIV infection, the clinical manifestation resembles tuberculosis in HIV-seronegative individuals with the cardinal clinical features of fever, night sweats and weight loss.

### Pulmonary TB

As in HIV-seronegative patients, the typical features of pulmonary tuberculosis in HIV patients with circulating CD4+ T-cell counts of more than 200/ $\mu$ l are upper-lobe infiltrates with or without cavities. Acid-fast bacilli (AFBs) can often be detected on examination of the sputum. As immunodeficiency progresses, non-cavernous atypical presentations or tuberculous pleuritis become more prominent. Bronchopulmonary symptoms, such as cough and hemoptysis are often absent when tuberculosis occurs in the advanced stages of HIV infection. The acid-fast stain is positive in approximately 5 percent of cases where infiltrates are not visible on standard chest x-ray (Ackah 1995). With progressive immunodeficiency, hematogenous and lymphatic spread of mycobacteria is more common, leading to the clinical picture of miliary (Elliott 1993) or localized extrapulmonary tuberculosis (Mayanja-Kizza 2001). Because CD4+ T-lymphocytes are required for granuloma formation, these features are usually absent on histopathological examination of tissue from these patients (Nambuya 1988).

### Extrapulmonary TB

As mentioned earlier, extrapulmonary tuberculosis occurs predominantly in co-infected patients with CD4+ T-cell counts of less than 200/ $\mu$ l. The most common feature of extrapulmonary tuberculosis is cervical lymphadenopathy. The involved nodes are firm and generally not painful on palpation. The formation of abscesses and draining fistulas, as well as fever and malaise are common.

Tuberculous meningitis often presents with unspecific prodromal symptoms, such as headache, nausea and vomiting followed by elevated temperature and clinical signs of meningeal irritation. The basal meninges are usually involved and cranial palsies of the IIIrd and VIth nerves are common. Mono-, hemi-, or paraparesis as well as seizures can occur. In case of doubt, a lumbar puncture should be performed without delay.

In febrile patients with abdominal pain and ascites, peritoneal tuberculosis must be included in the differential diagnosis.

A micronodular pattern is seen on chest x-ray in miliary tuberculosis (lat. *miliun effusum* = millet). On radiological criteria alone, miliary tuberculosis cannot be distinguished from pulmonary cryptococcosis. Miliary dissemination of tuberculosis can also be detected on abdominal ultrasound of the spleen and liver and may involve the adrenals (cave: Addison's disease) too.

Other extrapulmonary manifestations include pericarditis, osteoarthritis, and urogenital or skin tuberculosis. Practically every organ can be involved.

## Diagnosis

The diagnostic steps to approach an HIV-infected patient with possible tuberculosis do not differ from those used on the immunocompetent host (Lange 2004). In the differential diagnosis, tuberculosis has to be distinguished primarily from diseases caused by non-tuberculous mycobacteria, from cryptococcosis, histoplasmosis, sarcoidosis, lymphoma, and solid malignant tumors.

The diagnosis is made on clinical, microbiological and radiological grounds. Sputum and other biological materials are evaluated for the presence of acid-fast-staining rods on microscopy. The sensitivity and specificity of sputum-microscopy is poor. Approximately 5,000 – 10,000 mycobacteria/ml are necessary for a routine microscopic diagnosis of acid-fast bacteria in a sample. Approximately 50 % of all patients with culture positive pulmonary tuberculosis have no detectable AFBs on examination of three consecutive sputum samples. In addition, discrimination against non-tuberculous mycobacteria is not possible by microscopy.

When AFBs are detected in the sputum or in the bronchoalveolar lavage, the patient should be treated in isolation. There is, however, uncertainty about the duration of isolation. As a rule of thumb, isolation should be kept ongoing until AFBs are undetectable on three sputum samples obtained on different days or until the culture result confirms the presence of non-tuberculous mycobacteria. Patients with MDR tuberculosis should be kept in isolation until sputum cultures turn negative.

When pulmonary tuberculosis is suspected, three sputum samples should be obtained in the morning on different days for microscopy and culture. If patients are unable to cough productively, an attempt to induce sputum by the inhalation of 3 percent hypertonic sodium chloride should be made. Alternatively, early morning gastric aspirate can also be examined for mycobacteria. The acidic gastric aspirate should be buffered in phosphate solution prior to transportation to the laboratory. In patients with advanced stages of HIV infection, the likelihood of smear-positive tuberculosis is decreased. Bronchoscopy is usually indicated if the suspicion of tuberculosis remains high, but no AFBs are found on microscopic examination of sputum. Bronchial secretions or bronchoalveolar lavage is not superior to sputum in the diagnosis of tuberculosis in patients with HIV infection (Conde 2000), but a bronchoscopy may be very helpful in differentiating between tuberculosis and other diseases in the differential diagnosis (Narayanswami 2003), particularly since the coincidence of more than one pulmonary process has been seen in patients with HIV infection. In the case of tuberculosis, histopathological examination of trans-bronchial biopsies may yield typical caseating granulomas and giant cells and may show AFBs. On the day following the bronchoscopy, sputum should again be sampled for analysis, as the diagnostic yield for AFBs is high following the intervention even if no bacteria were detected in the lavage.

For the diagnosis of extrapulmonary tuberculosis, biological samples (heparinized venous blood, CSF, urine, pleural, pericardial, and peritoneal fluid) should be examined. Biopsies from lymph nodes, pleura, peritoneum, synovia, pericardium, etc., are also suitable for the diagnosis of extrapulmonary tuberculosis.

The gold standard in the diagnosis of tuberculosis is the cultural identification of MTB in liquid (2 to 4 weeks) or solid (3 to 5 weeks) media. A culture will be considered “negative” only if no bacteria are identified after 6 to 8 weeks. Non-



tuberculous mycobacteria usually grow much faster than MTB and can be identified in a specialized laboratory often within two weeks. All new clinical isolates of MTB should undergo resistance testing.

For rapid diagnosis, mycobacterial DNA can be detected by PCR in biological specimens.

This is especially helpful in differentiating the species, when acid-fast bacilli are found on microscopic analysis. In this setting, a positive MTB-PCR is more than 95 percent sensitive for the diagnosis of tuberculosis. Unfortunately, the sensitivity of the MTB-PCR is decreased to around 40-77 % in smear-negative sputum samples (Barnes 1997). In extrapulmonary tuberculosis, where acid fast stains often remain negative, or when a rapid diagnosis is needed, for example in TB-meningitis, MTB-PCR should be performed in the initial routine evaluation. For PCR analysis, biopsies should not be fixed in formalin but rather be preserved in "HOPE" (Hepes-glutamic acid buffer-mediated organic solvent protection effect) media (Oleret 2001).

Because the use of mycobacterial PCRs in the setting of acid-fast negative stains can lead to false results, these results should always be questioned.

A positive tuberculin skin test can detect an immunological memory to previous or ongoing contact with MTB antigens. However, in HIV-1 infected patients with CD4+ T-cell counts of less than 200/ $\mu$ l, the tuberculin skin test is usually non-reactive (Fisk 2003). False positive results may be found in patients who were BCG-vaccinated or who had contact to non-tuberculous mycobacteria. The test should only be performed intradermally according to the method described by Mendel and Mantoux (until recently the Tine-test was still widely used in some European countries). The standardized dose that is recommended by the WHO and the IUATLD is 2 TU in 0.1ml of PPD RT23/Tween 80. In the United States and some other countries, 5 TU PPD-S, which is thought to be similar in strength, is in use. Following the intradermal oculation of the injection, the diameter of the induration along the short axis of the lower arm is measured by the ball-point technique (Sokal 1975).

In HIV-infected patients, an induration of  $\geq 5$  mm is positive by definition of the IDSA (Jasmer 2002). The IDSA guidelines for the interpretation of the tuberculin skin test are based on results of clinical studies that were conducted with 5 TU PPD-S in the United States and therefore cannot be directly translated to the situation in other countries, where different antigens are used and where, in certain regions, a large number of individuals have been vaccinated with BCG. In the past years, new diagnostic tools for the diagnosis of infection with MTB have been developed. The ELISPOT (T-SPOT-TB Test) and ELISA (Quantiferon-Gold-in-tube Test) detect the secretion of  $\gamma$ -interferon by mononuclear cells in venous blood, specific for MTB peptides, ESAT-6 and CFP-10. These tests are more sensitive and specific for the diagnosis of MTB infection and are superior to the TST in patients with immunosuppression (Chapman 2002, Dheda 2005, Ferrara 2006,). However, in patients with advanced immunosuppression, a substantial proportion of ELISA results are indeterminate and the performance of these assays in patients with HIV infection and low CD4+ T-cell counts still needs to be evaluated in clinical practice.

Radiographic changes in tuberculosis are often unspecific and can vary substantially. While tuberculosis can mimic a variety of other pulmonary diseases, pulmo-

nary tuberculosis can be present without obvious changes on the chest x-ray. Classical findings are diffuse upper lobe infiltrations, cavitations and reticulo-nodular infiltrations. Calcifications and scarring may be a sign of previous pulmonary tuberculosis and a clue to reactivated disease. In miliary tuberculosis, the chest x-ray shows a disseminated micronodular pattern. Patients with low CD4+ T-cell counts often present with tuberculous pleural effusion without pulmonary infiltrates. In case of doubt, a CT scan of the thorax should be made, if possible. When extrapulmonary tuberculosis is diagnosed, pulmonary imaging to detect a lung focus should be performed as well as abdominal sonography to identify abscesses, bowel thickening or ascites.

## Therapy

In uncomplicated cases, tuberculosis can be treated successfully with a standard 6-month course. First-line drugs include rifampin, isoniazid, ethambutol, pyrazinamide and streptomycin. Isoniazid and rifampin are the most potent of these drugs. Streptomycin is not orally available and is delivered i.v. or i.m.; it should only be included in the treatment regimen if one of the other four first-line drugs is contraindicated (drug resistance, toxicity, etc.). To avoid the development of drug resistance, active tuberculosis should always be treated initially with a combination of four drugs. Standard therapy is a two-month course of rifampin, isoniazid, ethambutol and pyrazinamide, followed by a four-month course of rifampin and isoniazid. Isoniazid should always be co-administered with pyridoxine (vitamin B6) to prevent the development of peripheral polyneuropathy. Both drugs are available in fixed combinations.

The duration of infectivity of a patient with pulmonary tuberculosis depends on the extent of pulmonary infiltrates and cavitations. Sputum should be regularly (initially every week) evaluated for the presence of AFBs by microscopy and viable mycobacteria by culture until the end of treatment. The infectivity of a patient is low once AFBs are repeatedly absent on smears. However, viable mycobacteria can usually be cultured from sputum for a few weeks following microscopic conversion. Failure of therapy occurs in the presence of drug resistance, non-compliance or insufficient treatment duration (Sonnenberg 2001, Korenromp 2003). If sputum cultures are still positive after two months of treatment, or in cases where the initial treatment regimen was different from quadruple therapy including rifampin and isoniazid, the duration of therapy should be extended to 9 months or more. Despite successful initial therapy, recurrence of tuberculosis occurs more often in HIV-seropositive than HIV-seronegative individuals (Sonnenberg 2001).

Prior to and during therapy with ethambutol, color vision should be examined. Audiometry should be performed when streptomycin is used. Dosages of ethambutol and pyrazinamide need to be adjusted in patients with renal insufficiency. In patients with liver disease (including drug-induced hepatitis), the choice of first-line drugs is limited as rifampin, isoniazid and pyrazinamide can worsen the liver injury. Alternatively, a combination of ethambutol, streptomycin, cycloserine, moxifloxacin and/or linezolid may be tried. Since this therapy is no different to that for multi-drug-resistant tuberculosis, these patients should be treated in specialized centers.

Following the initiation of antituberculous therapy, liver enzymes, serum creatinine and full blood counts should be performed on a regular basis (e.g. initially every week for two months, then every four weeks). Hyperuricemia is common when pyrazinamide is used. A mild, non-gouty polyarthralgia can be treated with allopurinol and non-steroidal antiinflammatories. Arthralgia can also be induced by rifampin and rifabutin.

## Drug side effects

The most important side effects of antituberculous drugs are listed in Table 1.

Table 1: Antituberculous drugs

Antituberculous drugs	Recommended daily dose	Common side effects	Drug interactions	Comments
Rifampin (RMP)	10 mg/kg  > 50 kg: 600 mg < 50 kg: 450 mg	elevation of liver enzymes, toxic hepatitis, allergy, fever; gastrointestinal disorders: anorexia, nausea, vomiting, abdominal pain; discoloration of urine/body fluids thrombopenia	many drug interactions: induces cytochrome p450, reduces effectiveness of oral contraceptive pill; for ART drug interactions see table 3	monitor LFTs
Rifabutin (RB)	300 - 450 mg/day	gastrointestinal discomfort, discoloration of urine and other body fluids, uveitis, elevated liver enzymes, arthralgia	weaker inducer of cytochrome p450 than rifampin; for ART drug interactions see table 3	monitor LFTs generally preferred over rifampin in patients treated with ART drugs (see table 3)
Isoniazid (INH)	5 mg/kg  maximum 300 mg/day, administer vitamin B6	peripheral neuropathy, elevated liver enzymes, hepatitis; CNS side effects: psychosis, convulsions	avoid ddC, d4T, ddI	avoid alcohol, preexisting liver damage
Ethambutol (EMB)	40-55 kg: 800 mg/day  56-75 kg: 1.2 g/day  76-90 kg: 1.6 g/day	optic neuritis, hyperuricemia, peripheral neuropathy (rare)	antacids may decrease absorption	baseline screen for visual acuity + color perception, repeated monthly contraindicated in pts with preexisting lesions of N. opticus
Pyrazinamide (PZA)	ca. 30 mg/kg/day	arthralgia, hyperuricemia, hepatitis, gastrointestinal discomfort		hyperuricemia: uricosuric agents, monitor LFTs

Table 1: Antituberculous drugs

Antituberculous drugs	Recommended daily dose	Common side effects	Drug interactions	Comments
Streptomycin (SM) i.v./i.m. administration only	0.75 – 1 g maximum cumulative dose 50 g  < 50 kg: 0.75 g/day > 50 kg: 1 g/day	auditory and vestibular nerve damage, renal damage, allergies, nausea, skin rash, leukopenia, thrombopenia, pancytopenia, hemolytic anemia		audiometry; cumulative dose should not be exceeded; monitor renal function; should not be used in pregnancy
Capreomycin i.v./i.m. administration only	15 – 30 mg/kg/day max. 1 g/day maximum cumulative dose: 50 g > 50 kg: 1 g < 50 kg: 0.75 g	renal damage, Bartter-like syndrome, auditory nerve damage		audiometry, cumulative dose should not be exceeded, monitor renal function, should not be used in pregnancy
Prothionamide	0,75 g - 1 g/day	CNS disorders, liver damage, gastrointestinal discomfort	slowly increase dosage	monitor LFTs
Moxifloxacin (MOX)	400 mg/ day	gastrointestinal discomfort, headache, dizziness, hallucin.		similar activity as rifampin, drug resistance is still rare
Ciprofloxacin (CFL)	2 x 500 or 750 mg/day	gastrointestinal discomfort, CNS disorders, tendon rupture (rare)		not approved for treatment in children; in adults rather use moxifloxacin
Cycloserine	10 – 15 mg/kg day  maximum 1,000 mg/day	CNS disorders, anxiety, confusion, dizziness, psychosis, seizures, headache	aggravates CNS side effects of INH and PTH, CNS side effects occur usually within the first 2 weeks	contraindicated in epileptics
Linezolid	600 mg BID	thrombopenia, anemia, CNS disorders		evidence for clinical use relies on case reports, expensive

Patients who exhibit severe side effects should always be treated as inpatients. Reintroduction of the same drug should be avoided if vestibular dysfunction occurs on streptomycin therapy, visual dysfunction occurs on ethambutol therapy or renal failure, shock or thrombocytopenia occurs on rifampin therapy. Treatment must then be continued with other antituberculous drugs.

If toxic hepatitis occurs, all drugs should be stopped until the serum bilirubin and transaminases have normalized. In many cases, it is possible to reintroduce the causative drug – usually isoniazid, rifampin or pyrazinamide – in an escalating dosage without further hepatic complications.

When all drugs that could possibly be responsible for a given side effect are stopped and symptoms resolve, drugs can be reintroduced one by one, beginning with the drug that is least likely to cause the adverse effect. As stated above, all drugs should be started at low dosages and dosages should be increased stepwise (Table 2). When no adverse effects occur after 3 days, additional drugs can be added. The drug that is most likely to be responsible for an adverse effect should be the last to be restarted if no alternative is available. If pyrazinamide, ethambutol or streptomycin seems to be responsible for an adverse effect, therapy should be continued without these drugs. In all cases where second line drugs are used, it is usually necessary to prolong the duration of treatment.

Table 2: Re-Introduction of antituberculous drugs following drug reaction

Drug	Day 1	Day 2	Day 3
INH	50 mg	300 mg	5 mg/kg/d (max 300 mg/d)
Rifampin	75 mg	300 mg	10 mg/kg/d (max 600 mg/d)
Pyrazinamide	250 mg	1000 mg	25 mg/kg/d (max 2.5 g/d)
Ethambutol	100 mg	500 mg	25 mg/kg/d for 2 months & then 15 mg/kg/d
Streptomycin	125 mg	500 mg	15 mg/kg/d i.m., also available i.v.

## ART and tuberculosis therapy

Independent of the status of antiretroviral therapy (ART), uncomplicated tuberculosis in HIV-infected persons can be treated using standard therapy over 6 months with a similar success rate to that of HIV-seronegative individuals (Burman 2001, Chaisson 1996, Hung 2003). If the therapeutic response is delayed, for example when sputum cultures still show growth of MTB after 2 months of therapy, the duration of MTB-therapy should be extended to at least 9 months. In practice, parallel treatment with antituberculous drugs and ART can be problematic. Following initiation of antituberculous therapy, patients treated with ART experience paradoxical reactions, with increasing lymphadenopathy, fever or increasing pulmonary infiltrates, five times more often than ART-naïve patients (Narita 1998, Breen 2005) In patients coinfecting with HIV and MTB, an acute exacerbation of a TH1 immune response against mycobacterial antigens seems to be responsible for the reaction (Bourgarit 2006). In addition, adherence to the large number of drugs and pharmacological interactions of antituberculous and antiviral drugs complicate the synchronous simultaneous treatment of both infections. Both rifampin and protease inhibitors (PIs) are metabolized by cytochrome P450 3A. As drug levels are unre-

dictable, concomitant therapy with PIs and rifampin is generally not recommended (exception: ritonavir ± saquinavir and ritonavir-hyperboosted lopinavir) (Updated Guidelines 2004) (Table 3). Either the combination of 2 nucleoside reverse transcriptase inhibitors (NRTIs) with the non-nucleoside reverse transcriptase inhibitor efavirenz, or the suboptimal combination of 3 NRTIs, are possible therapeutic options for treating HIV infection when tuberculosis is treated with rifampin. As an alternative to rifampin, rifabutin, another rifamycine, is a weaker inducer of cytochrome P450-3A and can also be co-administered with PIs, although dosage adjustments have to be considered (table 4). There are no valid clinical data on the usage of rifamycines and enfurvirtide or tenofovir, but both drugs may be safe to use as they are not metabolized by cytochrome P450-3A.

Table 3: Recommendations for coadministering antiretroviral therapy with Rifampin (Updated Guidelines 2004, modified\*)

	Antiretroviral dosage adjustment	Rifampin dosage adjustment
Fosamprenavir	Should not be used together	
Atazanavir	Should not be used together	
Indinavir	Should not be used together	
Nelfinavir	Should not be used together	
Ritonavir	None	None (600 mg/day)
Saquinavir	Should not be used together	
Lopinavir/Ritonavir	Lopinavir/ ritonavir 3 capsules + 300 mg Ritonavir BID	None (600 mg/day)
Saquinavir/Ritonavir	Saquinavir 400 mg BID, Ritonavir 400 mg BID	None (600 mg/day)
Efavirenz	600*- 800 mg/day	None (600 mg/day)
Nevirapine	200 mg BID	None (600 mg/day)
Delavirdine	Should not be used together	

\* Manosuthi 2005

Treatment of active tuberculosis always has clinical priority over the treatment of HIV.

When tuberculosis occurs in patients with advanced immunodeficiency and less than 100 CD4+ T-cells/ $\mu$ l, the risk of mortality is high, and parallel treatment of both infections is indicated (Dean 2002). Even in this situation, it is recommended that antituberculous therapy be started first and the initiation of ART be delayed for at least two weeks. Providing the antituberculous therapy is tolerated, ART should be introduced. However, patients need to be monitored closely, as the risk of immune reconstitution syndrome is very high.

Table 4: Recommendations for coadministering antiretroviral therapy with rifabutin (Updated Guidelines 2004)

	Antiretroviral dosage adjustment	Rifabutin dosage adjustment
Amprenavir	None	↓ 150 mg/day or 300 mg 3/week
Fosamprenavir	None	↓ 150 mg/day or 300 mg 3/week
Atazanavir	None	↓ 150 mg every other day or 150 mg 3/week
Indinavir	↑ 1000 mg TID	↓ 150 mg/day or 300 mg 3/week
Nelfinavir	↑ 1000 mg TID	↓ 150 mg/day or 300 mg 3/week
Ritonavir	None	↓ 150 mg every other day or 150 mg 3/week
Saquinavir	Should not be used together	
Lopinavir/Ritonavir	None	↓ 150 mg every other day or 150 mg 3/week
Ritonavir with Amprenavir, Fosamprenavir, Atazanavir, Indinavir or Saquinavir	None	↓ 150 mg every other day or 150 mg 3/week
Efavirenz	None	↑ 450 mg/day or 600 mg 3/week
Nevirapine	None	↑ 300 mg/day or 300 mg 3/week
Delavirdine	Should not be used together	

In patients who develop tuberculosis with CD4+ T-cell counts of 100 – 200/ $\mu$ l, the initiation of ART can be delayed for at least two months; by this time, the number of antituberculous drugs has been reduced to two for maintenance therapy. When tuberculosis occurs at CD4+ T-cell counts of above 200/ $\mu$ l, completion of antituberculous treatment prior to the initiation of ART is usually recommended. Patients who are on ART when tuberculosis develops should remain on antiviral treatment, although the therapy may have to be modified depending on the compatibility with antituberculous drugs (Dean 2002).

Patients with advanced immunodeficiency, especially in high burden countries, remain at high risk of developing TB despite ART (Lawn 2005a, b, Bonnet AIDS 2006), as the function of CD4+ T-cells is not fully restored by ART alone in these patients (Sutherland 2006, Lange 2003). However, the most important factor for the

success of antituberculous treatment is drug adherence. In the case of non-compliance, the development of drug resistance and relapses are common. The World Health Organization recommends that all patients with tuberculosis should therefore be treated with directly observed therapy (DOT).

## Therapy of latent tuberculosis

HIV-infected patients with LTBI have a much greater risk of developing active tuberculosis compared to HIV-seronegative controls. The efficacy of prophylactic isoniazid treatment to prevent tuberculosis in HIV-infected patients with LTBI has been demonstrated in several randomized and controlled studies (Bucher 1999). However, ART-naïve patients with a negative tuberculin skin test do not benefit from either primary (Bucher 1999) or secondary prophylaxis of tuberculosis (Churchyard 2003). In addition, chemoprophylaxis with INH has no positive effect on the overall mortality of these patients (Woldehanna 2004). Offering INH preventative chemotherapy to all HIV-infected subjects in a country with a high incidence of TB only reduced the TB incidence from 11.9 to 9.0 per 100 person years (Grant 2005). Although ART has a very beneficial effect on the prognosis of patients who developed active tuberculosis and were treated, the effects of ART on patients with LTBI are so far not known. For the treatment of LTBI, a 9-month course of isoniazid and pyridoxine is usually recommended. A recent Cochrane review showed that in comparison to INH monotherapy, short course multi-drug regimens were much more likely to require discontinuation of treatment due to adverse hepatic effects (Woldehanna 2004). Very recently, however, others have found no evidence of liver injury associated with rifampin and pyrazinamide short course treatment in HIV-infected patients (Gordin 2004).

## Drug resistant tuberculosis

Despite declining numbers of tuberculosis cases in many industrialized nations in recent years, the proportion of multidrug-resistant tuberculosis (MDR = at least resistance against rifampin and isoniazid) is rising in many countries. In Germany, in 2004, 13.9 % of all MTB isolates were resistant against one of the standard drugs; 2.5 % of the isolates were MDR-resistant (RKI 2006). In the future, an increase in the number of patients with drug-resistant MTB is expected worldwide. In some areas, such as the Baltic region, the rate of INH-resistant isolates is already greater than 25 % (Morozova 2003). Under these circumstances, selection of the correct drug for treatment of LTBI becomes problematic.

Where possible, patients with MDR tuberculosis should be treated in specialized centers familiar with second-line antituberculous drugs, and should not be discharged before producing repeatedly negative sputum cultures.

## References

1. Ackah AN, Coulibaly D, Digbeu H, et al. Response to treatment, mortality, and CD4 lymphocyte counts in HIV-infected persons with tuberculosis in Abidjan, Cote d'Ivoire. *Lancet* 1995;345:607-10. <http://amedeo.com/lit.php?id=7898177>
2. Badri M, Ehrlich R, Wood R, et al. Association between tuberculosis and HIV disease progression in a high tuberculosis prevalence area. *Int J Tuberc Lung Dis* 2001;5:225-32. <http://amedeo.com/lit.php?id=11326821>



3. Barnes PF. Rapid diagnostic tests for tuberculosis: progress but no gold standard. *Am J Respir Crit Care Med* 1997;155:1497-8. <http://amedeo.com/lit.php?id=15220119>
4. Bonnet MMB, Pinoges LLP, Varaine FFV, et al. Tuberculosis after HAART initiation in HIV-positive patients from five countries with a high tuberculosis burden. *AIDS* 2006; 20:1275-79
5. Bourgarit A, Crcelain G, Martinez V, et al. Explosion of a tuberculin-specific TH1 immuneresponse induces immune restoration syndrome in tuberculosis and HIV-coinfected patients. *AIDS* 2006; 20:F1-F7
6. Breen RAM, Smith CJ, Cropley I, et al. Does immune reconstitution syndrome promote tuberculosis in patients receiving highly active antiretroviral therapy? *AIDS* 2005; 19:1201-06
7. Bucher HC, Griffith LE, Guyatt GH, et al. Isoniazid prophylaxis for tuberculosis in HIV infection: a meta-analysis of randomized controlled trials. *Aids* 1999;13:501-7. <http://amedeo.com/lit.php?id=10197379>
8. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001;164:7-12. <http://amedeo.com/lit.php?id=11435233>
9. Chaisson RE, Clermont HC, Holt EA, et al. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *Am J Respir Crit Care Med* 1996;154:1034-8. <http://amedeo.com/lit.php?id=8887603>
10. Chapman AL, Munkanta M, Wilkinson KA, et al. Rapid detection of active and latent tuberculosis infection in HIV-positive individuals by enumeration of *Mycobacterium tuberculosis*-specific T cells. *Aids* 2002;16:2285-93. <http://amedeo.com/lit.php?id=12441800>
11. Churchyard GJ, Fielding K, Charalambous S, et al. Efficacy of secondary isoniazid preventive therapy among HIV-infected Southern Africans: time to change policy? *Aids* 2003;17:2063-70. <http://amedeo.com/lit.php?id=12824791>
12. Conde MB, Soares SL, Mello FC, et al. Comparison of sputum induction with fiberoptic bronchoscopy in the diagnosis of tuberculosis: experience at an acquired immune deficiency syndrome reference center in Rio de Janeiro, Brazil. *Am J Respir Crit Care Med* 2000;162:2238-40. <http://amedeo.com/lit.php?id=11112145>
13. Corbett EL, Watt CJ, Walker N, et al. The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003;163:1009-21. <http://amedeo.com/lit.php?id=12742798>
14. Corbett EL, Marston B, Churchyard GJ et al. Tuberculosis in sub-Saharan Africa: Opportunities, challenges and change in the era of antiretroviral treatment. *Lancet* 2006; 367: 926-37
15. Dean GL, Edwards SG, Ives NJ, et al. Treatment of tuberculosis in HIV-infected persons in the era of highly active antiretroviral therapy. *Aids* 2002;16:75-83. <http://amedeo.com/lit.php?id=11741165>
16. Dheeda K, Lalvani A, Miller RF, et al. Performance of a T-cell based diagnostic test for tuberculin infection in HIV-infected individuals is independant of CD4 count. *AIDS* 2005; 19: 2038-41
17. Dye C, Espinal MA, Watt CJ, et al. Worldwide incidence of multidrug-resistant tuberculosis. *J Infect Dis* 2002;185:1197-202. <http://amedeo.com/lit.php?id=11930334>
18. Elliott AM, Halwiindi B, Hayes RJ, et al. The impact of human immunodeficiency virus on presentation and diagnosis of tuberculosis in a cohort study in Zambia. *J Trop Med Hyg* 1993;96:1-11. <http://amedeo.com/lit.php?id=8429569>
19. Ferrara G, Losi M, D'Amico R, et al. Use in routine clinical practice of two commercial blood tests for diagnosis of infection with *Mycobacterium tuberculosis*: a prospective study. *Lancet* 2006; 367: 1328-34
20. Field MG. HIV and AIDS in the Former Soviet Bloc. *N Engl J Med* 2004;351:117-20. <http://amedeo.com/lit.php?id=15247350>
21. Fisk TL, Hon HM, Lennox JL, et al. Detection of latent tuberculosis among HIV-infected patients after initiation of highly active antiretroviral therapy. *Aids* 2003;17:1102-4. <http://amedeo.com/lit.php?id=12700468>
22. Girardi E, Antonucci G, Vanacore P, et al. Impact of combination antiretroviral therapy on the risk of tuberculosis among persons with HIV infection. *AIDS*. 2000; 14:1985-91. <http://amedeo.com/lit.php?id=10997404>
23. Gordin FM, Cohn DL, Matts JP, et al. Hepatotoxicity of rifampin and pyrazinamide in the treatment of latent tuberculosis infection in HIV-infected persons: is it different than in HIV-uninfected persons? *Clin Infect Dis*. 2004;39:561-5. <http://amedeo.com/lit.php?id=15356822>
24. Grant AD, Charalambous S, Fielding KL, et al. Effect of routine isoniazid preventive therapy on tuberculosis incidence among HIV-infected men in south Africa. *JAMA* 2005; 293: 2719-25
25. Havlir DV, Barnes PF. Tuberculosis in patients with human immunodeficiency virus infection. *N Engl J Med* 1999;340:367-73. <http://amedeo.com/lit.php?id=9929528>

26. Hung CC, Chen MY, Hsiao CF, et al. Improved outcomes of HIV-1-infected adults with tuberculosis in the era of highly active antiretroviral therapy. *Aids* 2003;17:2615-22. <http://amedeo.com/lit.php?id=14685055>
27. Jasmer RM, Nahid P, Hopewell PC. Clinical practice. Latent tuberculosis infection. *N Engl J Med* 2002;347:1860-6. <http://amedeo.com/lit.php?id=12466511>
28. Korenromp EL, Scano F, Williams BG, et al. Effects of human immunodeficiency virus infection on recurrence of tuberculosis after rifampin-based treatment: an analytical review. *Clin Infect Dis* 2003;37:101-12. <http://amedeo.com/lit.php?id=12830415>
29. Kirk O, Gatell JM, Mocroft A, et al. Infections with *Mycobacterium tuberculosis* and *Mycobacterium avium* among HIV-infected patients after the introduction of highly active antiretroviral therapy. Euro-SIDA Study Group JD. *Am J Respir Crit Care Med* 2000;162:865-72. <http://amedeo.com/lit.php?id=10988097>
30. Kruuner A, Hoffner SE, Sillastu H, et al. Spread of drug-resistant pulmonary tuberculosis in Estonia. *J Clin Microbiol* 2001;39:3339-45. <http://amedeo.com/lit.php?id=11526173>
31. Lalvani A, Pathan AA, McShane H, et al. Rapid detection of *Mycobacterium tuberculosis* infection by enumeration of antigen-specific T cells. *Am J Respir Crit Care Med* 2001;163:824-8. <http://amedeo.com/lit.php?id=11282752>
32. Lange C, Lederman MM, Medvik K, et al. Nadir CD4+ T-cell count and numbers of CD28+ CD4+ T-cells predict functional responses to immunizations in chronic HIV-1 infection. *AIDS* 2003; 17: 2015-23
33. Lange C, Schaaf B, Dalhoff K. [HIV and lung]. *Pneumologie* 2004;58:416-27. <http://amedeo.com/lit.php?id=15216435>
34. Lawn SD, Bekker LG, Wood R. How effective does HAART restore immune responses to *Mycobacterium tuberculosis*? Implications for tuberculosis control. *AIDS* 2005a; 19:1113-24
35. Lawn SD, Badri M, Wood R. Tuberculosis among HIV-infected patients receiving HAART: long term incidence and risk factors in a South African cohort. *AIDS* 2005b; 19:2109-16
36. Manas E, Pulido F, Pena JM, et al. Impact of tuberculosis on the course of HIV-infected patients with a high initial CD4 lymphocyte count. *Int J Tuberc Lung Dis* 2004;8:451-7. <http://amedeo.com/lit.php?id=15141738>
37. Manosuthi W, Sungkanuparph S, Thakkinstian A, et al. Efavirenz levels at 24-week efficacy in HIV-infected patients with tuberculosis receiving highly active antiretroviral therapy and rifampicin. *AIDS* 2005; 19: 1481-86
38. Mayanja-Kizza H, Wajja A, Wu M, et al. Activation of beta-chemokines and CCR5 in persons infected with human immunodeficiency virus type 1 and tuberculosis. *J Infect Dis* 2001;183:1801-4. <http://amedeo.com/lit.php?id=11372034>
39. Morozova I, Riekstina V, Sture G, et al. Impact of the growing HIV-1 epidemic on multidrug-resistant tuberculosis control in Latvia. *Int J Tuberc Lung Dis* 2003;7:903-6. <http://amedeo.com/lit.php?id=12971677>
40. Nambuya A, Sewankambo N, Mugerwa J, et al. Tuberculous lymphadenitis associated with human immunodeficiency virus (HIV) in Uganda. *J Clin Pathol* 1988;41:93-6. <http://amedeo.com/lit.php?id=3343383>
41. Narayanswami G, Salzman SH. Bronchoscopy in the human immunodeficiency virus-infected patient. *Semin Respir Infect* 2003;18:80-6. <http://amedeo.com/lit.php?id=12840788>
42. Narita M, Ashkin D, Hollender ES et al. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Respir Crit Care Med* 1998;158:157-61. <http://amedeo.com/lit.php?id=9655723>
43. Olert J, Wiedorn KH, Goldmann T, et al. HOPE fixation: a novel fixing method and paraffin-embedding technique for human soft tissues. *Pathol Res Pract* 2001;197:823-6. <http://amedeo.com/lit.php?id=11795830>
44. Robert-Koch-Institut. Report on the epidemiology of tuberculosis in Germany for 2004. Berlin 2006, 80p
45. Schaberg T, Hauer B, Haas WH, et al. [Latent tuberculosis infection: recommendations for preventive therapy in adults in Germany]. *Pneumologie* 2004;58:255-70. <http://amedeo.com/lit.php?id=15098162>
46. Sokal JE. Editorial: Measurement of delayed skin-test responses. *N Engl J Med* 1975;293:501-2. <http://amedeo.com/lit.php?id=1152865>
47. Sonnenberg P, Glynn JR, Fielding K, et al. HIV and pulmonary tuberculosis: the impact goes beyond those infected with HIV. *Aids* 2004;18:657-62. <http://amedeo.com/lit.php?id=15090771>
48. Sonnenberg P, Glynn JR, Fielding K, et al. How soon after infection with HIV does the risk of tuberculosis start to increase? A retrospective cohort study in South African gold miners. *J Infect Dis* 2005;191:150-8. <http://amedeo.com/lit.php?id=15609223>

49. Sonnenberg P, Murray J, Glynn JR, et al. HIV-1 and recurrence, relapse, and reinfection of tuberculosis after cure: a cohort study in South African mineworkers. *Lancet* 2001;358:1687-93. <http://amedeo.com/lit.php?id=11728545>
50. Steinbrook R. The AIDS epidemic in 2004. *N Engl J Med* 2004;351:115-7. <http://amedeo.com/lit.php?id=15247349>
51. Surendran A. AIDS, TB hit Eastern Europe. *Nat Med* 2004;10:323. <http://amedeo.com/lit.php?id=15057215>
52. Sutherland R, Yang H, Scriba P, et al. Impaired IFN-gamma-secreting capacity in mycobacterial antigen-specific CD4 T Cells during chronic HIV-1 infection despite long term HAART. *AIDS* 2006; 20:821-29
53. Toossi Z. Virological and immunological impact of tuberculosis on human immunodeficiency virus type 1 disease. *J Infect Dis* 2003;188:1146-55. <http://amedeo.com/lit.php?id=14551885>
54. UNAIDS report for 2003: most deaths and new infections ever; some good news. *AIDS Treat News* 2003;3. <http://www.amedeo.com/lit.php?id=14717110>
55. Updated Guidelines for the Use of Rifamycins for the Treatment of Tuberculosis Among HIV-Infected Patients Taking Protease Inhibitors or Nucleoside Reverse Transcriptase Inhibitors: Division of Tuberculosis Elimination, CDC, 2004. [http://www.cdc.gov/nchstp/tb/TB\\_HIV\\_Drugs/TOC.htm](http://www.cdc.gov/nchstp/tb/TB_HIV_Drugs/TOC.htm)
56. Whalen CC, Nsubuga P, Okwera A, Johnson JL, et al. Impact of pulmonary tuberculosis on survival of HIV-infected adults: a prospective epidemiologic study in Uganda. *AIDS*. 2000;14:1219-28. <http://amedeo.com/lit.php?id=10894287>
57. Woldehanna S, Volmink J. Treatment of latent tuberculosis infection in HIV infected persons. *Cochrane Database Syst Rev*. 2004(1):CD000171. <http://www.amedeo.com/lit.php?id=14973947>
58. Wood R, Maartens G, Lombard CJ. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr* 2000;23:75-80. <http://amedeo.com/lit.php?id=10708059>

## Atypical mycobacteriosis (MAC)

Atypical mycobacterioses are usually synonymous for infections with *Mycobacterium avium* complex (MAC). Although MAC is by far the most frequent pathogen, numerous other atypical mycobacterioses exist that cause a similar disease pattern, such as *M. celatum*, *M. kansasii*, *M. xenopi* or *M. genavense*. MAC bacteria are ubiquitous and can be found in diverse animal species, on land, in water and in food. Exposure prophylaxis is therefore not possible. Consequently, isolation of infected patients is not necessary. While MAC may be detectable in the sputum or stool of asymptomatic patients (colonization), only patients with massive immunodeficiency and less than 50 CD4+ T-cells/ $\mu$ l develop disease (Horsburgh 1999). This used to include up to 40 % of AIDS patients in the pre-HAART era (Nightingale 1992).

The infection has now become very rare in industrialized countries (Karakousis 2004). However, it remains important, as it has developed into a completely new disease in the HAART era. It previously occurred mainly with a chronic, disseminated course of disease, often in patients with wasting syndrome. MAC infections under HAART are now almost always localized and related to an immune reconstitution syndrome. The disease now occurs with manifestations that were previously never seen (see below).

### Signs and symptoms

The symptoms of *disseminated* MAC infection are unspecific. When the CD4+ T-cell count is less than 100/ $\mu$ l, fever, weight loss and diarrhea should always lead to consideration of atypical mycobacteriosis. Abdominal pain may also occur. As described above, disseminated MAC infection has now become rare.

*Localized* forms are far more frequent. These include, above all, lymph node abscesses, which may occur practically everywhere. We have seen abscesses in cervical, inguinal and also abdominal lymph nodes, some of which developed fistulae and resolved only slowly even after surgical intervention. Any abscess appearing whilst on HAART (with severe immunosuppression) is highly suspicious of MAC! In addition to skin lesions, localized forms include osteomyelitis, particularly of the vertebrae, and septic arthritis (observed: knee, hand, fingers).

### Diagnosis

Diagnosis of the disseminated form is difficult. Blood cultures (heparinized blood) should always be sent to a reference laboratory. Although atypical mycobacteria usually grow more rapidly than TB bacteria, the culture and differentiation from TB may take weeks. In cases presenting with anemia, bone marrow aspiration is often successful. If atypical mycobacteria are detected in the stool, sputum or even BAL, it is often difficult to distinguish between infection requiring treatment and mere colonization. In such cases, treatment should not be initiated if general symptoms are absent. This is also true for *Mycobacterium kansasii* (Kerbirou 2003).

Laboratory evaluations typically show elevated alkaline phosphatase (AP) - a raised AP in severely immunosuppressed patients is always suspicious of MAC. Similarly, MAC infection should be considered in any cases of anemia and constitutional

symptoms. Cytopenia, particularly anemia, often indicates bone marrow involvement. Ultrasound reveals enlargement of the liver and spleen. Lymph nodes are often enlarged, but become apparent due to their number rather than their size (Gordin 1997). Here, differential diagnoses should always include TB or malignant lymphoma.

Direct specimens should always be obtained for localized forms, as identification of the organism from material drained from the abscess is usually successful.

## Treatment

Treatment of MAC infection detected from culture is complex. Similarly to TB, monotherapy does not suffice. Since 1996, many clinicians prefer the combination of a macrolide (clarithromycin or azithromycin) with ethambutol and rifabutin (Shafran 1996). In the past, this treatment was given lifelong; today it is generally considered sufficient to treat for at least six months and until a HAART-induced increase in the CD4+ T-cell count to above 100/ $\mu$ l has been achieved. After publication of data indicating that rifabutin may be omitted from the regimen (Dunne 2000), the multicenter, randomized ACTG 223 Study demonstrated survival benefit with the triple combination C+R+E compared to C+E and C+R – mortality rates were halved in the triple combination arm (Benson 2003).

Due to the high potential for interactions, however, rifabutin can be discontinued after several weeks when clinical improvement is observed. The clarithromycin dose should not exceed 500 mg bid. In at least two randomized studies, there was a significantly higher number of deaths in treatment arms with a higher clarithromycin dose, for reasons that remain unclear (Chaisson 1994, Cohn 1999). Instead of clarithromycin, azithromycin can also be given, which is cheaper (difference more than 50 Euro/month) and interacts less with cytochrome P450 enzymes. Azithromycin and clarithromycin have comparable efficacy in combination with ethambutol (Ward 1998).

In disseminated illnesses, treatment should be monitored through regular blood cultures. Cultures must be negative after 8 weeks, at the latest. In the localized form, the response can be assessed better clinically. Every MAC therapy has a high potential for side effects and drug interactions. The concomitant medications, including HAART, should be carefully examined – dose adjustments are frequently required and there may be contraindications (see Drugs section).

Reserve drugs such as amikacin, quinolones or clofazimine are only required in rare cases today. It is important to perform resistance testing for all atypical mycobacterial infections with species other than *M. avium* complex.

We have generally stopped treatment of localized MAC infections when the abscess has healed – this usually takes several months. In individual cases, steroids may be helpful temporarily. However, there are no specific guidelines for treatment of local MAC infections.

## Prophylaxis

In the USA, large placebo-controlled trials have shown that the macrolides, clarithromycin and azithromycin, as well as rifabutin, significantly reduce MAC morbidity and mortality when used for primary prophylaxis in severely immuno-

compromised patients (Havlir 1996, Nightingale 1992, Pierce 1996, Oldfield 1998). Prophylaxis also saves costs (Sendi 1999). However, MAC infections are more rare in Europe. As a result, and because of concerns over compliance and development of resistance, few patients in Europe receive primary MAC prophylaxis (Lundgren 1997).

For patients failing currently available HAART regimens and without new treatment options, prophylaxis with a macrolide should be considered at low CD4+ T-cell counts (below 50/ $\mu$ l). Weekly dosing with azithromycin is convenient for patients and has comparable efficacy to daily rifabutin (Havlir 1996).

Primary prophylaxis and maintenance therapies can be discontinued quite safely at CD4+ T-cell counts above 100/ $\mu$ l (Currier 2000, El Sadr 2000, Shafran 2002, Aberg 2003). It is possible that even partial viral suppression suffices for MAC-specific immune reconstitution (Havlir 2000). Complete recovery as a result of immune reconstitution is possible (Aberg 1998).

Treatment/prophylaxis of MAC (daily doses, if not specified otherwise)

<b>Acute therapy</b>		
Treatment of choice	Clarithromycin + ethambutol + possibly rifabutin	Clarithromycin 1 tbl. à 500 mg bid plus ethambutol 3 tbl. à 400 mg qd plus rifabutin 2 tbl. à 150 mg qd
Alternative	Azithromycin + ethambutol + possibly rifabutin	Azithromycin 1 tbl. à 600 mg qd plus ethambutol 3 tbl. à 400 mg qd plus rifabutin 2 tbl. à 150 mg qd
<b>Maintenance therapy</b>		As for acute therapy, but without rifabutin Discontinue if > 100 CD4+ T-cells/ $\mu$ l > 6 months
<b>Primary prophylaxis</b>		Consider for CD4+ T-cells < 50/ $\mu$ l Discontinue if > 100 CD4+ T-cells/ $\mu$ l > 3 months
Treatment of choice	Azithromycin	Azithromycin 2 tbl. à 600 mg/week
Alternative	Clarithromycin	Clarithromycin 1 tbl. à 500 mg bid

## References

1. Aberg JA, Williams PL, Liu T, et al. A study of discontinuing maintenance therapy in human immunodeficiency virus-infected subjects with disseminated *Mycobacterium avium* complex: AIDS Clinical Trial Group 393 Study Team. *J Infect Dis* 2003; 187: 1046-52. <http://amedeo.com/lit.php?id=12660918>
2. Aberg JA, Yajko DM, Jacobson MA. Eradication of AIDS-related disseminated mycobacterium avium complex infection after 12 months of antimycobacterial therapy combined with HAART. *J Infect Dis* 1998, 178:1446-9. <http://amedeo.com/lit.php?id=9780266>
3. Benson CA, Williams PL, Currier JS, et al. A prospective, randomized trial examining the efficacy and safety of clarithromycin in combination with ethambutol, rifabutin, or both for the treatment of disseminated *Mycobacterium avium* complex disease in persons. *Clin Infect Dis* 2003; 37:1234-43. <http://amedeo.com/lit.php?id=14557969>
4. Chaisson RE, Benson CA, Dube MP, et al. Clarithromycin therapy for bacteremic *Mycobacterium avium* complex disease. A randomized, double-blind, dose-ranging study in patients with AIDS. *Ann Intern Med* 1994, 121:905-11. <http://amedeo.com/lit.php?id=7978715>

5. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. *Clin Infect Dis* 1999, 29:125-33. <http://amedeo.com/lit.php?id=10433575>
6. Currier JS, Williams PL, Koletar SL, et al. Discontinuation of *Mycobacterium avium* complex prophylaxis in patients with antiretroviral therapy-induced increases in CD4+ cell count. *Ann Intern Med* 2000, 133:493-503. <http://amedeo.com/lit.php?id=11015162>
7. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with HIV. *Clin Infect Dis* 2000, 31:1245-52. <http://amedeo.com/lit.php?id=11073759>
8. El-Sadr WM, Burman WJ, Grant LB, et al. Discontinuation of prophylaxis for *Mycobacterium avium* complex disease in HIV-infected patients who have a response to ART. *N Engl J Med* 2000, 342:1085-92. <http://amedeo.com/lit.php?id=10766581>
9. Gordin FM, Cohn DL, Sullam PM, Schoenfelder JR, Wynne BA, Horsburgh CR Jr. Early manifestations of disseminated *Mycobacterium avium* complex disease: a prospective evaluation. *J Infect Dis* 1997, 176:126-32. <http://amedeo.com/lit.php?id=9207358>
10. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. *N Engl J Med* 1996, 335:392-8. <http://amedeo.com/lit.php?id=8676932>
11. Havlir DV, Schrier RD, Torriani FJ, et al. Effect of potent antiretroviral therapy on immune responses to *Mycobacterium avium* in HIV-infected subjects. *J Infect Dis* 2000, 182:1658-63. <http://amedeo.com/lit.php?id=11069237>
12. Horsburgh CR Jr. The pathophysiology of disseminated *Mycobacterium avium* complex disease in AIDS. *J Infect Dis* 1999, Suppl 3:S461-5. <http://amedeo.com/lit.php?id=10099120>
13. Karakousis PC, Moore RD, Chaisson RE. *Mycobacterium avium* complex in patients with HIV infection in the era of highly active antiretroviral therapy. *Lancet Infect Dis* 2004, 4:557-65. <http://amedeo.com/lit.php?id=15336223>
14. Kerbiriou L, Ustianowski A, Johnson MA, Gillespie SH, Miller RF, Lipman MC. HIV type 1-related pulmonary *Mycobacterium xenopi* infection: a need to treat? *Clin Infect Dis* 2003; 37: 1250-4. <http://amedeo.com/lit.php?id=14557971>
15. Lundgren JD, Phillips AN, Vella S, et al. Regional differences in use of antiretroviral agents and primary prophylaxis in 3122 European HIV-infected patients. *J Acquir Immune Defic Syndr Hum Retroviro* 1997, 16:153-60. <http://amedeo.com/lit.php?id=9390566>
16. Nightingale SD, Byrd LT, Southern PM, et al. Incidence of *Mycobacterium avium*-intracellulare complex bacteremia in HIV-positive patients. *J Infect Dis* 1992, 165:1082-5. <http://amedeo.com/lit.php?id=1349906>
17. Oldfield EC 3rd, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. *Clin Infect Dis* 1998, 26:611-9. <http://amedeo.com/lit.php?id=9524832>
18. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced AIDS. *N Engl J Med* 1996, 335:384-91. <http://amedeo.com/lit.php?id=8663871>
19. Sendi PP, Craig BA, Meier G, et al. Cost-effectiveness of azithromycin for preventing *Mycobacterium avium* complex infection in HIV-positive patients in the era of HAART. *J Antimicrob Chemother* 1999, 44:811-7. <http://amedeo.com/lit.php?id=10590283>
20. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of *Mycobacterium avium* complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med* 1996, 335:377-83. <http://amedeo.com/lit.php?id=8676931>
21. Shafran SD, Mashinter LD, Phillips P, et al. Successful discontinuation of therapy for disseminated *Mycobacterium avium* complex infection after effective antiretroviral therapy. *Ann Intern Med* 2002;137:734-7. <http://amedeo.com/lit.php?id=12416943>
22. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with HIV infection. *Clin Infect Dis* 1998, 27:1278-85. <http://amedeo.com/lit.php?id=9827282>

## Herpes simplex

Infections with herpes simplex viruses are a frequent and inconvenient problem for HIV-infected patients (Chang 1995). Two viruses should be distinguished. HSV-1 is transmitted by direct contact with mucosal membranes, as well as by kissing, and causes the typical, itchy perioral herpes blisters on the lips, tongue, gums or buccal mucosa. HSV-2 is sexually transmitted and leads to herpetiform lesions on the penis, vagina, vulva and anus. HSV-2-associated lesions significantly increase the risk of transmission of HIV (Freeman 2006). Herpes lesions have a tendency to spread with decreasing immune status. Chronic disease is frequent, particularly with severe immunodeficiency (below 100 CD4<sup>+</sup> T-cells/ $\mu$ l). In severe cases, other organs may be affected. These include mainly the esophagus (ulcers), CNS (encephalitis), eyes (keratitis, keratoconjunctivitis, uveitis) and respiratory tract (pneumonitis, bronchitis). In such cases and with persistence of lesions for a period of more than four weeks, herpes simplex infection is an AIDS-defining illness.

## Signs and symptoms

The typical blisters itch and burn. Oral involvement may impair food intake. In cases of genital or anal herpes (proctitis!), urination and defecation can be very painful. Extensive lesions may occur with severe immunosuppression. Regional lymph nodes are often enlarged. The clinical symptoms of disseminated disease depend on the organs affected.

## Diagnosis

Diagnosis of oral, genital or perianal herpes can often be made clinically. If there is doubt, swabs should be taken, placed in viral culture media and rapidly transported to the laboratory. The diagnosis of organ manifestations usually requires histology. Diagnosis is particularly difficult for HSV encephalitis, as cerebrospinal fluid often does not help. Serologies are only useful if they are negative, therefore making HSV infection improbable.

## Treatment

For patients with a good immune status and only discrete lesions, topical treatment with acyclovir cream or ointment is adequate. Penciclovir cream is probably as effective as acyclovir (Chen 2000) and allegedly less irritant, although significantly more expensive. In general, every treatment, whether topical, oral or systemic, is more effective if started early.

The nucleoside analog acyclovir remains the treatment of choice for systemic treatment. Acyclovir inhibits the DNA polymerase of herpes viruses. Resistance is rare, despite the fact that this agent has been used since 1977 and numerous generics are now available (Levin 2004). Acyclovir is usually well tolerated and effective against both HSV-1 and HSV-2. Severe cases with mucocutaneous or organ involvement should be treated immediately intravenously. As CNS levels are lower than in plasma, the dose should be increased to treat encephalitis. If acyclovir is to be given intravenously, renal blood values should be checked.



Valacyclovir and famciclovir are equally effective alternatives to acyclovir (Ormod 2000, Conant 2002), though substantially more expensive (more than 100 Euro/week!) and not yet licensed for treatment of immunocompromised patients. The main advantage is their improved oral bioavailability – they require less frequent dosing. Brivudin remains a good alternative for HSV-1 and VZV. However, it is possible that this dihydropyrimidine dehydrogenase inhibitor causes mitotoxicity and reduces the efficacy of HIV drugs (U. Walker 2005, personal communication). Foscarnet should only be used in exceptional cases due to its toxicity.

Newer drugs that, unlike acyclovir, do not inhibit DNA polymerase but helicase, another herpes virus enzyme, have been more effective than acyclovir and well tolerated in animal studies – their actual value remains to be shown (Kleymann 2002, 2003).

A local anesthetic that can be produced by the pharmacist can be prescribed in addition for painful mucocutaneous lesions. Unfortunately, the approved tetracaine solution (Herviros™) has been taken off the market. Some pharmacists can, however, make-up something similar.

## Prophylaxis

Primary prophylaxis is not recommended. However, a meta-analysis of almost 2,000 patients in 8 randomized studies showed that acyclovir can reduce the risk of both HSV and HZV disease by more than 70 %. Even mortality was reduced by 22 % (Ioannidis 1998). The introduction of HAART has changed the relevance of this data. Nevertheless, it can still make sense, even today, to treat persistent recurrences with long-term low dose acyclovir or valacyclovir (DeJesus 2003, Warren 2004).

### Treatment/prophylaxis of HSV infection (daily doses)

<b>Acute therapy</b>		Duration: 7-14 days
Treatment of choice	Acyclovir	Acyclovir 1 tbl. à 400 mg 5x/day
Severe cases		Acyclovir ½-1 amp. à 500 mg tid (5-10 mg/kg tid) i.v.
Alternatives	Valacyclovir	Valacyclovir 2 tbl. à 500 mg tid
Alternatives	Famciclovir	Famciclovir 1 tbl. à 250 mg tid
Alternatives	Brivudin	Brivudin 1 tbl. à 125 mg qd
<b>Prophylaxis</b>		Not recommended

## References

1. Chang E, Absar N, Beall G. Prevention of recurrent herpes simplex virus infections in HIV-infected persons. *AIDS Patient Care* 1995, 9:252-5. <http://amedeo.com/lit.php?id=11361407>
2. Chen XS, Han GZ, Guo ZP, et al. A comparison of topical application of penciclovir 1% cream with acyclovir 3% cream for treatment of genital herpes: a randomized, double-blind, multicentre trial. *Int J STD AIDS* 2000, 11:568-73. <http://amedeo.com/lit.php?id=10997497>
3. Conant MA, Schacker TW, Murphy RL, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. *Int J STD AIDS* 2002, 13:12-21. <http://amedeo.com/lit.php?id=11802924>

4. DeJesus E, Wald A, Warren T, et al. Valacyclovir for the suppression of recurrent genital herpes in HIV-infected subjects. *J Infect Dis* 2003,; 188: 1009-16. <http://amedeo.com/lit.php?id=14513421>
5. Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with HIV infection: a meta-analysis of randomized individual patient data. *J Infect Dis* 1998, 178:349-59. <http://amedeo.com/lit.php?id=9697714>
6. Kleymann G, Fischer R, Betz UA, et al. New helicase-primase inhibitors as drug candidates for the treatment of herpes simplex disease. *Nat Med* 2002;8:392-8. <http://amedeo.com/lit.php?id=11927946>
7. Kleymann G. New antiviral drugs that target herpesvirus helicase primase enzymes. *Herpes* 2003;10:46-52. <http://amedeo.com/lit.php?id=14577954>
8. Levin MJ, Bacon TH, Leary JJ. Resistance of herpes simplex virus infections to nucleoside analogues in HIV-infected patients. *Clin Infect Dis* 2004, 39 Suppl 5:S248-57. <http://amedeo.com/lit.php?id=15494896>
9. Ormrod D, Scott LJ, Perry CM. Valaciclovir: a review of its long term utility in the management of genital herpes simplex virus and cytomegalovirus infections. *Drugs* 2000, 59:839-63. <http://amedeo.com/lit.php?id=10804039>
10. Safrin S. Treatment of acyclovir-resistant herpes simplex virus infections in patients with AIDS. *J Acquir Immune Defic Syndr* 1992, Suppl 1:S29-32. <http://amedeo.com/lit.php?id=1602361>
11. Warren T, Harris J, Brennan CA. Efficacy and safety of valacyclovir for the suppression and episodic treatment of herpes simplex virus in patients with HIV. *Clin Infect Dis* 2004, 39 Suppl 5:S258-66. <http://amedeo.com/lit.php?id=15494897>

## Herpes zoster

Herpes zoster is the reactivation of an earlier infection with varicella virus, which subsequently resides lifelong in the spinal ganglia. Herpes zoster episodes occur even in HIV patients with relatively good immune status, and are also seen during immune reconstitution (Martinez 1998). With more advanced immunodeficiency, herpes zoster tends to become generalized. In addition to involvement of one or more dermatomes, dangerous involvement of the eye (affecting the ophthalmic branch of the trigeminal nerve, “herpes zoster ophthalmicus”, with corneal involvement) and ear (herpes zoster oticus) may occur. Most feared is involvement of the retina with necrotizing retinitis. The neurological complications include meningoencephalitis, myelitis and also involvement of other cranial nerves (Brown 2001).

### Signs and symptoms

There are often prodromal signs with headache, malaise and photophobia, accompanied only rarely by fever. The affected areas are initially hypersensitive, and then become pruritic and/or painful within hours or days. Pain can precede lesions by several days. Lesions often show segmental (always unilateral!) erythema with herpetiform blisters within one or more dermatomes. Lesions ulcerate, are often hemorrhagic, and gradually dry up. They should be kept dry and clean to avoid bacterial superinfection.

Involvement of several dermatomes often leaves treatment-resistant pain syndromes with zoster neuralgia. Post-herpetic neuralgia can be assumed if pain persists even after more than a month (Gnann 2002).

### Diagnosis

Cutaneous involvement usually allows clinical diagnosis of herpes zoster. However, diagnosis may be difficult especially on the extremities and in complicated zoster cases. Typical cases do not require further diagnostic tests. If there is uncertainty, a swab may be taken from a blister and sent to the laboratory in viral culture media. An immunofluorescence assay is presumably more reliable. VZV encephalitis is only detectable through analysis of CSF by PCR. Herpes zoster oticus should be considered in cases of unilateral, peracute hearing loss, which is not always visible from the outside. Either examine the ear yourself or consult an ENT specialist! For visual impairment the same rules apply as for CMV retinitis – refer to the ophthalmologist as quickly as possible!

### Treatment

Monosegmental zoster can be treated on an outpatient basis with oral acyclovir. Rapid initiation of treatment is important. Systemic therapy is always necessary, and doses are higher than for HSV. Lesions dry up more rapidly if calamine lotion is used, which also relieves pain. Wear gloves! Lesions are highly infectious initially, and unvaccinated individuals without a history of chickenpox should not come into close contact with a case of herpes zoster.

Analgesics (novaminsulfone, or better still tramadol) should be given generously. Any complicated, multi-segmental or facial herpes zoster should always be treated with intravenous therapy. This can also be done in ambulatory care with a competent nursing service.

As with HSV, several alternatives for treatment include valacyclovir, famciclovir and brivudin (see HSV). The unpleasant post-herpetic neuralgia allegedly occurs less frequently under these drugs than under acyclovir in HIV-negative patients (Gnann 2002). However, valacyclovir, famciclovir and brivudin have not been tested widely in HIV patients, and are not licensed for treatment of immunocompromised patients. They are also substantially more expensive (up to 120 Euro/week) than the numerous acyclovir formulations. Acyclovir resistance may occur in the thymidine kinase gene, but is rare (Gershon 2001, Saint-Leger 2001). In these cases, foscarnet can be given.

Pain management of post-herpetic neuralgia is problematic. Carbamazepine or gabapentin only partially help. Steroids are generally not advised (Gnann 2002).

## Prophylaxis

Varicella vaccination, previously contraindicated in HIV patients, seems to be fairly safe and effective in the HAART era for patients with more than 400 CD4+ T-cells/ $\mu$ l, as shown in a placebo-controlled study (Gershon 2001). It should be considered if VZV serology is negative. In individuals with negative serology and exposure to VZV (highly infectious!), administration of hyperimmunoglobulin (2 mg/kg i.v.) may be attempted in individual cases. Long-term primary prophylaxis is not advised. Some dermatologists, however, do recommend long-term therapy with low doses if there are persistently recurring episodes.

Treatment/prophylaxis of VZV infection (daily doses)

<b>Acute therapy</b>		Duration: at least 7 days
Treatment of choice	Acyclovir	Acyclovir 1 tbl. à 800 mg 5x/day
Severe cases		Acyclovir 1-2 amp. à 500 mg tid (10 mg/kg tid) i.v.
Alternatives	Valacyclovir	Valacyclovir 2 tbl. à 500 mg tid
Alternatives	Famciclovir	Famciclovir 2 tbl. à 250 mg tid
Alternatives	Brivudin	Brivudin 1 tbl. à 125 mg qd
<b>Prophylaxis</b>		Not recommended

## References

1. Brown M, Scarborough M, Brink N, Manji H, Miller R. Varicella zoster virus-associated neurological disease in HIV-infected patients. *Int J STD AIDS* 2001, 12:79-83.  
<http://amedeo.com/lit.php?id=11236108>
2. Gershon AA. Prevention and treatment of VZV infections in patients with HIV. *Herpes* 2001, 8:32-6.  
<http://amedeo.com/lit.php?id=11867015>
3. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med* 2002, 347:340-6.

4. Martinez E, Gatell J, Moran Y, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. *Clin Infect Dis* 1998, 27:1510-3.  
<http://amedeo.com/lit.php?id=9868668>
5. Saint-Leger E, Caumes E, Breton G, et al. Clinical and virologic characterization of acyclovir-resistant varicella-zoster viruses isolated from 11 patients with AIDS. *Clin Infect Dis* 2001, 33:2061-7.  
<http://amedeo.com/lit.php?id=11702291>

## Progressive multifocal leukoencephalopathy

PML is a severe demyelinating disease of the central nervous system. It is caused by JC virus (JCV), a polyoma virus found worldwide. JCV was named after the initials of the first patient, from which this simple DNA virus was first isolated in 1971 (Major 1992). JC therefore has no connection, as is often wrongly assumed, with Jakob-Creutzfeld syndrome. As seroprevalence is high, at up to 80 %, latent persistent infection is assumed. Only impaired cellular immunity leads to reactivation of JCV and manifestation of disease. It seems certain that JCV reaches the CNS via leukocytes, and affects mainly oligodendrocytes and therefore the cells comprising the myelin sheaths. Destruction of these is macroscopically apparent as multifocal demyelination. The main focus of disease is the white matter of the cerebral hemispheres, but the cerebellum and in some cases the grey matter may also be affected. Severe immunodeficiency is frequently seen, but not obligatory for development of PML. In contrast to CMV or MAC infection, PML does not always indicate the final stages of HIV infection. Although CD4+ T-cells are usually below 100/ $\mu$ l at manifestation of disease, PML may also occur at above 200 CD4+ T-cells/ $\mu$ l. The decrease in incidence is not as marked as with other OIs. After cerebral toxoplasmosis, it is now probably the second most common neurological OI (Antinori 2001).

Prognosis was poor in the pre-HAART era. The median interval between the onset of the first symptoms and death was between 3 and 6 months. Patients usually died of secondary complications after being bedridden for many weeks. The prognosis is slightly better at CD4+ T-cell counts above 200/ $\mu$ l (Berger 1998). Disease progression seems to be much slower under HAART, and even complete remission seems possible (Albrecht 1998). However, these effects are not as impressive as for other OIs: in a Spanish study of 118 PML patients on HAART, 64 % were still alive 2.2 years after diagnosis (Berenguer 2003). Complete remissions are not the rule, even under sufficient HAART. They mainly occur in cases of inflammatory PML, which occurs in the course of an immune reconstitution syndrome (Du Pasquier 2003, Hoffmann 2003).

## Signs and symptoms

Although there is a broad spectrum of PML symptoms due to the variety of localized areas of demyelination, the clinical signs and course of disease have several common characteristics. In addition to cognitive disorders, which may range from mild impairment of concentration to dementia, focal neurological deficits are very typical of PML. Mono- and hemiparesis are observed most frequently, as well as speech and even visual deficits. We have seen several blind patients with PML. These deficits may be isolated and initially present as discrete changes in coordination, rapidly leading to considerable disabilities. Epileptic seizures may occur. Loss of sensibility, fever, and headache are rare and are usually more typical of cerebral toxoplasmosis.

## Diagnosis

Clinical suspicion of PML should be rapidly confirmed radiologically. But beware: a CCT scan is not helpful – it does not clearly reveal the (hypodense) lesions. MRI is much more sensitive for detecting both the number and size of lesions than CCT and usually shows high signal intensity lesions in T2-weighted imaging and in FLAIR sequence, which are hypointense in T1-w and usually show no gadolinium enhancement or mass effect. HAART may result in inflammatory courses that may involve significant enhancement (see Immune reconstitution syndrome). Exclusion of grey matter is typical – since this is a leukoencephalopathy. Also of note: lesions are almost always asymmetrical!

MRI often allows distinction from cerebral toxoplasmosis or lymphoma. However, the huge, extensive lesions covering an entire hemisphere that are often shown in textbooks are not always present. Every PML starts small – very discrete, localized, solitary lesions can occur and certainly do not exclude the diagnosis. PML can occur everywhere in the brain, and there are no typically susceptible areas. Lesions are often parieto-occipital or periventricular, but the cerebellum may also be involved. It is important that the images are assessed by a radiologist or clinician familiar with PML. Even then, it is difficult to distinguish PML from HHV-6 infection (Caserta 2004) or HIV leukoencephalopathy (Langford 2002).

Clinicoradiological diagnosis is therefore not definitive. Examination of cerebrospinal fluid is important. Generally, if there is no other co-infection, unspecific inflammatory signs are absent, although the total protein content is usually slightly elevated. Pleocytosis is rarely seen, and more than 100/3 cells make PML unlikely. CSF should always be tested for JCV. Newer PCR methods have a sensitivity of around 80 % and a specificity of over 90 %. A CSF sample should be sent to a JCV-experienced laboratory.

PML is very probable in cases of clinicoradiological suspicion and positive JCV PCR. In such cases, brain biopsies are no longer recommended today. Nevertheless, negative PCR does not exclude the diagnosis. Levels of JCV viral load may vary significantly and do not correlate with the extent of lesions (Eggers 1999, Garcia 2002, Bossolasco 2005). Unfortunately, JCV PCR is even less useful in the HAART era – many patients with PML have a low or undetectable JCV CSF viral load under HAART (Bossolasco 2005). Stereotactic brain biopsy may become necessary in individual cases.

## Treatment

A specific PML treatment is not available. Numerous strategies such as foscarnet, interferon, immune stimulants and even steroids have been abandoned after only modest successes. Cytosine arabinoside is also no longer recommended following the disappointing results of a randomized study (Hall 1998). Cidofovir and camptothecin are the two new drugs currently being discussed. It is feared that these drugs will have a similar fate in controlled studies. Camptothecin is an alkaloid cytostatic, which inhibits topoisomerase I, a nuclear enzyme that is required for DNA and therefore also JCV replication (O'Reilly 1997). Currently, only data from case studies and a small series of patients exist (Vollmer-Haase 1997, Royal 2003). In the small, usually uncontrolled studies described to date, cidofovir has had positive

effects in some, but not all cases (De Luca 2001, Gasnault 2001, Herrero-Romero 2001, Marra 2002, Wyen 2004). So far, a real benefit has not been proven. Our own experience has been rather disappointing and, in a retrospective analysis of 35 patients, cidofovir was even associated with a poorer prognosis. However, this chiefly reflects the frustration of patients and clinicians – cidofovir was mainly used in cases of progressive disease (Wyen 2004), and should therefore only be used in exceptions if HAART or optimization is not possible, or patients deteriorate clinically despite sufficient HAART.

In our view, the absolute priority should currently be to optimize ART in cases of PML. In 1998, we were able to show that prognosis significantly improved under HAART (Albrecht 1998). This has been confirmed by several other groups (Clifford 1999, Dworkin 1999, Gasnault 1999, Tantisiriwat 1999). As synergism between HIV and JCV has been demonstrated *in vitro*, maximal HIV suppression should at least be achieved. Although progression of disease has been described under sufficient antiretroviral therapy, HAART often remains the only real hope for patients today.

#### Treatment/prophylaxis of PML

##### Acute therapy

Treatment of choice	HAART	The most important goal is maximal HIV suppression and immune reconstitution!!!
Experimental	Cidofovir	Cidofovir 5 mg/kg i.v. every 7-14 days (plus probenecid/hydration per protocol, see Drugs section)

<b>Prophylaxis</b>	Not available	
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## Prophylaxis

There is none. Exposure prophylaxis is also not possible.

## References

1. Albrecht H, Hoffmann C, Degen O, et al. HAART significantly improves the prognosis of patients with HIV-associated progressive multifocal leukoencephalopathy. *AIDS* 1998, 12:1149-1154. <http://amedeo.com/lit.php?id=9677163>
2. Antinori A, Ammassari A, Giancola ML, et al. Epidemiology and prognosis of AIDS-associated progressive multifocal leukoencephalopathy in the HAART era. *J Neurovirol* 2001, 7:323-8. <http://amedeo.com/lit.php?id=11517411>
3. Berenguer J, Miralles P, Arrizabalaga J, et al. Clinical course and prognostic factors of progressive multifocal leukoencephalopathy in patients treated with highly active antiretroviral therapy. *Clin Infect Dis* 2003, 36: 1047-52. <http://amedeo.com/p2.php?id=12684918>
4. Berger JR, Levy RM, Flomenhoft D, et al. Predictive factors for prolonged survival in AIDS-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 1998, 44:341-9. <http://amedeo.com/lit.php?id=9749600>
5. Caserta MT. Human Herpesvirus 6 Infection of the Central Nervous System. *Curr Infect Dis Rep* 2004, 6: 316-321.
6. Clifford DB, Yiannoutsos C, Glicksman M et al. HAART improves prognosis in HIV-associated progressive multifocal leukoencephalopathy. *Neurology* 1999, 52:623-5. <http://amedeo.com/lit.php?id=10025799>
7. De Luca A, Giancola ML, Ammassari A, et al. Potent anti-retroviral therapy with or without cidofovir for AIDS-associated progressive multifocal leukoencephalopathy: extended follow-up of an observational study. *J Neurovirol* 2001, 7:364-8. <http://amedeo.com/lit.php?id=11517418>



8. Di Giambenedetto S, Cingolani A, Marzocchetti A, et al. Profound reduction of the diagnostic sensitivity of JCV DNA in CSF for AIDS-associated progressive multifocal leukoencephalopathy (PML) in the HAART era. Abstract 12/2, 9th EACS 2003, Warsaw, Poland.
9. Du Pasquier RA, Koranik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol* 2003; 9 Suppl 1:25-31.
10. Dworkin MS, Wan PC, Hanson DL, Jones JL. Progressive multifocal leukoencephalopathy: improved survival of HIV-infected patients in the protease inhibitor era. *J Infect Dis* 1999, 180:621-5. <http://amedeo.com/lit.php?id=10438348>
11. Eggers C, Stellbrink HJ, Buhk T, Dorries K. Quantification of JC virus DNA in the cerebrospinal fluid of patients with HIV-associated progressive multifocal leukoencephalopathy - a longitudinal study. *J Infect Dis* 1999, 180:1690-4. <http://amedeo.com/lit.php?id=10515834>
12. Garcia De Viedma D, Diaz Infantes M, Miralles P, et al. JC virus load in progressive multifocal leukoencephalopathy: analysis of the correlation between the viral burden in cerebrospinal fluid, patient survival, and the volume of neurological lesions. *Clin Infect Dis* 2002, 34:1568-75. <http://amedeo.com/lit.php?id=12032891>
13. Gasnault J, Kousignian P, Kahraman M, et al. Cidofovir in AIDS-associated progressive multifocal leukoencephalopathy: a monocenter observational study with clinical and JC virus load monitoring. *J Neurovirol* 2001, 7:375-81. <http://amedeo.com/lit.php?id=11517420>
14. Gasnault J, Taoufik Y, Goujard C, et al. Prolonged survival without neurological improvement in patients with AIDS-related PML on potent combined antiretroviral therapy. *J Neurovirol* 1999, 5:421-9. <http://amedeo.com/lit.php?id=10463864>
15. Hall CD, Dafni U, Simpson D, et al. Failure of cytarabine in progressive multifocal leukoencephalopathy associated with HIV infection. *N Engl J Med* 1998, 338:1345-51. <http://amedeo.com/lit.php?id=9571254>
16. Herrero-Romero M, Cordero E, Lopez-Cortes LF, de Alarcon A, Pachon J. Cidofovir added to HAART in AIDS-associated progressive multifocal leukoencephalopathy. *AIDS* 2001, 15:809.
17. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leukoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry* 2003;74:1142-4. <http://amedeo.com/lit.php?id=12876257>
18. Langford TD, Letendre SL, Marcotte TD, et al. Severe, demyelinating leukoencephalopathy in AIDS patients on antiretroviral therapy. *AIDS* 2002, 16:1019-29. <http://amedeo.com/lit.php?id=11953468>
19. Major EO, Amemiya K, Tornatore CS, Houff SA, Berger JR. Pathogenesis and molecular biology of progressive multifocal leukoencephalopathy, the JC virus-induced demyelinating disease of the human brain. *Clin Microbiol Rev* 1992, 5:49-73. <http://amedeo.com/lit.php?id=1310438>
20. Marra CM, Rajcic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* 2002, 16:1791-7. <http://amedeo.com/lit.php?id=12218391>
21. O'Reilly S. Efficacy of camptothecin in progressive multifocal leukoencephalopathy. *Lancet* 1997, 350:291.
22. Royal W 3rd, Dupont B, McGuire D, et al. Topotecan in the treatment of acquired immunodeficiency syndrome-related progressive multifocal leukoencephalopathy. *J Neurovirol* 2003; 9:411-9. <http://amedeo.com/lit.php?id=12775425>
23. Tantisiriwat W, Tebas P, Clifford DB, et al: Progressive multifocal leukoencephalopathy in patients with AIDS receiving HAART. *Clin Infect Dis* 1999, 28:1152-4. <http://amedeo.com/lit.php?id=10452651>
24. Vollmer-Haase J, Young P, Ringelstein EB. Efficacy of camptothecin in progressive multifocal leukoencephalopathy. *Lancet* 1997, 349:1366.
25. Wyen C, Hoffmann C, Schmeier N, et al. Progressive Multifocal Leukoencephalopathy in Patients on Highly Active Antiretroviral Therapy: Survival and Risk Factors of Death. *J Acquir Immune Defic Syndr* 2004, 37:1263-1268. <http://amedeo.com/lit.php?id=15385733>

## Bacterial pneumonia

Bacterial pneumonia occurs even with relatively good immune status (above 200 CD4+ T-cells/ $\mu$ l). It is not as closely associated with immunodeficiency, and the decrease in incidence since the HAART era has been more moderate than for other opportunistic infections. Only recurring, radiologically and culturally detected acute pneumonia (more than one episode in the last 12 months) is considered AIDS-defining. As with HIV-negative patients, community-acquired pneumonia should be distinguished from nosocomial pneumonia. Travel history is important, particularly for community-acquired pneumonia.

The bacteria that are most frequently found to cause community-acquired pneumonia in HIV patients are *Pneumococcus* and *Hemophilus influenzae*. *Mycoplasma* is important to consider, particularly in younger patients. *Klebsiella*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* are other common pathogens. *Legionella* are rare. I.v. drug users develop community-acquired pneumonia significantly more often than other patient groups.

Nosocomial pneumonia is often caused by hospital germs (*Klebsiella*, *Staphylococcus*, *Pseudomonas*). In such cases, treatment depends on local resistance patterns and experience (Gant 2000, Vogel 2000).

## Signs and symptoms/ Diagnosis

Acute, usually high, fever and productive cough are typical. Breathing may be painful because of accompanying pleuritis, but real dyspnea is rare. Auscultation almost always allows distinction from PCP. If something can be heard, PCP is unlikely! Chest radiography secures the diagnosis. CRP is significantly elevated, LDH usually normal. It is essential to take several blood cultures at body temperatures above 38.5°C before starting treatment. Sputum culture is a simple method allowing determination of etiology in approximately half of all cases – however, its overall utilization remains controversial (Cordero 2002).

## Treatment

### General

Treatment of bacterial pneumonia in HIV patients is similar to that in HIV-seronegative patients. Therapy should always begin empirically, without waiting for sputum or blood culture results. Many HIV patients with bacterial pneumonia can be treated as outpatients. Patients with poor immune status, very high fever (above 39.5°C), poor compliance, signs of organ failure, CNS disorders (confusion) and poor vital signs (tachypnea, tachycardia, hypotonia), as well as older patients (above 65 years), should be hospitalized immediately.

Sufficient hydration is important in all patients. If patients remain in ambulatory care, this means that they must drink a lot (more than 2 l daily). The use of supportive therapy with expectorants or mucolytics such as N-acetylcysteine or antitussives is controversial. On adequate therapy, improvement can be expected within 48-72 hours. If patients, especially the severely immunocompromised, have a persistent fever the treatment must be reconsidered after 72 hours, at the latest. It

should be noted that the current first line therapies are not effective against *Pseudomonas aeruginosa*!

### **Medication**

Different drugs are possible for ambulatory treatment. Even an attempt with penicillin may be justified in some circumstances – depending on local rates of *Pneumococcus* and *Hemophilus influenzae* resistance. HIV patients frequently develop allergies.

Aminopenicillins are effective against *Hemophilus influenzae* and various gram negatives. However, when combined with clavulanic acid, which is active against beta-lactamase-producing bacteria, they are associated with more gastrointestinal complaints.

Newer oral cephalosporins have a broader spectrum against gram negatives, while at the same time having good efficacy against *Pneumococcus* and *Hemophilus*. They are, however, comparatively expensive.

Macrolides are advantageous for atypical bacteria such as *Mycoplasma*, *Chlamydia* and *Legionella* – but the proportion of macrolide-resistant *Pneumococcus* is increasing (14 % in Germany). Weaknesses also exist in the *Hemophilus* strains.

For quinolones, it should be noted that ciprofloxacin has no or only weak efficacy against many important pathogens. Therefore only newer quinolones should be used.

If patients are hospitalized, intravenous administration is possible initially. In these cases, at least two antibiotics should be combined.

Targeted treatment after isolation of the pathogen, and, in particular, treatment of nosocomial pneumonia, should depend on local resistance patterns and the recommendations of the in-house microbiologist.

### **Prophylaxis**

The Pneumovax™ vaccine provides effective protection. It should be utilized in all HIV patients with adequate immune status (above 200 CD4+ T-cells/ $\mu$ l).

Empiric treatment/prophylaxis of community-acquired bacterial pneumonia (daily doses) - there may be significant differences in price!

<b>Outpatient</b>		Duration: 7-10 days
Mild	Amoxicillin + clavulanic acid	1 tbl. à 875/125 mg tid
Mild	Clarithromycin	1 tbl. à 500 mg bid
Mild	Roxithromycin	1 tbl. à 300 mg qd
Mild	Cefuroxim	1 tbl. à 500 mg bid
Mild	Cefpodoxim	1 tbl. à 200 mg bid
Mild	Moxifloxacin	1 tbl. à 400 mg qd
<b>Inpatient</b>		
Severe	Piperacillin (+ tazobactam)	Tazobac® 1 bottle à 4.5 g i.v. tid <b>plus</b>
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd <b>or</b> clarithromycin 1 tbl. à 500 mg bid
Severe	Ceftriaxon	Ceftriaxon 1 infusion à 2 g qd i.v. <b>plus</b>
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd <b>or</b> clarithromycin 1 tbl. à 500 mg bid
Severe	Cefuroxim	Cefuroxim 1 infusion à 1.5 g tid i.v. <b>plus</b>
	+ macrolide	roxithromycin 1 tbl. à 300 mg qd <b>or</b> clarithromycin 1 tbl. à 500 mg bid
<b>Prophylaxis</b>	Vaccination (pneumococcal polysaccharide)	Pneumovax 23® pre-filled syringe i.m.

## References

1. Cordero E, Pachon J, Rivero A, et al. Usefulness of sputum culture for diagnosis of bacterial pneumonia in HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002, 21:362-7. <http://amedeo.com/lit.php?id=12072920>
2. Gant V, Parton S. Community-acquired pneumonia. *Curr Opin Pulm Med* 2000, 6:226-33. <http://amedeo.com/lit.php?id=10782708>
3. Rimland D, Navin TR, Lennox JL, et al. Prospective study of etiologic agents of community-acquired pneumonia in patients with HIV infection. *AIDS* 2002, 16:85-95. <http://amedeo.com/lit.php?id=11741166>
4. Vogel F, Worth H, Adam D, et al. Rationale Therapie bakterieller Atemwegsinfektionen. Empfehlungen einer Expertengruppe der Paul-Ehrlich-Gesellschaft für Chemotherapie e.v. und der Deutschen Atemwegsliga. *Chemotherapie Journal* 2000, 1:3-23. <http://hiv.net/link.php?id=163>

## Cryptosporidiosis

Cryptosporidiosis is a parasitic intestinal disease with fecal-oral transmission. It is mainly caused by the protozoon *Cryptosporidium parvum* (2 genotypes exist, genotype 1 is now also known as *C. hominis*), and may affect both immunocompetent and immunocompromised hosts (very good review in: Chen 2002). First described in 1976, cryptosporidia are among the most important and most frequent causes of diarrhea worldwide. Important sources of infection for this intracellular parasite include animals, contaminated water and food. The incubation period lasts approximately 10 days. While diarrhea almost always resolves within a few days in otherwise healthy hosts or in HIV patients with CD4+ T-cell counts greater than 200/ $\mu$ l, cryptosporidiosis is often chronic in AIDS patients. Particularly in severely immunocompromised patients (below 50 CD4+ T-cells/ $\mu$ l), diarrhea may become life threatening due to water and electrolyte losses (Colford 1996). Only chronic, and not acute, cryptosporidiosis is AIDS-defining.

### Signs and symptoms

The typical watery diarrhea can be so severe that it leads to death as a result of electrolyte loss and dehydration. 20 bowel movements daily are not uncommon. Tenesmus is frequent, and there is often nausea and vomiting. However, the symptoms are highly variable. Fever is usually absent. The biliary ducts may occasionally be affected, with elevation of biliary enzymes. Pancreatitis is also possible.

### Diagnosis

When sending in stool samples, it is important to specifically inform the laboratory of the clinical suspicion. Otherwise cryptosporidia are often overlooked. If the laboratory is experienced and receives the correct tip, just one stool sample is usually sufficient for detection. Antibodies or other diagnostic tests are, in contrast, not helpful. The differential diagnosis should include all diarrhea-causing pathogens.

### Treatment

No specific treatment has been established to date. Diarrhea is self-limiting with a good immune status; therefore, poor immune status should always be improved with HAART – and this often leads to resolution (Carr 1998, Miao 2000). To ensure absorption of antiretroviral drugs, symptomatic treatment with loperamide and/or opium tincture (controlled drug prescription, to the maximum doses!) is advised. If this is unsuccessful, treatment with other anti-diarrheal medications, perhaps even sandostatin, can be attempted. Sufficient hydration is important – this may even require infusions.

We have seen good results in individual cases with the antihelminthic agent nitazoxanide (Cryptaz™ or Alinia™). Nitazoxanide proved to be effective in a small, randomized study and is possibly the first drug with real efficacy for treating cryptosporidia (Rossignol 2001). In a Mexican pilot study, approximately two thirds of the patients responded to therapy (Rossignol 1998). However, a study in African children showed an effect only in HIV-negative and not in HIV-infected children (Amadi 2002). The data available was not sufficient for the FDA, so nitazoxanide

has only been licensed in the USA for non-immunosuppressed children under 11 years of age. There is no approval for AIDS patients, either in the USA or in Germany, and this is unlikely to change in the near future. There are often problems with health insurance providers as a result. However, it is possible to obtain nitazoxanide through an expanded access program, by contacting the manufacturer, Romark, directly: <http://romark.com>. In the near future, an alternative, rifaximine (Normix™ 400 mg) will possibly be available. It is a new absorbable antibiotic that is already licensed in the USA and a few European lands as an anti-diarrheal. The first data on cryptosporidiosis are very promising (Kokkoutou 2005).

If immune reconstitution cannot be achieved and the health insurance provider refuses, options become very limited: paromomycin, a nonabsorbed aminoglycoside antibiotic, is available in powder and tablet form, and has been used by many clinicians since a small, uncontrolled study showed a favorable effect on diarrhea (White 2001). In the only double-blind randomized study to date, however, there was no advantage over placebo (Hewitt 2000). There is possibly an effect in combination with azithromycin (Smith 1998).

#### Treatment/prophylaxis of cryptosporidiosis (daily doses)

<b>Acute therapy</b>		
Symptomatic	Loperamide +	Loperamide 1 cap à 2 mg 2–6 times daily <b>or</b> loperamide solution 10 ml (10 ml = 2 mg) 2–6 times daily <b>and/or</b>
	opium tincture	opium tincture 1 % = 5–15 drops qid
Symptomatic	Octreotide	Sandostatin solution for injection 1 amp à 50 µg s.c. bid or tid (increase dose slowly)
Curative attempt	Nitazoxanide	Nitazoxanide 1 tbl. à 500 mg bid
<b>Prophylaxis</b>		Exposure prophylaxis: no tap water

## Prophylaxis

There is no generally accepted prophylaxis, although retrospective analyses have reported a protective effect of rifabutin and clarithromycin (Holmberg 1998). In our opinion, it is more important that patients, at least in countries with hygiene problems, do not drink tap water. Contact with human and animal feces should be avoided. We have observed that patients mainly become ill during the summer months, often after swimming in rivers. Cryptosporidia are resistant to most disinfectants. In hospital, however, the usual hygiene measures (gloves!) are adequate. Patients need not be isolated, but should not be put in the same room as other significantly immunocompromised patients.

## References

1. Amadi B, Mwiya M, Musuku J, et al. Effect of nitazoxanide on morbidity and mortality in Zambian children with cryptosporidiosis: a randomised controlled trial. *Lancet* 2002, 360:1375-1380. <http://amedeo.com/lit.php?id=12423984>
2. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1 associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet* 1998, 351:256-61. <http://amedeo.com/lit.php?id=9457096>

3. Chen XM, Keithly JS, Paya CV, LaRusso NF. Cryptosporidiosis. *N Engl J Med* 2002, 346: 1723-31.
4. Colford JM Jr, Tager IB, Hirozawa AM, et al. Cryptosporidiosis among patients infected with HIV. Factors related to symptomatic infection and survival. *Am J Epidemiol* 1996, 144:807-16. <http://amedeo.com/lit.php?id=8890659>
5. Griffiths JK. Treatment for AIDS-associated cryptosporidiosis. *J Infect Dis* 1998, 178:915-6.
6. Hewitt RG, Yiannoutsos CT, Higgs ES, et al. Paromomycin: No more effective than placebo for treatment of cryptosporidiosis in patients with advanced HIV infection. *Clin Inf Dis* 2000, 31:1084-92. <http://amedeo.com/lit.php?id=11049793>
7. Holmberg SD, Moorman AC, Von Bargen JC, et al. Possible effectiveness of clarithromycin and rifabutin for cryptosporidiosis chemoprophylaxis in HIV disease. *JAMA* 1998, 279:384-6. <http://amedeo.com/lit.php?id=9459473>
8. Miao YM, Awad-El-Kariem FM, Franzen C, et al. Eradication of cryptosporidia and microsporidia following successful antiretroviral therapy. *J Acquir Immune Defic Syndr* 2000, 25: 124-9. <http://amedeo.com/lit.php?id=11103042>
9. Rossignol JF, Ayoub A, Ayers MS. Treatment of diarrhea caused by *Cryptosporidium parvum*: a prospective randomized, double-blind, placebo-controlled study of Nitazoxanide. *J Infect Dis* 2001, 184:103-6. <http://amedeo.com/lit.php?id=11398117>
10. Smith NH, Cron S, Valdez LM, Chappell CL, White AC Jr. Combination drug therapy for cryptosporidiosis in AIDS. *J Infect Dis* 1998, 178:900-3. <http://amedeo.com/lit.php?id=9728569>
11. White AC, Cron SG, Chappell CL. Paromomycin in cryptosporidiosis. *Clin Inf Dis* 2001, 32:1516-7.

## Cryptococcosis

Infection with the yeast *Cryptococcus neoformans* is feared, even though it is a rare AIDS-defining illness in areas such as Europe. In the USA and Southeast Asia, cryptococcosis is much more frequent and it is one of the most important AIDS-defining illnesses worldwide. *C. neoformans* is probably transmitted via inhalation. Bird droppings are an important reservoir. The pulmonary infection may remain subclinical in immunocompetent patients, but is almost always followed by disseminated disease in HIV patients. Apart from the lungs, the main manifestation after hematogenic spread is in the CNS. CSF examination is therefore obligatory in every suspected case. However, isolated skin manifestations and lymphadenitis also occur. Organ involvement, such as in the urogenital or gastrointestinal tract, is rare.

Cryptococcosis almost always occurs with severe immunodeficiency. In a collection of 114 cases, 87 % had less than 100 CD4+ T-cells/ $\mu$ l; the median CD4+ T-cell count was 30/ $\mu$ l (Weitzel 1999). Cryptococcosis is fatal if untreated. Treatment is lengthy, complicated and should be managed only on an inpatient basis. Relapses were frequent in the pre-HAART era and occurred in at least 15 % of cases. In addition, cryptococcosis occurs relatively frequently in the presence of an immune reconstitution syndrome.

### Signs and symptoms

The CNS manifestation with encephalitis is the most frequent (ca. 80 %). Patients complain mainly of headache and fever. Clouding of consciousness (confusion) rapidly progresses over a few days. Disorders of gait, hearing or vision as well as paresis, particularly of the cranial nerves, may occur; in such cases intracranial pressure is almost always increased! However, meningeal symptoms are usually absent. In the course of an immune reconstitution syndrome, clinical symptoms are often atypical and characterized by extensive abscesses (Manfredi 1999).

Pulmonary disease leads to symptoms of atypical pneumonia with unproductive cough and chest pain. Skin lesions can initially resemble molluscum contagiosum, and later become confluent in the form of larger, ulcerative lesions.

### Diagnosis

Cryptococcosis is life threatening, and the mortality rate in larger studies is between 6 and 25 % (Saag 2000). There is no time to lose during diagnostic testing. Rapid examination of the lungs and CNS in particular should be initiated in every suspected case (e.g. positive cryptococcal antigen test). The chest x-ray usually does not reveal much; therefore, an HRCT scan must be performed if pulmonary involvement is suspected. The spectrum of morphology on the image is very variable: diffuse, small lesions similar to tuberculosis may occur, but there can also be sharply defined infiltrates reminiscent of bronchopneumonia. Cavitation and bronchiectasis may also be present. Every attempt should therefore be made to clearly identify the causative organism by BAL.

An MRI scan of the head should always be performed if there are neurological symptoms. However, in contrast to toxoplasmosis and cerebral lymphoma, it usually does not reveal much, and isolated or multiple mass lesions (cryptococcomas)



are very rare. Nevertheless, intracranial pressure is often increased (fundoscopy: papillary edema?).

The most important test for cryptococcosis is lumbar puncture (after fundoscopy and MRI!). Diagnosis can be made via India ink stain in almost all cases. CSF must be examined even in cases with pulmonary or other manifestation to exclude CNS involvement. Cryptococcal antigen in the blood (titer > 1:8) is a good parameter and should always be determined. Blood cultures are also often positive. With cutaneous involvement, the diagnosis is usually made from a biopsy.

## Treatment

Meningitis immediately requires a combination of antimycotics during the acute phase of treatment, followed by maintenance therapy with fluconazole (Saag 2000). Combination prevents resistance and allows reduction of acute therapy to 4-6 weeks. The choice of combination is not clearly defined. In Germany, combination therapy with the three antimycotics amphotericin B, flucytosine and fluconazole is often used for meningitis. The triple therapy leads to complete remission of meningitis in around 80 % of cases (Weitzel 1999), and therefore possibly a slightly higher rate than under dual therapy with amphotericin B and flucytosine as favored in the United States (van der Horst 1997).

However, recent data is raising questions as to the superiority of triple therapy. In one smaller, randomized study of 64 patients in Thailand, the combination of amphotericin B and flucytosine was the most effective treatment, according to measurements of cryptococcal clearance in the CSF (Brouwer 2004). It was even significantly better than triple therapy and also amphotericin B and fluconazole.

Nevertheless, in view of the toxicity of flucytosine (which is now only available for infusion, but not in tablet form), we currently prefer the combination of amphotericin B and fluconazole. In untreated patients, we almost always start HAART during the acute phase of treatment.

In addition to having significantly lower toxicity, liposomal amphotericin B is slightly more effective than conventional amphotericin B (Leenders 1997, Hamill 1999). However, even combinations with liposomal amphotericin B are very toxic. Daily monitoring of kidney and liver enzymes, blood count and electrolytes are highly recommended. Fluconazole should be administered as an infusion, particularly in confused patients.

In cases of isolated pulmonary involvement (CSF negative!) or other extracerebral manifestations, we treat without flucytosine and complete the acute therapy with amphotericin B and fluconazole within two instead of four weeks. If there is a positive cryptococcal antigen test without evidence of CNS, pulmonary or other infection, we treat with fluconazole alone.

Treatment success is monitored based on the clinical course and repeated lumbar punctures. CSF is negative in approximately 60 % of cases after two weeks (Saag 2000). When this is the case, maintenance therapy or secondary prophylaxis can be started, though not sooner than after four weeks of acute therapy. If there is increased intracranial pressure, CSF drainage may become necessary. Steroids are ineffective (Saag 2000).

## Prophylaxis

Fluconazole is given as secondary prophylaxis or maintenance therapy. It is significantly more effective than itraconazole – in a very large randomized study, the relapse rate in the fluconazole arm was only 4 % compared to 23 % in the itraconazole arm, resulting in discontinuation of the study before completion (Saag 1999). Fluconazole can probably be discontinued with sufficient immune reconstitution (above 200 CD4+ T-cells/ $\mu$ l, undetectable viral load for three to six months), as demonstrated in several studies (Aberg 2002, Kirk 2002, Vibhagool 2003, Mussini 2004), and after at least six months of maintenance therapy. It is prudent to check for cryptococcal antigen before stopping (Mussini 2004). Positive results require continuation of treatment.

Primary prophylaxis against *Cryptococcus neoformans* is not recommended, as survival benefit was not demonstrated, even in endemic areas such as Thailand (McKinsey 1999, Chariyalertsak 2002). Exposure can presumably also not be prevented.

Treatment/prophylaxis of cryptococcosis (daily doses, unless specified otherwise), see also Drugs section for further details!

<b>Acute therapy</b>		Duration: always at least six weeks
Treatment of choice	Amphotericin B	Amphotericin B 0.5-0.75 mg/kg qd <b>or</b> liposomal amphotericin B 3 mg/kg qd (preparation by pharmacy)
	+ fluconazole	<b>plus</b> fluconazole 1 bottle à 200 mg i.v. bid <b>or</b> fluconazole 1 cap. à 200 mg bid
	+ flucytosine *	<b>plus</b> flucytosine 1 bottle à 250 ml (2.5 g) i.v. qid (= 100-150 mg/kg distributed in four separate doses)
<b>Maintenance therapy</b>		Discontinuation possible from > 200 CD4+ T-cells/ $\mu$ l > 3-6 months
Treatment of choice	Fluconazole	Fluconazole 1-2 cap. à 200 mg qd
Alternative	Itraconazole	Itraconazole 2 cap. à 100 mg bid
<b>Primary prophylaxis</b>		Not recommended

**\*Note:** We usually omit flucytosine. Instead, we begin with HAART during the acute therapy phase in those patients, who are almost always HAART naive.

## References

1. Aberg JA, Price RW, Heeren DM, Bredt B. A pilot study of the discontinuation of antifungal therapy for disseminated cryptococcal disease in patients with AIDS, following immunologic response to antiretroviral therapy. *J Infect Dis* 2002, 185:1179-82. <http://amedeo.com/lit.php?id=11930330>
2. Brouwer AE, Rajanuwong A, Chierakul W, et al. Combination antifungal therapies for HIV-associated cryptococcal meningitis: a randomised trial. *Lancet* 2004, 363:1764-7. <http://amedeo.com/lit.php?id=15172774>

3. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, et al. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced HIV infection in Thailand. *Clin Infect Dis* 2002, 34:277-84. <http://amedeo.com/lit.php?id=11740718>
4. Hamill RJ, Sobel J, El-Sadr W, et al. Randomized double blind trial of Ambisome and amphotericin B in acute cryptococcal meningitis in AIDS patients. 39th ICAAC 1999, San Francisco; Abstract 1161
5. Kirk O, Reiss P, Uberti-Foppa C, et al. Safe interruption of maintenance therapy against previous infection with four common HIV-associated opportunistic pathogens during potent antiretroviral therapy. *Ann Intern Med* 2002, 137:239-50. <http://amedeo.com/lit.php?id=12186514>
6. Leenders AC, Reiss P, Portegies P, et al. Liposomal amphotericin B (AmBisome) compared with amphotericin B both followed by oral fluconazole in the treatment of AIDS-associated cryptococcal meningitis. *AIDS* 1997, 11:1463-71. <http://amedeo.com/lit.php?id=9342068>
7. Manfredi R, Pieri F, Pileri SA, Chiodo F. The changing face of AIDS-related opportunism: cryptococcosis in the HAART era. Case reports and literature review. *Mycopathologia* 1999, 148:73-8. <http://amedeo.com/lit.php?id=11189746>
8. McKinsey DS, Wheat LJ, Cloud GA, Itraconazole prophylaxis for fungal infections in patients with advanced HIV infection: randomized, placebo-controlled, double-blind study. *Clin Infect Dis* 1999, 28:1049-56. <http://amedeo.com/lit.php?id=10452633>
9. Mussini C, Pezzotti P, Miro JM, et al. Discontinuation of maintenance therapy for cryptococcal meningitis in patients with AIDS treated with highly active antiretroviral therapy: an international observational study. *Clin Infect Dis* 2004, 38:565-71. <http://amedeo.com/lit.php?id=14765351>
10. Saag MS, Cloud GA, Graybill JR, et al. A comparison of itraconazole versus fluconazole as maintenance therapy for AIDS-associated cryptococcal meningitis. *Clin Infect Dis* 1999, 28:291-6. <http://amedeo.com/lit.php?id=10064246>
11. Saag MS, Graybill RJ, Larsen RA, et al. Practice guidelines for the management of cryptococcal disease. Infectious Diseases Society of America. *Clin Infect Dis* 2000, 30:710-8. <http://amedeo.com/lit.php?id=10770733>
12. van der Horst CM, Saag MS, Cloud GA, et al. Treatment of cryptococcal meningitis associated with the AIDS. *N Engl J Med* 1997, 337:15-21. <http://amedeo.com/lit.php?id=9203426>
13. Vibhagool A, Sungkanuparph S, Mootsikapun P, et al. Discontinuation of secondary prophylaxis for cryptococcal meningitis in HIV-infected patients treated with highly active antiretroviral therapy: a prospective, multicenter, randomized study. *Clin Infect Dis* 2003, 36:1329-31. <http://amedeo.com/lit.php?id=12746781>
14. Weitzel A, Arasteh K, Mertenskötter T, et al. Kryptokokkosen bei HIV-positiven Patienten in Deutschland – eine Auswertung 24 deutscher Zentren. In: Brockmeyer NH et al. HIV-Infekt, Springer-Verlag; 1999.

## Salmonella septicemia

Infection with non-typhoid *Salmonella*, which typically only causes enteritis in healthy individuals, can lead to severe septicemia in immunocompromised patients (Jacobs 1985). In Central Europe, *Salmonella* septicemia is rare in HIV patients, and accounts for less than 1% of AIDS cases. In the Swiss cohort of over 9,000 patients, only 22 cases of recurring salmonellosis were documented over a period of nine years (Burkhardt 1999). In Southern Europe or Africa, salmonellosis is much more frequent. The most important reservoir is infected food, particularly poultry. Relapses are frequent. In addition to septicemia, atypical infections with osteomyelitis, empyema, pulmonary abscesses, pyelonephritis or meningitis have been described (Albrecht 1992, Nadelman 1985). Recurring, non-typhoid *Salmonella* septicemia is considered an AIDS-defining illness.

### Signs and symptoms/diagnosis

Patients are often severely ill. Chills and high fever are usually present. If treatment is delayed, there is always a danger of septic shock. Diarrhea may be absent.

Blood cultures mainly lead to isolation of enteritis-causing *Salmonella* strains such as *S. enteritidis* and *S. typhimurium*. The pathogens causing typhoid or paratyphoid fever, *S. typhi* and *S. paratyphi*, are rare.

### Treatment

Ciprofloxacin is the treatment of choice (Jacobson 1989). Although oral bioavailability is good, we prefer intravenous dosing. Cephalosporins such as cefotaxime or ceftriaxone are also effective. In contrast, resistance to co-trimoxazole or ampicillin has increased. One week of treatment with ciprofloxacin or ceftriaxone is usually enough. Maintenance therapy should continue for 6-8 months and not be stopped too early (Hung 2001). However, lifelong secondary prophylaxis, which was propagated in the past (Nelson 1992), no longer seems necessary.

### Prophylaxis

Drug prophylaxis is not recommended. However, HIV patients should generally be told to pay attention to food hygiene.

Treatment/prophylaxis of *Salmonella* sepsis (daily doses)

<b>Acute therapy</b>		7-14 days
Treatment of choice	Ciprofloxacin	Ciprofloxacin 1 bottle à 200 mg i.v. bid
Alternative	Ceftriaxone	Ceftriaxone 1 bottle à 2 g i.v. qd
<b>Prophylaxis</b>		
	For relapses	Ciprofloxacin 1 tbl. à 500 mg bid (6-8 months)

## References

1. Albrecht H, Stellbrink HJ, Fenske S, Steiner P, Greten H. Salmonella typhimurium lung abscesses in an HIV-infected patient: successful treatment with oral ciprofloxacin. *AIDS* 1992, 6:1400-1.
2. Burckhardt B, Sendi P, Pfluger D, et al. Rare AIDS-defining diseases in the Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis* 1999, 18:399-402. <http://amedeo.com/lit.php?id=10442416>
3. Hung CC, Hsieh SM, Hsiao CF, Chen MY, Sheng WH. Risk of recurrent non-typhoid Salmonella bacteraemia after early discontinuation of ciprofloxacin as secondary prophylaxis in AIDS patients in the era of HAART. *AIDS* 2001, 15:645-7.
4. Jacobs JL, Gold JW, Murray HW, Roberts RB, Armstrong D. Salmonella infections in patients with the AIDS. *Ann Intern Med* 1985, 102:186-8. <http://amedeo.com/lit.php?id=3881072>
5. Jacobson MA, Hahn SM, Gerberding JL, et al. Ciprofloxacin for Salmonella bacteremia in the AIDS. *Ann Intern Med* 1989, 110:1027-1029.
6. Nadelman RB, Mathur-Wagh U, Yancovitz SR, Mildvan D. Salmonella bacteremia associated with the AIDS. *Arch Intern Med* 1985, 145:1968-71. <http://amedeo.com/lit.php?id=3904653>
7. Nelson MR, Shanson DC, Hawkins DA, Gazzard BG. Salmonella, Campylobacter and Shigella in HIV-seropositive patients. *AIDS* 1992, 6:1495-8. <http://amedeo.com/lit.php?id=1362879>

## Immune reconstitution inflammatory syndrome (IRIS)

For the first time, in mid-1997 and early 1998, two groups described atypical manifestations of CMV retinitis (Jacobsen 1997) and MAC disease with abscess formation (Race 1998) in HIV patients within a few weeks of initiation of HAART. Although the pathogens, pathogenesis and localization were very different, all these illnesses had a distinct inflammatory component and were associated with significant immune reconstitution in these patients. It was therefore suspected early on that these presentations could constitute a syndrome during which a latent infection present at initiation of therapy is fought more effectively by the recovering immune system (Overviews: DeSimone 2000, Shelbourne 2005).

Meanwhile, manifestations of numerous diseases have been attributed to the now established term “immune reconstitution inflammatory syndrome” (IRIS). These usually differ significantly from the courses of diseases seen during the pre-HAART era. One should not be surprised by grotesque, “atypical” clinical or radiological findings. IRIS has 3 rules:

1. Anything is possible!
2. Nothing is as it was in the pre-HAART era!
3. IRIS does not mean that HAART has failed! In addition, the patients usually have a good prognosis.

How frequently does IRIS occur? In our experience, a frequency of 5-10 % in patients with less than 200 CD4+ T-cells/ $\mu$ l is realistic. A high viral load before initiation of therapy or a rapid drop on HAART seems to be an important predictive factor for IRIS (Hoffmann 1999, Shelbourne 2005). However, the overall prevalence rate of 25 % cited elsewhere seems slightly too high (French 2000). However, if only the patients, who for example were infected with mycobacteria or *Cryptococcus* before HAART was started, are taken into account, rates of 30 % were reached (Shelbourne 2005).

**Mycobacterial IRIS.** For MAC, the number of published cases with grotesque, fistular lymphadenitis, cutaneous or muscular abscesses, osteomyelitis, nephritis or meningitis is too large to be cited here. In a total of 83 patients starting HAART with a CD4+ T-cell count of less than 200/ $\mu$ l, we have seen 6 mycobacterioses, among these 4 MAC infections, within the first weeks of beginning therapy (Hoffmann 1999). Lymph node abscesses usually occur during the first weeks on HAART. Not all cases are avium: IRIS cases with *Mycobacterium xenopi* or *Mycobacterium kansasii* have also recently been described (Chen 2004, Phillips 2005).

There are now also numerous reports on tuberculosis (John 1998, Chien 1998), which are reminiscent of the “paradox” reactions to TB treatment known since the 1950s. Common to all these patients is the fact that they initially deteriorate drastically under sufficient tuberculostatic treatment and HAART-induced immune reconstitution. Meningitis, as well as marked lymphadenopathy with unspecific histology, can complicate the course of disease, but respond astonishingly rapidly and well to steroids. In one study, four out of five patients, who had clinically developed atypical mycobacterioses after HAART and significant improvements in

CD4+ T-cell levels, showed a significantly increased MAC-specific T-cell response *in vitro* – proving in all likelihood that this phenomenon is indeed caused by the unmasking of subclinical infections (Foudraine 1999).

**CMV IRIS.** In addition to mycobacteriosis, numerous cases of unusual CMV infections under HAART have been published. Inflammatory CMV retinitis with vitritis that may lead to visual impairment, papillitis and macular edema, can now be described as a distinct syndrome, differing significantly from the course of CMV retinitis seen in the pre-HAART era (Jacobson 1997, Whitcup 2000). Neovascularization endangers vision even after resolution (Wright 2003). A prospective study was conducted in 30 patients with CMV retinitis that had reached levels of more than 60 CD4+ T-cells/ $\mu$ l for at least 2 months on HAART. Of these, 19 patients (63 %) developed symptomatic vitritis, in some cases with considerable loss of vision (Karavellas 1999). In one small prospective cohort, the proportion reached 12 out of 14 patients (Whitcup 1999). As with MAC disease, *in vitro* studies have shown that the CMV-specific immune response is improved most significantly in those patients developing vitritis (Mutimer 2002, Stone 2002). Inflammatory CMV manifestations are not limited to the retina and may involve other organs (Gilquin 1997).

**PML IRIS.** The course of inflammatory PML that occurs during an IRIS is different from the infaust prognosis seen during the pre-HAART era (Cinque 2001, Colzanos 1999, Kotecha 1998, Miralles 2001). Clinical symptoms are often more fulminant initially, and on radiology, there is a contrast enhancement which is otherwise atypical for PML, that may resolve over time. Patients have a better prognosis, and PML seems to even resolve completely (Hoffmann 2003, Du Pasquier 2003). We are following several patients with inflammatory PML who have been asymptomatic for years, some of whom live without any residual symptoms. However, fatal cases of inflammatory PML have also been reported (Safdar 2002). In our experience, steroids are ineffective, although there have been accounts of positive results (Nuttall 2004).

**Cryptococcal IRIS.** Numerous cases with inflammatory courses of disease have been described (Manfredi 1999, Woods 1998, Cinti 2001, Breton 2002, Jenny-Avital 2002, King 2002, Boelaert 2004, Lortholary 2005, Shelbourne 2005, Skiest 2005), and after MAC/TBC and CMV, cryptococci are probably the most important pathogens that can cause an IRIS. In particular, severely immunocompromised patients who start with HAART after cryptococcal therapy should be watched closely for the first few weeks and months. Newer studies show that 10-30 % of patients with co-infections develop a cryptococcal IRIS (Lortholary 2005, Shelbourne 2005). The MRI usually shows choriomeningitis with significant enhancement in the choroid plexus. Cryptococcal antigen in the CSF is positive, although culture remains negative (Boelaert 2004). The intracranial pressure is often particularly high (Shelbourne 2005). As well as meningitis, lymphadenitis can also occur (Skiest 2005).

**Other infections.** There are now various case studies. These include leishmaniasis (Jiménez-Expósito 1999), pneumocystosis (Barry 2002, Koval 2002), cerebral toxoplasmosis (Tsambiras 2001, Stout 2002, Ghosn 2003) and herpes infections (Fox 1999). Herpes zoster and hepatitis B or C episodes also seem to occur on HAART, particularly during the first weeks (Behrens 2000, Chung 2002, Manegold

2001, Martinez 1998, Domingo 2001). HHV-8-associated Kaposi's sarcoma can worsen significantly on HAART in the presence of an IRIS (Bower 2005, Leidner 2005). Increasing dermatological problems such as exacerbation of pre-existing folliculitis or skin disease have also been reported (Handa 2001). There are even reports about parvovirus and leprosy (Nolan 2003, Couppie 2004).

**Other diseases.** Diseases other than opportunistic infections are now recognized to occur under IRIS. These include autoimmune diseases such as Graves' disease, lupus, Sweet's and Reiter's syndromes, Guillain-Barré syndrome, acute porphyria and sarcoidosis, to name but a few (Bevilacqua 1999, Behrens 1998, Fox 1999, Gilquin 1998, Makela 2002, Mirmirani 1999, Neumann 2003, Piliero 2003). Two cases of Peyronie's disease, a fibrosis of the penis, were reported (Rogers 2004)! These reports do lead one to wonder whether all of these manifestations are truly induced by immune reconstitution or perhaps merely chance occurrences. While most publications initially offered little information on the etiology beyond purely hypothetical discussions, it has recently become apparent that changes in the cytokine profile are involved in the pathogenesis of IRIS, together with an activation of the cellular immune response. However, it seems that the mechanisms differ according to disease and genetic profile (Price 2001, Shelbourne 2005).

## Consequences

Patients starting HAART with less than 200 CD4+ T-cells/ $\mu$ l (and particularly those who have a high viral load) require close clinical monitoring during the first weeks. It is important to be alert especially in very immunocompromised patients who have previously declined antiretroviral treatment, but now feel physically "affected" (subfebrile?) and want to start HAART "after thinking about it for a long time". Latent infections are often present in such cases, and these will rapidly become apparent as immune reconstitution occurs. The poorer the immune status, and the longer its duration, the higher the danger of IRIS!

Chest radiography, abdominal ultrasound and fundoscopy should be included in routine investigations of such patients before starting treatment. Clinical examination, often gladly overlooked today, is to be taken seriously! The suggestion by some authors to start MAC prophylaxis even before HAART in severely immunocompromised patients seems problematic. Prophylaxis cannot prevent MAC IRIS (Phillips 2002 + 2005). Prospective clinical studies have yet to prove whether administration of IL-2 or GM-CSF is worthwhile, as was recently postulated (Pires 2005).

Mycobacterioses in particular should be treated generously with steroids. One should always be prepared for atypical localizations, findings and disease courses of opportunistic infections.

## References

1. Aberg JA, Chin-Hong PV, McCutchan A, et al. Localized osteomyelitis due to *Mycobacterium avium* complex in patients with HIV receiving HAART. *Clin Infect Dis* 2002, 35:E8-E13. <http://amedeo.com/lit.php?id=12060894>
2. Barry SM, Lipman MC, Deery AR, Johnson MA, Janossy G. Immune reconstitution pneumonitis following *Pneumocystis carinii* pneumonia in HIV-infected subjects. *HIV Med* 2002, 3:207-11. <http://amedeo.com/lit.php?id=12139660>



3. Behrens G, Knuth C, Schedel I, Mendila M, Schmidt RE. Flare of SLE following HAART. *Lancet* 1998, 351:1057-8.
4. Behrens GM, Meyer D, Stoll M, Schmidt RE. Immune reconstitution syndromes in HIV infection following effective antiretroviral therapy. *Immunobiology* 2000, 202:186-93. <http://amedeo.com/lit.php?id=10993293>
5. Bevilacqua S, Hermans P, Van Laethem Y, Demaubeuge J, Clumeck N. Sweet's syndrome in an HIV-infected patient. *AIDS* 1999, 13: 728-9.
6. Boelaert JR, Goddeeris KH, Vanopdenbosch LJ, Casselman JW. Relapsing meningitis caused by persistent cryptococcal antigens and immune reconstitution after the initiation of highly active antiretroviral therapy. *AIDS* 2004, 18:1223-4.
7. Breton G, Seilhean D, Cherin P, Herson S, Benveniste O. Paradoxical intracranial cryptococcoma in an HIV-infected man being treated with combination antiretroviral therapy. *Am J Med* 2002, 113: 155-7.
8. Chen F, Sethi G, Goldin R, Wright AR, Lacey CJ. Concurrent granulomatous *Pneumocystis carinii* and *Mycobacterium xenopi* pneumonia: an unusual manifestation of HIV immune reconstitution disease. *Thorax* 2004, 59:997-999. <http://amedeo.com/lit.php?id=15516479>
9. Chien JW, Johnson JL. Paradoxical reactions in HIV and pulmonary TB. *Chest* 1998, 114: 933-6. <http://amedeo.com/lit.php?id=9743188>
10. Chung RT, Evans SR, Yang Y, et al. Immune recovery is associated with persistent rise in HCV RNA, infrequent liver test flares, and is not impaired by HCV in co-infected subjects. *AIDS* 2002, 16:1915-1923. <http://amedeo.com/lit.php?id=12351951>
11. Cinque P, Pierotti C, Vignani MG, et al. The good and evil of HAART in HIV-related progressive multifocal leukoencephalopathy. *J Neurovirol* 2001, 7:358-63. <http://amedeo.com/lit.php?id=11517417>
12. Cinti SK, Armstrong WS, Kauffman CA. Recurrence of increased intracranial pressure with antiretroviral therapy in an AIDS patient with cryptococcal meningitis. *Mycoses* 2001, 44:497-501.
13. Collazos J, Mayo J, Martinez E, Blanco MS. Contrast-enhancing progressive multifocal leukoencephalopathy as an immune reconstitution event in AIDS patients. *AIDS* 1999, 13: 1426-1428.
14. Couppie P, Abel S, Voinchet H, et al. Immune reconstitution inflammatory syndrome associated with HIV and leprosy. *Arch Dermatol*. 2004, 140:997-1000. <http://amedeo.com/lit.php?id=15313818>
15. DeSimone JA, Pomerantz RJ, Babinchak TJ. Inflammatory reactions in HIV-1-infected persons after initiation of HAART. *Ann Intern Med* 2000, 133:447-54. <http://amedeo.com/lit.php?id=10975963>
16. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with HIV-1 infection. *Am J Med* 2001, 110:605-9. <http://amedeo.com/lit.php?id=11382367>
17. Du Pasquier RA, Korálnik IJ. Inflammatory reaction in progressive multifocal leukoencephalopathy: harmful or beneficial? *J Neurovirol* 2003, 9 Suppl 1:25-31. <http://amedeo.com/lit.php?id=12709868>
18. Foudraine NA, Hovenkamp E, Notermans DW, et al. Immunopathology as a result of HAART in HIV-1-infected patients. *AIDS* 1999, 13:177-84. <http://amedeo.com/lit.php?id=10202823>
19. Fox PA, Barton SE, Francis N, et al. Chronic erosive herpes simplex virus infection of the penis, a possible immune reconstitution disease. *HIV Med* 1999, 1:10-8. <http://amedeo.com/lit.php?id=11737324>
20. Fox PA, Boag FC, Hawkins DA, Francis N. Acute porphyria following commencement of indinavir. *AIDS* 1999, 13: 622-3.
21. French MA, Lenzo N, John M, et al. Immune restoration disease after the treatment of immunodeficient HIV-infected patients with HAART. *HIV Med* 2000, 1:107-15. <http://amedeo.com/lit.php?id=11737333>
22. Ghosn J, Paris L, Ajzenberg D, et al. Atypical toxoplasmic manifestation after discontinuation of maintenance therapy in a HIV type 1-infected patient with immune recovery. *Clin Infect Dis* 2003; 37: E112-4. <http://amedeo.com/lit.php?id=13130422>
23. Gilquin J, Piketty C, Thomas V et al. Acute CMV infection in AIDS patients receiving combination therapy including protease inhibitors. Abstract 629, 4th CROI 1997, Washington, USA.
24. Gilquin J, Viard JP, Jubault V, Sert C, Kazatchkine MD. Delayed occurrence of Graves' disease after immune restoration with HAART. *Lancet* 1998, 352:1907-8.
25. Handa S, Bingham JS. Dermatological immune restoration syndrome: does it exist? *J Eur Acad Dermatol Venereol* 2001, 15:430-2. <http://amedeo.com/lit.php?id=11763384>
26. Hoffmann C, Degen O, Horst HA, van Lunzen J, Stellbrink HJ. Immune reconstitution in severely immunocompromised patients initiating HAART – the critical first months. 7. Deutscher AIDS-Kongress 1999, Essen, F1088.

27. Hoffmann C, Horst HA, Albrecht H, Schlote W. Progressive multifocal leucoencephalopathy with unusual inflammatory response during antiretroviral treatment. *J Neurol Neurosurg Psychiatry* 2003, 74:1142-4. <http://amedeo.com/lit.php?id=12876257>
28. Hoffmann C, Horst HA, Degen O, van Lunzen J, Stellbrink HJ. Manifestation of Mycobacterial Lymphadenitis after Initiating of HAART. Abstract 22172, 12th World AIDS Conference 1998, Geneva, Suisse.
29. Jacobson MA, Zegans M, Pavan PR, et al. Cytomegalovirus retinitis after initiation of HAART. *Lancet* 1997, 349:1443-5.
30. Jenny-Avital ER, Abadi M. Immune reconstitution cryptococcosis after initiation of successful highly active antiretroviral therapy. *Clin Infect Dis* 2002; 35: E128-33. <http://amedeo.com/lit.php?id=12471589>
31. Jiménez-Expósito MJ, Alonso-Villaverde C, Sardà P, Masana L. Visceral leishmaniasis in HIV-infected patients with non-detectable HIV-1 viral load after HAART. *AIDS* 1999, 13:152-3.
32. John M, French MA. Exacerbation of the inflammatory response to mycobacterium tuberculosis after antiretroviral therapy. *Med J Aust* 1998, 169: 473-4.
33. Karavellas MP, Plummer DJ, Macdonald JC, et al. Incidence of immune recovery vitritis in cytomegalovirus retinitis patients following institution of successful HAART. *J Infect Dis* 1999, 179: 697-700. <http://amedeo.com/lit.php?id=9952380>
34. King MD, Perlino CA, Cinnamon J, Jernigan JA. Paradoxical recurrent meningitis following therapy of cryptococcal meningitis: an immune reconstitution syndrome after initiation of highly active antiretroviral therapy. *Int J STD and AIDS* 2002, 13: 724-726.
35. Kotecha N, George MJ, Smith TW, Corvi F, Litofsky NS. Enhancing progressive multifocal leukoencephalopathy: an indicator of improved immune status? *Am J Med* 1998, 105:541-3.
36. Koval CE, Gigliotti F, Nevins D, Demeter LM. Immune reconstitution syndrome after successful treatment of *Pneumocystis carinii* pneumonia in a man with HIV type 1 infection. *Clin Infect Dis* 2002, 35:491-3.
37. Makela P, Howe L, Glover S, Ferguson I, Pinto A, Gompels M. Recurrent Guillain-Barre Syndrome as a complication of immune reconstitution in HIV. *J Infect* 2002, 44:47-9.
38. Manegold C, Hannoun C, Wywiol A, et al. Reactivation of hepatitis B virus replication accompanied by acute hepatitis in patients receiving HAART. *Clin Infect Dis* 2001, 32: 144-8.. Abstract: <http://amedeo.com/lit.php?id=11118394>
39. Manfredi R, Pieri F, Pileri SA, Chiodo F. The changing face of AIDS-related opportunism: cryptococcosis in the HAART era. Case reports and literature review. *Mycopathologia* 1999, 148:73-8. <http://amedeo.com/lit.php?id=11189746>
40. Martinez E, Gatell J, Moran Y, et al. High incidence of herpes zoster in patients with AIDS soon after therapy with protease inhibitors. *Clin Infect Dis* 1998, 27:1510-3. <http://amedeo.com/lit.php?id=9868668>
41. Miralles P, Berenguer J, Lacruz C, et al. Inflammatory reactions in progressive multifocal leukoencephalopathy after HAART. *AIDS* 2001, 15:1900-2. <http://amedeo.com/lit.php?id=11579261>
42. Mirmirani P, Maurer TA, Herndier B, et al. Sarcoidosis in a patient with AIDS: a manifestation of immune restoration syndrome. *J Am Acad Dermatol* 1999, 41:285-6.
43. Mutimer HP, Akatsuka Y, Manley T, et al. association between immune recovery uveitis and a diverse intraocular cytomegalovirus-specific cytotoxic T cell response. *J Infect Dis* 2002, 186: 701-5. <http://amedeo.com/lit.php?id=12195359>
44. Neumann S, Kreth F, Schubert S, Mossner J, Caca K. Reiter's syndrome as a manifestation of an immune reconstitution syndrome in an hiv-infected patient: successful treatment with doxycycline. *Clin Infect Dis* 2003; 36: 1628-9.
45. Nolan RC, Chidlow G, French MA. Parvovirus b19 encephalitis presenting as immune restoration disease after highly active antiretroviral therapy for HIV infection. *Clin Infect Dis* 2003; 36: 1191-4. <http://amedeo.com/lit.php?id=12715316>
46. Nuttall JJ, Wilmshurst JM, Ndong AP, et al. Progressive multifocal leukoencephalopathy after initiation of highly active antiretroviral therapy in a child with advanced HIV infection: a case of immune reconstitution inflammatory syndrome. *Pediatr Infect Dis J* 2004, 23:683-5. <http://amedeo.com/lit.php?id=15247614>
47. Phillips P, Chan K, Hogg R, et al. Azithromycin prophylaxis for *Mycobacterium avium* complex during the era of HAART: evaluation of a provincial program. *Clin Infect Dis* 2002, 34: 371-8. <http://amedeo.com/lit.php?id=11774085>
48. Pileri PJ, Fish DG, Preston S, et al. Guillain-Barre syndrome associated with immune reconstitution. *Clin Infect Dis* 2003; 36:e111-4. <http://amedeo.com/lit.php?id=12715328>

49. Price P, Mathiot N, Krueger R, Stone S, Keane NM, French MA. Immune dysfunction and immune restoration disease in HIV patients given HAART. *J Clin Virol* 2001, 22:279-87. <http://amedeo.com/lit.php?id=11564593>
50. Race EM, Adelson-Mitty J, Kriegel GR, et al. Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease. *Lancet* 1998, 351:252-5. <http://amedeo.com/lit.php?id=9457095>
51. Rogers GD, French MA. Peyronie's disease in men with HIV responding to highly active antiretroviral therapy. *HIV Med* 2004, 5:185-6.
52. Safdar A, Rubocki RJ, Horvath JA, et al. Fatal immune restoration disease in HIV type 1-infected patients with progressive multifocal leukoencephalopathy: impact of antiretroviral therapy-associated immune reconstitution. *Clin Infect Dis* 2002; 35: 1250-7. <http://amedeo.com/lit.php?id=12410486>
53. Stone SF, Price P, Tay-Kearney ML, French MA. Cytomegalovirus (CMV) retinitis immune restoration disease occurs during HAART-induced restoration of CMV-specific immune responses within a pre-dominant Th2 cytokine environment. *J Infect Dis* 2002, 185:1813-7. <http://amedeo.com/lit.php?id=12085331>
54. Stout JE, Lai JC, Giner J, Hamilton CD. Reactivation of retinal toxoplasmosis despite evidence of immune response to highly active antiretroviral therapy. *Clin Infect Dis* 2002; 35:E37-9. <http://amedeo.com/lit.php?id=12145740>
55. Tsambiras PE, Larkin JA, Houston SH. Toxoplasma encephalitis after initiation of HAART. *AIDS Read* 2001, 11:608-10. <http://amedeo.com/lit.php?id=11806173>
56. Whitcup SM. Cytomegalovirus retinitis in the era of HAART. *JAMA* 2000, 283:653-7. <http://amedeo.com/lit.php?id=10665706>
57. Woods ML, MacGinley R, Eisen DP, Allworth AM. HIV combination therapy: partial immune restitution unmasking latent cryptococcal infection. *AIDS* 1998, 12: 1491-4. <http://amedeo.com/lit.php?id=9727570>
58. Wright ME, Suzman DL, Csaky KG. Extensive retinal neovascularization as a late finding in human immunodeficiency virus-infected patients with immune recovery uveitis. *Clin Infect Dis* 2003;36:1063-6. <http://amedeo.com/lit.php?id=12684920>

## Wasting syndrome

Classic wasting syndrome is defined as involuntary weight loss of at least 10 % of original body weight, accompanied by persistent diarrhea (at least two bowel movements daily for more than 30 days) or extreme fatigue and/or fever without apparent infectious etiology. Wasting syndrome is therefore a classical exclusion diagnosis and really more of an epidemiological instrument than a specific disease – with thorough and competent searching, a specific causative agent can usually be found. Although very frequent in the past, classic wasting syndrome has become rare in the HAART era. In a large study conducted in 2000, however, 14 % of patients still indicated having lost more than 10 % of their original body weight (Wanke 2000). Wasting rates are even higher in intravenous drug users (Campa 2005). Weight loss remains an independent risk factor for mortality, even in the HAART era, and every patient should be weighed regularly! In one large study, mortality risk in patients with a loss greater than 10 % of body weight was more than 4-6-fold above that of patients with stable body weight (Tang 2002). Patients with classic wasting syndrome are often extremely weak. The risk for opportunistic infections is significantly elevated (Dworkin 2003). There is also cognitive impairment in these patients (Dolan 2003).

## Diagnosis

The causes of wasting syndrome are complex. First, it is necessary to exclude or treat opportunistic infections (TB, MAC, cryptosporidiosis and microsporidiosis). If there are none to be found, several reasons remain that may contribute, even in combination, to wasting syndrome. These include metabolic disorders, hypogonadism, poor nutrition and malabsorption syndromes (overview: Grinspoon 2003).

Therefore it is important to start with a thorough history. Does the patient have a sensible diet? How are meals distributed throughout the day? Is the patient depressed? Which drugs, which HAART is being taken? Distinction from antiretroviral-induced lipoatrophy (d4T? ddI?) is often difficult. Significant weight loss also occurs frequently on interferon (Garcia-Benayas 2002), but rapidly resolves after finishing treatment. In addition, hypogonadism should be ruled out (measurement of testosterone). There are several simple tests for malabsorption syndromes. It is prudent to start with testing albumin, TSH and cholesterol levels.

Further tests such as D-xylose absorption or biopsies of the small intestine should only be initiated after consulting a gastroenterologist. Other tests to determine body composition (DEXA, densitometry, bioelectrical impedance analysis) should only be conducted in centers experienced in wasting syndrome in AIDS patients.

## Therapy

Wasting syndrome always requires competent diet counseling. Exercise, if possible, is also good. Of course, both only have limited success. Supportive parenteral nutrition only helps if there are problems with absorption (Kotler 1990, Melchior 1996). Effective HAART is important, ideally without drugs that cause lipoatrophy such as d4T or ddI, possibly even omitting nucleoside analogs completely. Severe

lipoatrophy may require complete omission of nucleoside analogs (see chapter on Nuke sparing).

Beyond this, many kinds of drug treatment have been attempted. However, these have limited success and are often problematic.

Megestrol acetate, a synthetic gestagenic hormone, shows some benefit as an appetite stimulant in wasting syndrome, as demonstrated in a double-blind, randomized study (Von Roenn 1994). Its main problems are typical steroidal side effects, including hypogonadism (which should really be avoided in cases of wasting syndrome). We therefore do not currently recommend the use of this drug.

What about THC (dronabinol)? Dronabinol, the main active ingredient in marijuana, has been licensed in the US since 1985 as Marinol™, and may be prescribed for pharmacy formulation as drops or hard gel capsules. This drug is certainly attractive for many patients and is sometimes actively demanded. Prescription should be carefully considered, particularly in view of the significant cost (approx. 600 Euros per month for the usual dose of 5 mg tid). Without a clear diagnosis of wasting syndrome, the health insurance may cause substantial problems (contact beforehand!). Some health insurances reject the request in general. The effect on wasting syndrome is moderate at best, if detectable at all (Beal 1995). It is probably even weaker than megestrol acetate (Timpone 1997).

Hypogonadism is a frequent problem in patients with wasting syndrome. It is therefore useful to determine testosterone levels (age-dependent!). If levels are low, testosterone substitution has proven useful, both for weight gain and quality of life (Grinspoon 1998). A dose of 250 mg testosterone is given i.m. every 3-4 weeks, and there is a variety of less expensive generic names. The effect is sustained, even with long-term use (Grinspoon 1999). If testosterone levels are normal, substitution in cases of wasting syndrome is not indicated. In women, one should generally be very cautious with administration of androgenic hormones. There are other anabolic steroids available in addition to testosterone, such as oxandrolone or nandrolone. However, these are likely to be associated with more side effects, particularly related to the liver (Corcoran 1999). Positive effects have been demonstrated for the anabolic steroid oxymetholone in a small, double-blind, randomized study (Hengge 2003). However, the extremely high elevation of transaminases, which sometimes occurs, prevents the broader use of this drug.

Side effects as well as the high cost also limit the use of growth hormones, for which long-term data is still not available (Mulligan 1993, Schambelan 1996). However, the results of a more recent metaanalysis suggest that growth hormone may be more effective than anabolic steroids or testosterone in wasting syndrome (Moyle 2004).

## References

1. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. *J Pain Symptom Manage* 1995;10:89-97.  
<http://amedeo.com/lit.php?id=7730690>
2. Corcoran C, Grinspoon S. Treatments for wasting in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1999, 340:1740-50.
3. Dolan S, Montagno A, Wilkie S, et al. Neurocognitive Function in HIV-Infected Patients With Low Weight and Weight Loss. *J Acquir Immune Defic Syndr* 2003; 34: 155-64.  
<http://amedeo.com/lit.php?id=14526204>

4. Dworkin MS, Williamson JM. AIDS wasting syndrome: trends, influence on opportunistic infections, and survival. *J AIDS* 2003; 33: 267-73. <http://amedeo.com/lit.php?id=12794565>
5. Garcia-Benayas T, Blanco F, Soriano V. Weight loss in HIV-infected patients. *N Engl J Med* 2002, 347: 1287-8.
6. Grinspoon S, Corcoran C, Anderson E, Hubbard J, Basgoz N, Klibanski A. Sustained anabolic effects of long-term androgen administration in men with AIDS wasting. *Clin Infect Dis* 1999, 28:634-636.
7. Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998;129:18-26. <http://amedeo.com/lit.php?id=9652995>
8. Grinspoon S, Mulligan K. Weight loss and wasting in patients infected with human immunodeficiency virus. *Clin Infect Dis* 2003; 36: S69-78. <http://amedeo.com/lit.php?id=12652374>
9. Hengge UR, Stocks K, Faulkner S, et al. Oxymetholone for the treatment of HIV-wasting: a double-blind, randomized, placebo-controlled phase III trial in eugonadal men and women. *HIV Clin Trials* 2003; 4:150-63. <http://amedeo.com/lit.php?id=12815555>
10. Kotler DP, Tierney AR, Culpepper-Morgan JA, Wang J, Pierson RN Jr. Effect of home total parenteral nutrition on body composition in patients with AIDS. *J Parenter Enteral Nutr* 1990;14:454-458. <http://amedeo.com/lit.php?id=2122017>
11. Melchior J, Chastang C, Gelas P, et al. Efficacy of 2-month total parenteral nutrition in AIDS patients: a controlled randomized prospective trial. *AIDS* 1996;10:379-384. <http://amedeo.com/lit.php?id=8728041>
12. Mulligan K, Grunfeld C, Hellerstein MK, et al. Anabolic effects of recombinant human growth hormone in patients with wasting associated with HIV infection. *J Clin Endocrinol Metab* 1993, 77:956-962. <http://amedeo.com/lit.php?id=8408471>
13. Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting: a randomized, placebo-controlled trial. *Ann Intern Med* 1996, 125:873-882. <http://amedeo.com/lit.php?id=8967667>
14. Tang AM, Forrester J, Spiegelman D, et al. Weight loss and survival in HIV-positive patients in the era of highly active antiretroviral therapy. *J AIDS* 2002, 31: 230-6. <http://amedeo.com/lit.php?id=12394802>
15. Timpone JG, Wright DJ, Li N, et al. The safety and pharmacokinetics of single-agent and combination therapy with megestrol acetate and dronabinol for the treatment of HIV wasting syndrome. *AIDS Res Hum Retroviruses* 1997, 13:305-15. <http://amedeo.com/lit.php?id=9071430>
16. Von Roenn JH, Armstrong D, Kotler DP, et al. Megesterol acetate in patients with AIDS-related cachexia. *Ann Intern Med* 1994, 121:393-399. <http://amedeo.com/lit.php?id=7794302>
17. Wanke CA, Silva M, Knox TA, et al. Weight loss and wasting remain common complications in individuals infected with HIV in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2000, 31:803-5. <http://amedeo.com/lit.php?id=11017833>

## Rare OIs

by Christian Hoffmann and Gerd Fätkenheuer

The following describes several opportunistic infections that rarely occur in central Europe, or have become very rare as a result of HAART. These diseases include aspergillosis, bacillary angiomatosis, histoplasmosis, isosporiasis, coccidioidomycosis (*Coccidioides immitis*), visceral leishmaniasis, microsporidiosis, *Penicillium marneffeii* mycosis and rhodococcosis. These infections affect HIV patients more frequently than immunocompetent individuals, have more serious courses of disease than in HIV-negative patients and recur more frequently. Despite this, only three, namely histoplasmosis, isosporiasis and coccidioidomycosis, are AIDS-defining according to the current CDC/WHO classification.

## Aspergillosis

Aspergillosis occurs almost only in severely immunocompromised patients. However, it is not AIDS defining. In the largest series described worldwide to date with 342 (!) cases of invasive aspergillosis, almost all patients had less than 50 CD4+ T-cells/ $\mu$ l (Mylonakis 1998). The only way to reach a reliable diagnosis is biopsy. The lung is often primarily affected (pneumonia, tracheobronchitis). The patients, who are usually severely ill, complain of fever, cough, dyspnea and chest pain. Hemoptysis frequently occurs. In addition to the lungs, nearly all other organs can be involved, particularly the CNS (Mylonakis 2000). Initial manifestations can even take the form of rhinosinusitis or abscesses (kidneys, liver) (Hunt 2000).

Aspergillosis particularly occurs in HIV patients on long-term (too long) steroid treatment for another OI. Severe neutropenia ( $< 1,000$  leucocytes) is another risk factor. *Aspergillus fumigatus* is by far the most frequent pathogen. It is found in over 90 % of invasive aspergillosis cases. Therapy with amphotericin B (treatment of choice) and itraconazole has been reported most frequently (Keating 1994, Denning 1990). Even though there have been some new developments in recent years with the introduction of antimycotics such as caspofungin and voriconazole (Herbrecht 2002, Hoang 2001), the prognosis of aspergillosis remains fairly poor. Over 80 % of patients die of this complication. Early invasive diagnostics (CTs, culture, biopsies) are critical.

## References

1. Denning DW, Tucker RM, Hanson LH, Stevens DA. Itraconazole in opportunistic mycoses: cryptococcosis and aspergillosis. *J Am Acad Dermatol* 1990, 23:602-7. <http://amedeo.com/lit.php?id=1994248>
2. Herbrecht R; Denning DW; Patterson TF; et al. Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. *N Engl J Med* 2002, 347:408-15. <http://amedeo.com/lit.php?id=12167683>
3. Hoang A. Caspofungin acetate: an antifungal agent. *Am J Health Syst Pharm* 2001, 58:1206-14. <http://amedeo.com/lit.php?id=11449878>
4. Hunt SM, Miyamoto RC, Cornelius RS, Tami TA. Invasive fungal sinusitis in the AIDS. *Otolaryngol Clin North Am* 2000, 33:335-47. <http://amedeo.com/lit.php?id=10736408>
5. Keating JJ, Rogers T, Petrou M, et al. Management of pulmonary aspergillosis in AIDS: an emerging clinical problem. *J Clin Pathol* 1994, 47:805-9. <http://amedeo.com/lit.php?id=7962648>

6. Mylonakis E, Barlam TF, Flanigan T, Rich JD. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest* 1998, 114:251-62. <http://amedeo.com/lit.php?id=9674477>
7. Mylonakis E, Paliou M, Sax PE, Skolnik PR, Baron MJ, Rich JD. Central nervous system aspergillosis in patients with HIV infection. Report of 6 cases and review. *Medicine (Baltimore)* 2000, 79:269-80. <http://amedeo.com/lit.php?id=10941356>

## Bacillary angiomatosis

Bacillary angiomatosis was first described in the 1980s in HIV patients (Review: Maguina 2000). It is caused by the rickettsial species *Bartonella henselae* and *Bartonella quintana* ("Rochalimaea" until the beginning of the 1990s).

*Bartonella* occurs far more frequently in North and South America than in Europe. In one study of 382 febrile HIV patients in San Francisco, *Bartonella* was found to be the causative organism in 18 % (Koehler 2003). Bacillary angiomatosis remains an important differential diagnosis in all cases with skin lesions of unknown etiology. The pseudoneoplastic, vascular skin proliferation is very often clinically (and histologically) mistaken for Kaposi's sarcoma or hemangioma. Cats are the main host of *Bartonella henselae*, and the cat flea is the vector. *Bartonella quintana* frequently affects patients from poor social background, particularly the homeless. Several possible reservoirs have been discussed for such cases (Gasquet 1998).

The vascular nodules or tumors may be isolated, but are usually multiple and reminiscent of fresh Kaposi's sarcoma, with cherry red or purple nodules. One quarter of cases may have bone involvement with painful osteolytic foci (AP elevation!). Here, the skin lesions sometimes resemble dry hyperkeratotic changes such as those seen in psoriasis. Different organs may be affected. In a collection of 21 cases, 19 patients had skin, 5 bone and 4 liver involvement (Plettenberg 2000). Manifestations in lymph nodes, muscle, CNS, eye, gingiva and gastrointestinal tract have also been reported.

The incidence is presumably higher than generally assumed. The gram-negative bacteria are only visible on biopsy samples stained with Warthin Starry silver stain. Those who do not stain with this method will not find bacillary angiomatosis! Pathologists should be informed of the suspected diagnosis, as this stain is not performed routinely. PCR is also possible. Reference laboratories should be contacted for further diagnostic details.

Treatment of bacillary angiomatosis is with erythromycin (at least 4 weeks with 500 mg qid). Relapses are common, which is why some physicians favor therapy for at least three months. Even doxycycline is supposed to be effective, and is the therapy of choice for CNS involvement. Since transmission is mainly via cats, American guidelines recommend not having cats as pets. If there is no way around this, the cat should be healthy and older than one year. Scratches should be avoided.

## References

1. Cockerell CJ, LeBoit PE. Bacillary angiomatosis: a newly characterized, pseudoneoplastic, infectious, cutaneous vascular disorder. *J Am Acad Dermatol* 1990, 22:501-12. <http://amedeo.com/lit.php?id=2179301>
2. Gasquet S, Maurin M, Brouqui P, Lepidi H, Raoult D. Bacillary angiomatosis in immunocompromised patients. *AIDS* 1998, 12:1793-803. <http://amedeo.com/lit.php?id=9792380>
3. Koehler JE, Sanchez MA, Garrido CS, et al. Molecular epidemiology of bartonella infections in patients with bacillary angiomatosis-peliosis. *N Engl J Med* 1997, 337:1876-83. <http://amedeo.com/lit.php?id=9407154>



4. Koehler JE, Sanchez MA, Tye S, et al. Prevalence of Bartonella infection among human immunodeficiency virus-infected patients with fever. *Clin Infect Dis* 2003, 37:559-66.
5. LeBoit PE, Berger TG, Egbert BM, Beckstead JH, Yen TSB, Stoler MH. Bacillary angiomatosis: the histopathology and differential diagnosis of a pseudoneoplastic infection in patients with HIV disease. *Am J Surg Pathol* 1989, 13:909-920. <http://amedeo.com/lit.php?id=2802010>
6. Maguina C, Gotuzzo E. Bartonellosis. New and old. *Infect Dis Clin North Am* 2000, 14:1-22. Komplet Internet: <http://hiv.net/link.php?id=11>
7. Plettenberg A, Lorenzen T, Burtsche BT, et al. Bacillary angiomatosis in HIV-infected patients--an epidemiological and clinical study. *Dermatology* 2000, 201:326-31. <http://amedeo.com/lit.php?id=11146343>
8. Stoler MH, Bonfiglio TA, Steigbigel RB, et al. An atypical subcutaneous infection associated with AIDS. *Am J Clin Pathol* 1983, 80:714-718. <http://amedeo.com/lit.php?id=6637883>

## Histoplasmosis

*Histoplasma capsulatum* is a dimorphic mould, found mainly in moist soil and without a capsule despite its name. The South and Midwest of the USA are endemic areas, as are Central America and Africa. Inhalation of microconidia, the spores of *H. capsulatum*, can cause granulomatous disease in the lungs of immunocompetent individuals. In HIV patients with impaired immunity (85 % have less than 100 CD4+ T-cells/ $\mu$ l), infection leads to an acute, life-threatening disease with dry cough, fever, dyspnea and malaise (McKinsey 1998, Gutierrez 2005). Miliary TB and PCP are important differential diagnoses. Disseminated courses of disease may also occur, in which the fungus can be detected in bone marrow or by liver biopsy (Albrecht 1994). Skin (ulcerations) or CNS involvement may also occur (Calza 2003, Scheinfeld 2003, Wheat 2005).

Histoplasmosis is AIDS-defining. The pathogen can be detected quite reliably in the blood with an antigen test, similarly to the detection of cryptococcal antigen. Laboratory evaluations often reveal significantly elevated LDH and alkaline phosphatase as well as transaminases. Amphotericin B should be given as initial treatment. Liposomal amphotericin B (3 mg/kg daily for 14 days) is not only less toxic, but possibly also more effective (Johnson 2002). In milder cases, itraconazole (200 mg bid or tid) is effective, and can also be used as a secondary prophylaxis. It is significantly more effective than fluconazole (Wheat 2002), but is associated with a high risk of interactions, particularly with ritonavir (Crommentuyn 2004). With regard to other OIs, secondary prophylaxis for histoplasmosis can be discontinued if immune reconstitution is sufficient (Goldman 2004).

## References

1. Albrecht H, Stellbrink HJ, Petersen J, Patzak A, Jager H, Greten H. Disseminated histoplasmosis in AIDS. *Dtsch Med Wochenschr* 1994, 119:657-62.
2. Calza L, Manfredi R, Donzelli C, Marinacci G, Colangeli V, Chiodo F. Disseminated histoplasmosis with atypical cutaneous lesions in an Italian HIV-infected patient: another autochthonous case. *HIV Med* 2003, 4:145-8. <http://amedeo.com/lit.php?id=12702136>
3. Crommentuyn KM, Mulder JW, Sparidans RW, Huitema AD, Schellens JH, Beijnen JH. Drug-drug interaction between itraconazole and the antiretroviral drug lopinavir/ritonavir in an HIV-1-infected patient with disseminated histoplasmosis. *Clin Infect Dis*. 2004 Apr 15;38(8):e73-5. <http://amedeo.com/lit.php?id=15095234>
4. Goldman M, Zackin R, Fichtenbaum CJ, et al. Safety of discontinuation of maintenance therapy for disseminated histoplasmosis after immunologic response to antiretroviral therapy. *Clin Infect Dis* 2004, 38:1485-9. <http://amedeo.com/lit.php?id=15156489>

5. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med* 2002, 137: 105-9. <http://amedeo.com/lit.php?id=12118965>
6. McKinsey DS. Histoplasmosis in AIDS: advances in management. *AIDS Patient Care STDS* 1998, 12:775-81. <http://amedeo.com/lit.php?id=11362022>
7. Scheinfeld N. Diffuse ulcerations due to disseminated histoplasmosis in a patient with HIV. *J Drugs Dermatol* 2003, 2:189-91. <http://amedeo.com/lit.php?id=12852372>
8. Wheat LJ, Connolly P, Haddad N, et al. Antigen clearance during treatment of disseminated histoplasmosis with itraconazole versus fluconazole in patients with AIDS. *Antimicrob Agents Chemother* 2002, 46:248-50. <http://amedeo.com/lit.php?id=11751146>

## Isosporiasis

*Isospora belli* is a ubiquitous intestinal parasite. While it is rare in Europe, it is a great problem in the developing world (especially in the tropics and subtropics). Similar to cryptosporidiosis, this microbe may cause epidemic-type outbreaks in immunocompetent hosts. Patients suffer (at least with mild) enteritis-like complaints, but sometimes also very severe watery diarrhea, abdominal pain, cramps and nausea. In immunocompromised patients, chronic diarrhea and malnutrition may occur (review in: Goodgame 1996). Chronic isosporiasis with diarrhea lasting for more than four weeks is AIDS-defining. Detection of the relatively large oocysts is possible via normal stool sampling for parasites, as well as in acid-fast stains. Blood tests usually reveal eosinophilia (Certad 2003). Treatment is cotrimoxazole (960 mg daily for one week). Ciprofloxacin is slightly less effective (Verdier 2000).

## References

1. Certad G, Arenas-Pinto A, Pocater L, et al. Isosporiasis in Venezuelan adults infected with human immunodeficiency virus: clinical characterization. *Am J Trop Med Hyg* 2003, 69:217-22. <http://amedeo.com/lit.php?id=13677379>
2. Goodgame RW. Understanding intestinal spore-forming protozoa: cryptosporidia, microsporidia, isospora, and cyclospora. *Ann Intern Med* 1996, 124:429-41. <http://amedeo.com/lit.php?id=8554253>
3. Verdier RI, Fitzgerald DW, Johnson WD Jr, Pape JW. Trimethoprim-sulfamethoxazole compared with ciprofloxacin for treatment and prophylaxis of *Isospora belli* and *Cyclospora cayetanensis* infection in HIV-infected patients. A randomized, controlled trial. *Ann Intern Med* 2000, 132:885-8. <http://amedeo.com/lit.php?id=10836915>

## Coccidioidomycosis

Infection with the mould *Coccidioides immitis* is endemic in the Southwestern USA (Up to date review: Galgiani 2005). It should be considered in patients who have been in such regions. Laboratory personnel should be informed even in suspected cases, as there is a high risk of infection.

After inhalation of spores, the primary manifestation is in the lung (Pappagianis 1993). Approximately 1-3 weeks after exposure, a pneumonia-like illness develops with fever, cough, chest pain and general malaise. The infection, although often symptomatic, usually resolves in immunocompetent patients without sequelae. Occasionally, there is residual cavitation. Disseminated coccidioidomycosis beyond the lung and hilar lymph nodes (for example chronic meningoencephalitis) occurs practically only in significantly immunocompromised patients with CD4+ T-cell counts of less than 250/ $\mu$ l (Ampel 2001). It is AIDS-defining. Prognosis was poor

in the pre-HAART era. In an analysis of 602 patients with disseminated coccidioidomycosis, mortality after one year was 63 % (Jones 1995).

Amphotericin as well as azoles are effective (Hernandez 1997), and should be combined if necessary (Ampel 2005). Detailed recommendations for the different situations (meningeal or disseminated cases must be treated more intensively) can be found in the publication Galgiani 2005. Fluconazole should be given as maintenance therapy at high doses (400 mg). In the past few years, it seems that the disease has become rarer as a result of HAART, and that maintenance therapy can be discontinued when CD4+ T-cells are greater than 250/μl with only initial pulmonary involvement. However, lifelong treatment is still recommended for cases of meningeal involvement (Woods 2000, Ampel 2001, Galgiani 2005).

## References

1. Ampel NM. Coccidioidomycosis among persons with HIV infection in the era of HAART. *Sem Respir Infect* 2001, 16:257-62. <http://amedeo.com/lit.php?id=11740827>
2. Hernandez JL, Echevarria S, Garcia-Valtuille A, Mazorra F, Salesa R. Atypical coccidioidomycosis in an AIDS patient successfully treated with fluconazole. *Eur J Clin Microbiol Infect Dis* 1997, 16:592-4. <http://amedeo.com/lit.php?id=9323471>
3. Jones JL, Fleming PL, Ciesielski CA, Hu DJ, Kaplan JE, Ward JW. Coccidioidomycosis among persons with AIDS in the United States. *J Infect Dis* 1995, 171:961-6. <http://amedeo.com/lit.php?id=7706825>
4. Pappagianis D. Coccidioidomycosis. *Semin Dermatol* 1993, 12:301-9. <http://amedeo.com/lit.php?id=8312146>
5. Woods CW, McRill C, Plikaytis BD, et al. Coccidioidomycosis in HIV-infected persons in Arizona, 1994-1997: incidence, risk factors, and prevention. *J Infect Dis* 2000, 181:1428-34. <http://amedeo.com/lit.php?id=10753734>

## Leishmaniasis (visceral)

*Leishmania donovani* is a protozoon that is transmitted by sand flies. According to WHO, there are 12 million people infected with leishmania types worldwide. 350 million live in risk areas. Every year, up to 2 million new infections occur, almost two thirds of these in the cutaneous form. In Southern Europe, visceral leishmaniasis (kala azar) is frequent in HIV patients. In Spain, the majority of patients with visceral leishmaniasis are now HIV-infected (Pintado 2001). Although there is much in favor of it, leishmaniasis is not an AIDS-defining illness.

A review of 15 cases in Germany showed that all HIV patients were significantly immunosuppressed (usually less than 100 CD4+ T-cells/μl). A few patients had not been in endemic areas for several years (Albrecht 1998). Bone marrow involvement is reflected by the almost obligatory pancytopenia, which may be particularly severe in HIV patients (Pintado 2001). Other symptoms include fever, hepatosplenomegaly and mucocutaneous lesions. The diagnosis is usually made from bone marrow aspirate.

Treatment of visceral leishmaniasis is problematic (review: Olliario 2005). Although pentavalent antimony compounds have been used for about 60 years (e.g. Pentostam™ and Glucantime™, 20 mg/kg i.v. or i.m. daily for 28 days), these drugs are extremely toxic. In a randomized study, amphotericin B and meglumin antimonate were equivalent, with remission rates of approximately two thirds each – however, in both arms there were severe side effects in almost half the patients,

with nephrotoxicity under amphotericin B, and cardiotoxicity and pancreatitis under meglumine antimonate (Laguna 1999). The German Association for Tropical Medicine recommends liposomal amphotericin B as the treatment of choice (2-5 mg/kg daily). Relapses are frequent and occur in almost half of all cases. HAART seems to change this – another argument for inclusion in the AIDS classification (de La Rosa 2002, Fernandez-Cotarelo 2003).

A very promising new drug – due to its good tolerability and efficacy, and whilst it is the only orally bioavailable leishmaniasis drug - is miltefosine (Impavido™), an alkylphosphocholine analog that was initially developed for oncology, but showed no efficacy there. Miltefosine was licensed in Germany in 2004, and in 2005, Zentis obtained the “orphan-drug” status from the European Health Authority. This means a 10-year exclusive right to marketing permission, less fees, and accelerated processing of the application for approval.

It is still unclear how miltefosine inhibits leishmania metabolism, but a Phase III study in India demonstrated it to be highly effective (Sundar 2002). It is administered at a dose of 100 mg daily (monthly cost: almost 2,300 Euro!). We have successfully treated two patients with miltefosine to date.

## References

1. Albrecht H, Sobottka I, Emminger C, et al. Visceral leishmaniasis emerging as an important opportunistic infection in HIV-infected persons living in areas nonendemic for *Leishmania donovani*. Arch Pathol Lab Med 1996, 120:189-98. <http://amedeo.com/lit.php?id=8712898>
2. Albrecht H. Leishmaniosis - new perspectives on an underappreciated opportunistic infection. AIDS 1998, 12:2225-6.
3. de La Rosa R, Pineda JA, Delgado J, et al. Incidence of and risk factors for symptomatic visceral leishmaniasis among HIV type 1-infected patients from Spain in the era of HAART. J Clin Microbiol 2002, 40:762-7. <http://amedeo.com/lit.php?id=11880390>
4. Fernandez-Cotarelo MJ, Abellan Martinez J, Guerra Vales JM, et al. Effect of highly active antiretroviral therapy on the incidence and clinical manifestations of visceral leishmaniasis in human immunodeficiency virus-infected patients. Clin Infect Dis 2003, 37: 973-7. <http://amedeo.com/lit.php?id=13130410>
5. Laguna F, Lopez-Velez R, Pulido F, et al. Treatment of visceral leishmaniasis in HIV-infected patients: a randomized trial comparing meglumine antimoniate with amphotericin B. AIDS 1999, 13:1063-9. <http://amedeo.com/lit.php?id=10397536>
6. Pintado V, Martin-Rabadan P, Rivera ML, Moreno S, Bouza E. Visceral leishmaniasis in HIV-infected and non-HIV-infected patients. A comparative study. Medicine (Baltimore) 2001, 80:54-73. <http://amedeo.com/lit.php?id=11204503>
7. Sundar S, Jha TK, Thakur CP, et al. Oral miltefosine for Indian visceral leishmaniasis. N Engl J Med 2002, 347:1739-46. <http://amedeo.com/lit.php?id=12456849>

## Microsporidiosis

Microsporidiosis is an important cause of diarrhea in HIV patients. Microsporidia are obligate intracellular protozoa. At least four genera that are pathogenic in humans have been described. Of these, *Enterocytozoon bienersi* is probably the most important.

Even in Germany, microsporidia were previously among the most frequent diarrhea-causing microbes, and in the pre-HAART era, could be found in approximately one third of all patients and in some studies in up to two thirds of all HIV patients with chronic diarrhea (Sobottka 1998). The incidence of microsporidiosis has reduced significantly due to HAART, and is now only diagnosed occasionally.

Microsporidiosis is not AIDS defining, although chronic microsporidiosis almost always occurs in severely immunocompromised patients with CD4+ T-cell counts of less than 50 cells/ $\mu$ l. Diarrhea may be very severe and is usually watery, though not bloody. It is accompanied by abdominal pain, nausea and vomiting. Fever is almost always absent. Rarely, myositis, keratoconjunctivitis and sinusitis have been described. Infections of the biliary ducts are more frequent.

Even more than in the case of cryptosporidia, it is essential that the laboratory is experienced with making the diagnosis. Microsporidia are very small, and those who have never seen them and are not explicitly asked to detect them will not find them! Culture has not generally been established. Direct detection is most successful with specialized staining methods. Special transport or preparation is not necessary. Albendazole (1-2 tbl. à 400 mg bid for 4 weeks) is quite effective, but certainly not in every case. In particular, *Enterocytozoon bieneusi* is frequently resistant to albendazole. There have been repeated positive reports in such cases, especially from France, of treatment with fumagillin (watch for thrombocytopenia!), but the case numbers remain low (Molina 2002).

Case reports (Bicart-See 2000) are also available for niazoxanide (see cryptosporidiosis). There have also been positive reports of symptomatic treatment with thalidomide. HAART-induced immune reconstitution, however, seems to have the greatest effect (Carr 1998+2002, Maggi 2000).

## References

1. Carr A, Cooper DA. Fumagillin for intestinal microsporidiosis. *N Engl J Med* 2002, 347:1381.
2. Carr A, Marriott D, Field A, Vasak E, Cooper DA. Treatment of HIV-1 associated microsporidiosis and cryptosporidiosis with combination antiretroviral therapy. *Lancet* 1998, 351:256-61. <http://amedeo.com/lit.php?id=9457096>
3. Leder K, Ryan N, Spelman D, Crowe SM. Microsporidial disease in HIV-infected patients: a report of 42 patients and review of the literature. *Scand J Infect Dis* 1998, 30:331-8. <http://amedeo.com/lit.php?id=9817510>
4. Maggi P, Larocca AM, Quarto M, et al. Effect of antiretroviral therapy on cryptosporidiosis and microsporidiosis in patients infected with HIV virus type 1. *Eur J Clin Microbiol Infect Dis* 2000, 19:213-7. <http://amedeo.com/lit.php?id=10795595>
5. Molina JM, Tournour M, Sarfati C, et al. Fumagillin treatment of intestinal microsporidiosis. *N Engl J Med* 2002, 346:1963-9. <http://amedeo.com/lit.php?id=12075057>
6. Sobottka I, Schwartz DA, Schottelius J, et al. Prevalence and clinical significance of intestinal microsporidiosis in HIV-infected patients with and without diarrhea in Germany: a prospective coprodiagnostic study. *Clin Infect Dis* 1998, 26:475-80. <http://amedeo.com/lit.php?id=9502473>

## Nocardia

*Nocardia* are aerobic bacteria or actinomycetes that occur worldwide. Several species exist, which mainly cause pneumonia as well as systemic disease. In a collection of 30 cases of HIV patients with nocardiosis, pulmonary manifestation occurred in 21 cases (Uttamchandani 1994). Pulmonary manifestation of nocardiosis is often confused with tuberculosis. Extrapulmonary manifestation may occur in the skin, brain, nerves, muscle and bone. The immune response to *Nocardia* is cellular. As a result, there is generally an increased risk of pulmonary or systemic disease in immunosuppressed patients. In HIV patients, however, opportunistic infections with *Nocardia* are rare. Patients are usually significantly immunocompromised (Javaly 1992, Uttamchandani 1994). *Nocardia* respond well to sulfonamides such as

sulfadiazine even in HIV patients (Pintado 2003). In cases of suspected nocardiosis, an experienced laboratory should be consulted.

## References

1. Javaly K, Horowitz HW, Wormser GP. Nocardiosis in patients with human immunodeficiency virus infection. Report of 2 cases and review of the literature. *Medicine (Baltimore)*. 1992, 71:128-38.
2. Pintado V, Gomez-Mampaso E, Cobo J, et al. Nocardial infection in patients infected with the HIV. *Clin Microbiol Infect* 2003, 9:716-20. <http://amedeo.com/lit.php?id=12925115>
3. Uttamchandani RB, Daikos GL, Reyes RR, et al. Nocardiosis in 30 patients with advanced HIV infection: clinical features and outcome. *Clin Infect Dis*. 1994, 18:348-53. <http://amedeo.com/lit.php?id=94281413>

## Penicillium marneffeii

Most fungi belonging to the *Penicillium* species are not pathogenic. One exception is *Penicillium marneffeii*, which is a problem mainly for HIV patients in Southeast Asia, China, Hong Kong and Taiwan (Cooper 2000). In these areas, it is the most frequent fungal infection in AIDS beside cryptococcosis, and is considered AIDS-defining by many clinicians (but is not included in the CDC classification). The clinical symptoms consist of prolonged high fever, lymphadenopathy, weight loss, malaise, cough and hemoptysis, diverse cutaneous and mucocutaneous lesions (reminiscent of molluscum contagiosum) and abnormal liver enzymes. There is often hepatosplenomegaly. Disseminated cases also occur (Ma 2005).

Amphotericin B and itraconazole are effective treatments (Sirisanthana 1998). Primary prophylaxis is not recommended even with longer stays in endemic areas (Chariyalertsak 2002). To prevent relapses, however, patients who have had the disease should take itraconazole as a permanent prophylaxis (Supparatpinyo 1998). The only patient we have seen with *Penicillium marneffeii* had spent several months on vacation in Thailand (Sobottka 1996). For HIV patients who have been to Southeast Asia, this possibility should at least be considered.

## References

1. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, et al. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced HIV infection in Thailand. *Clin Infect Dis* 2002, 34:277-84. <http://amedeo.com/lit.php?id=11740718>
2. Cooper CR Jr, Haycocks NG. *Penicillium marneffeii*: an insurgent species among the penicillia. *J Eukaryot Microbiol* 2000, 47:24-8. <http://amedeo.com/lit.php?id=9831676>
3. Sirisanthana T, Supparatpinyo K. Epidemiology and management of penicilliosis in HIV-infected patients. *Int J Infect Dis* 1998, 3:48-53. <http://amedeo.com/lit.php?id=9831676>
4. Sobottka I, Albrecht H, Mack D, et al. Systemic *Penicillium marneffeii* infection in a German AIDS patient. *Eur J Clin Microbiol Infect Dis* 1996, 15:256-9.
5. Supparatpinyo K, Perriens J, Nelson KE, Sirisanthana T. A controlled trial of itraconazole to prevent relapse of *Penicillium marneffeii* infection in patients infected with the HIV. *N Engl J Med* 1998, 339:1739-43. <http://amedeo.com/lit.php?id=9845708>

## Rhodococcus

*Rhodococcus equi* (previously *Corynebacterium equi*) is a sporeless, gram-positive intracellular pathogen, which is ubiquitous in air, water and soil. *R. equi* has been found on all continents, and was first identified as a pathogen in young horses. For

half a century, only veterinarians were interested in this microorganism, but in the last two decades, it has been found more and more frequently in humans, primarily in significantly immunocompromised patients. In these patients, it causes severe granulomatous or abscess forming pneumonia, and sometimes also disseminated infection. The coryneform bacteria seen in sputum cultures are often confused with normal diphtheroid flora found in the mouth and therefore not diagnosed.

In 1986, the first case in an AIDS patient was described (Samies 1986). In a collection of 78 cases, mostly AIDS patients with less than 50 CD4+ T-cells/ $\mu$ l were affected. The main symptoms were fever, dyspnea and unproductive cough (Capdevila 1997). Cavitation, mainly in the upper lobes, is frequently seen radiologically (Capdevila 1997, Marchiori 2005). Rhodococci are best detected in sputum and blood cultures (Torres-Tortosa 2003).

Erythromycin, ciprofloxacin, rifampin and vancomycin are effective, and some of these drugs can also be combined. However, treatment is difficult and complete recovery is rare (Plum 1997), so that surgical measures may also be necessary if there is extensive cavitation.

Prognosis is rather poor. The extent to which this will change as a result of HAART remains controversial (Sanz-Moreno 2002, Torres-Tortosa 2003).

## References

1. Capdevila JA, Bujan S, Gavalda J, Ferrer A, Pahissa A. Rhodococcus equi pneumonia in patients infected with the HIV. Report of 2 cases and review of the literature. Scand J Infect Dis 1997, 9:535-41. <http://amedeo.com/lit.php?id=9571730>
2. Plum G, Fätkenheuer G, Hartmann P, et al. Secondary prophylaxis of Rhodococcus equi pneumonia in HIV infection: breakthrough despite rifampicin/erythromycin suppressive therapy. Clin Microbiol Infect 1997, 3:141-143.
3. Samies JH, Hathaway BN, Echols RM, et al. Lung abscess due to Corynebacterium equi: report of the first case in a patient with AIDS. Am J Med 1986, 80:685-688. <http://amedeo.com/lit.php?id=3963045>
4. Sanz-Moreno J, Flores-Segovia J, Olmedilla-Arregui G, et al. Rhodococcus equi pneumonia: HAART helps but does not cure lung infection. AIDS 2002, 16:509-11.
5. Torres-Tortosa M, Arrizabalaga J, Villanueva JL, et al. Prognosis and clinical evaluation of infection caused by Rhodococcus equi in HIV-infected patients: a multicenter study of 67 cases. Chest 2003, 123:1970-6. <http://amedeo.com/lit.php?id=12796176>

## Trypanosoma cruzi

*Trypanosoma cruzi* is a protozoan that is transmitted via contaminated feces of triatomid bugs (assassin bugs), found almost exclusively on the American continent. It causes Chagas disease, one of the most frequent causes of cardiomyopathy in South America.

HIV patients are more frequently affected and have higher levels of parasitemia (Sartori 2002), probably due to the fact that the *Trypanosoma*-specific immune response is mainly cellular in nature. In addition, a more frequent occurrence in HIV-infected patients is meningoencephalitis, which is usually severe and radiologically not distinguishable from cerebral toxoplasmosis or primary cerebral lymphoma. In HIV patients from South America, *Trypanosoma* infection should therefore be considered in the differential diagnosis (Silva 1999). However, treatment (for example benznidazole) is rarely successful.

## References

1. Silva N, O'Bryan L, Medeiros E, et al. Trypanosoma cruzi meningoencephalitis in HIV-infected patients. *J AIDS Hum Retrovirol* 1999, 20:342-9. <http://amedeo.com/lit.php?id=10096578>
2. Sartori AM, Neto JE, Nunes EV, et al. Trypanosoma cruzi parasitemia in chronic Chagas disease: comparison between HIV-positive and HIV-negative patients. *J Infect Dis* 2002, 186:872-5. <http://amedeo.com/lit.php?id=12198628>



## 13. Kaposi's Sarcoma

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Kaposi's sarcoma (KS) is a malignant, multifocal systemic disease that originates from the vascular endothelium and has a variable clinical course. The most frequent manifestation of the disease is skin lesions, but mucous membranes, the lymphatic system and viscera – in particular the lung and gastrointestinal tract – can be involved. Four clinical forms are described: classic KS, KS secondary to immunosuppression; endemic African KS; and the epidemic HIV-associated KS.

All types of KS are due to infection with human herpes virus-8 (HHV-8), which is transmitted sexually or via blood or saliva. Months before manifestation of the tumors, HHV-8 viremia leads to development of specific antibodies. A cutaneous eruption was described in association with HHV-8 seroconversion (Andreoni 2002).

In HIV-infected patients, KS is an AIDS-defining illness. Aggressive courses of disease, with lethal outcomes, have been observed in HIV patients with severe and untreated immunodeficiency. In such cases, the average survival time following diagnosis is less than one year. Since the introduction of HAART in 1996, the frequency of KS in HIV-infected patients has decreased sharply (by as much as 90% in the Department of Dermatovenereology at Frankfurt University Hospital), and the clinical course of disease has improved significantly. In many cases, stabilization or complete remission of tumors is possible with immune reconstitution and reduction of the HIV viral load. Of the available therapies, HAART is first line treatment. It can be used in combination with local treatments such as cryotherapy, retinoids, and radiation. Therapy with interferon-alpha, paclitaxel or chemotherapy with liposomal anthracyclines is only necessary if there is visceral progression of the disease whilst on HAART.

### Signs, symptoms and diagnosis

In contrast to the classical KS found in older men, in whom the tumors usually occur on the lower legs and feet, HIV-associated KS does not have a preferential pattern of localization. It can begin on any area of the skin, but may also appear on oral, genital, or ocular mucous membranes. Typical findings are initially solitary, or a few asymptomatic purple macules or nodules, which have a predilection for distribution along relaxed skin tension lines. Disease progression is variable: the macules or tumors can remain unchanged for months to years, or grow rapidly within a few weeks and disseminate. Rapid growth can lead to localized pain and a yellow-green discoloration of the area around the tumor as a result of hemorrhage. Further progression of the tumor can lead to central necrosis and ulceration. The tumors may bleed easily. Plaque-like and nodular KS lesions, often become confluent and can be accompanied by massive edema. In the oral cavity, the hard palate is frequently affected. Lesions begin with purplish erythema and progress to plaques and nodules that ulcerate easily. KS lesions may also involve the external genitalia including the foreskin and glans penis.

The **diagnosis of KS** in the skin and mucous membranes can usually be made based on the following clinical features:

1. Purple macules or nodules
2. Distribution along skin tension lines
3. Green-yellow discoloration around the tumors corresponding to hemorrhage
4. Surrounding edema
5. Dissemination of lesions, possibly with mucocutaneous involvement

This is particularly characteristic for patients in whom HIV infection or another form of immunodeficiency is known. If there is clinical doubt, the lesions should be biopsied to confirm the diagnosis histologically. The clinical presentation may pose a challenge, especially with the telangiectatic, ecchymotic, keloidal and hyperkeratotic variants.

The important features of KS on routine histology include:

1. Epidermis is usually intact.
2. Slit-like spaces formed by new, thin-walled and partly aberrant blood vessels running alongside normal dermal vessels and adnexal structures.
3. Extravasated erythrocytes around the new vessels.
4. Hemosiderin deposits.
5. Lymphocytic inflammatory infiltrate.
6. An infiltrate of oval- or spindle-shaped cells (spindle cell KS).

When KS resolves, either spontaneously or following therapy, it often leaves gray-brown to light brown hyperpigmentation for months to years (post-inflammatory hyperpigmentation), caused by hemosiderin deposits from extravasated erythrocytes. The accompanying lymphedema can also persist for a similar length of time, particularly on the lower legs.

HHV-8, which contributes to the development of the tumor, can be detected in tumor tissue by PCR. This can be a helpful diagnostic tool in cases where the histopathological diagnosis of Kaposi's sarcoma is uncertain. HHV-8 antibodies are often detected months before the clinical manifestation of the tumor. Neutralizing antibodies seem to control the HHV-8 infection and thus protect against the clinical manifestation of Kaposi's sarcoma (Kimball 2004). In patients with Kaposi's sarcoma the titres of neutralizing antibodies are low. The HIV tat-protein is able to promote the HHV-8 transmission directly, which could be an explanation for the high rate of KS in patients coinfecting with HHV-8 and HIV (Aoki 2004, Chandra 2003). Epidemiological studies have shown that a high regional incidence of KS (e.g. in Southern Italy, as well as in Central Africa) correlates with an increased regional HHV-8 seroprevalence. HHV-8 seems to mainly be transmitted sexually. The KS frequently seen in African children is presumably transmitted via saliva (Pauk et al. 2000). A saliva reservoir of HHV-8 was also found in adult HIV patients (Triantos 2004).

On initial diagnosis of KS, the following investigations help to stage the disease:

1. Complete cutaneous inspection of the patient (including oral and genital mucous membranes)
2. Lymph node ultrasound
3. Abdominal ultrasound
4. Upper GI endoscopy (optional, but always required with mucocutaneous tumors)
5. Lower GI endoscopy (optional, but always required with mucocutaneous tumors)
6. Chest radiography
7. Determination of CD4+ T-cell count and HIV viral load (is initiation or optimization of antiretroviral therapy necessary?)

## Prognosis and staging

HIV-associated KS ranges from indolent skin lesions to aggressive, disseminated disease with lymph node and visceral involvement. Left untreated, rapid tumor growth can lead to death of the patient within weeks. Malignant clonal tumor growth has been shown to occur in pulmonary KS. The introduction of HAART has significantly improved the prognosis for patients with KS. Patients with extensive visceral involvement often achieve complete remission.

Table 1. Staging of HIV-associated epidemic KS (from ACTG, Krown 1997)

Early stage	Late stage
<p>If <b>all</b> the following criteria are met:</p> <p>1. Tumor (T): 0 KS limited to skin and/or lymph nodes; minimal oral disease (non-nodular KS confined to hard palate)</p> <p>2. Immune system* (I): 0 CD4+ T-cells &gt; 200/μl</p> <p>3. Systemic illness (S): 0 No history of OI or thrush, no B symptoms* of HIV infection</p>	<p>If <b>one</b> of the following applies:</p> <p>1. Tumor (T): 1 Pulmonary or gastrointestinal KS; extensive oral KS; tumor-associated edema or ulceration</p> <p>2. Immune system* (I): 1 CD4+ T-cells &lt; 200/μl</p> <p>3. Systemic illness (S): 1 History of opportunistic infections, thrush, malignant lymphoma or HIV-associated neurological disease, B** symptoms of HIV infection</p>

\*CD4 cell count is not of any prognostic relevance in KS patients on HAART (Nasti 2003)

\*\* unexplained fever, night sweats or diarrhea persisting for more than two weeks, involuntary weight loss of >10%

The classification system for HIV-associated KS, published in 1993 and reviewed in 1997 by the AIDS Clinical Trials Group (ACTG, Krown 1997, table 1), was adapted by an Italian working group to address KS in the HAART era. However, the changes proposed by Nasti et al (2003) have not yet been validated and accepted on an international level. Of particular concern is the suggested omission of the

CD4+ T-cell count as a prognostic factor, which results in the classification of KS patients into those with a good (T0S0, T1S0, T0S1) and those with a bad prognosis (T1S1).

## Treatment

If KS is diagnosed in HIV-infected patients who have not yet been treated, or who are no longer being treated with antiretroviral drugs, it is essential to start HAART (see HAART chapter). If the HIV viral load can be reduced (ideally below the level of detection) and immune reconstitution is achieved with an increase in the CD4 T cell count, KS stabilizes or even resolves completely in many patients. The clinical observation that KS may resolve under HAART with protease inhibitors, even in the absence of a significant improvement in the immunological status, has been confirmed with the discovery of the direct anti-proliferative effects of the PIs indinavir and saquinavir (Sgadari 2002). The PI ritonavir has also been shown to have a direct anti-tumor effect (Pati 2002). In addition, the following treatment methods are available depending on the clinical stage of KS (table 1):

- Early stage (ACTG): Local treatment (see below). With progression: primary treatment with interferon- $\alpha$  combined with HAART; secondary treatment with liposomal anthracyclines.
- Late stage (ACTG): Primary treatment for stage T 0, I 0, S 1 with interferon- $\alpha$  in combination with HAART. Otherwise liposomal anthracyclines are the first choice for treatment. Should they fail, paclitaxel or combination chemotherapy (ABV regimen) can be used.

## Local therapy

Local therapy has the advantages of being (1) provided in the ambulatory care setting, (2) well-tolerated, and (3) less costly than in-patient therapy. The following methods are used depending on the size and location of tumors: cryosurgery, vinca alkaloids, intralesional bleomycin or intralesional interferons, soft x-ray radiation, electron beam therapy, cobalt radiation (fractionated), retinoids: 9-cis-retinoic acid, alitretinoin (Bodsworth 2001, Duvic 2000), and cosmetic camouflage. In addition to intralesional vinblastine, tumors of the buccal mucosa can be injected with 3 % sodium tetradecyl sulphate (which has comparable efficacy rates) (Ramirez-Amador 2002).

As Kaposi's sarcoma is a multifocal systemic disease, surgical treatment is limited to excisional biopsies for diagnosis and palliative removal of small tumors in cosmetically disturbing areas. Since tumors often extend further into the surroundings than is clinically visible and local trauma can lead to new tumors (Koebner phenomenon), local and regional recurrences can be expected. These can be prevented by radiation therapy: in order to reach the tumor cells spreading along the vascular channels, the field of radiation should be extended 0.5-1.0 cm beyond the edges of the tumor. KS is a strikingly radiosensitive tumor. Superficial macular or plaque-like KS lesions respond well to daily doses of 4-5 Gy (total dose 20-30 Gy, fractionated 3x/week) of soft x-ray radiation. To palliate fast growing tumors, a single dose of 8 Gy is recommended (Harrison 1998). For the treatment of extensive KS with edematous swelling and/or lymph node involvement, soft x-ray radiation,

originating from 50-kV beryllium-windowed units, as used in dermatology, is not sufficient. Such tumors should be treated with electron beam therapy with conventional fractionation (5x2 Gy per week) to a target volume total dose of 40 Gy.

Local chemo- and immunotherapy have the advantage of less or no systemic side effects compared to systemic treatments. Within the tumor, high concentrations of drugs with direct antiproliferative efficacy can be reached.

## Chemotherapy

Chemotherapy harbors particular risks for HIV-infected patients. Bone marrow suppression, induced by chemotherapy, can lead to deterioration of existing, HIV-associated cellular immunodeficiency and occurrence of acute, life-threatening opportunistic infections. To maintain a high quality of life for the patient for as long as possible, HIV-associated KS should only be treated by chemotherapy in the presence of clinical symptoms (e.g. pain), rapid tumor progression and/or visceral involvement. In such cases, even patients with a good immune status should receive PCP and toxoplasmosis prophylaxis with cotrimoxazole (480 mg/day or 960 mg 3x/week). The myelotoxic effects of chemotherapeutic drugs on a hematopoietic system that has already been impaired by HIV infection may require further treatment with erythropoietin or blood transfusions.

The chemotherapeutics that achieve the highest remission rates for KS are liposomal anthracyclines. Treatment with intravenous pegylated liposomal doxorubicin at a dose of 20 mg/m<sup>2</sup> body surface area every 2-3 weeks leads to partial remission in up to 80 % of treated patients. Treatment with intravenous liposomal daunorubicin 40 mg/m<sup>2</sup> body surface area every 2 weeks has slightly lower remission rates (Krown 2004, Rosenthal 2002, Osoba 2001, Cheung 1999).

In comparative studies, liposomal daunorubicin showed the same and doxorubicin a higher efficiency than the previous gold standard of KS treatment, which consisted of combination therapy with adriamycin, bleomycin and vincristine (ABV regimen). In a comparative study on patients with moderate to advanced KS, the combination of pegylated liposomal doxorubicin with HAART was substantially more effective than HAART alone (response rate 76 % versus 20 %) (Martin-Carbonero 2004). The most important side effects of anthracyclines are neutropenia and anemia. This usually occurs after 8-10 cycles. The cardiotoxicity associated with anthracyclines should also be considered. However, usually it only occurs with long-term administration (cumulative doses of 450 mg doxorubicin and higher). Macular and painful erythema of the palms and soles (palmoplantar erythrodysesthesia) is another notable side effect which can limit treatment.

Paclitaxel is also a very effective drug for the treatment of KS (Tulpule 2002). The recommended dose is 100 mg/m<sup>2</sup> body surface area administered intravenously over 3-4 hours every 2 weeks. Partial remission is achieved in up to 60 % of all treated patients. Paclitaxel is myelotoxic and almost always leads to alopecia, often after just one dose. Whether paclitaxel has important interactions with HAART drugs (increase of paclitaxel toxicity?) is still under investigation (Bundow 2004). For this reason, patients on HAART and paclitaxel need very careful monitoring. Paclitaxel acts by disrupting the structural reorganization of intracellular microtubuli. This leads to mitotic arrest and programmed cell death (apoptosis) (Bla-

gosklonny 2002). Paclitaxel can also be used successfully in those patients with tumor progression under anthracycline therapy.

Docitaxel (taxotere) seems to be an interesting alternative from the taxane group. It is FDA approved for the treatment of breast cancer, but very recently a phase II clinical trial showed that taxotere is effective and safe for the treatment of KS (Lim 2005). Relapses (following anthracycline or paclitaxel therapy) may also be treated with low dose oral etoposide (Evans 2002).

Table 2: Treatment recommendations for systemic therapy of Kaposi's sarcoma (evaluation of individual drugs in text)

Therapeutic agent	Dose	Requirement	Remission rate	Side effects
IFN- $\alpha$ (2a,b)	1-3 mil. I.U. sc daily until remission, followed by 3 x weekly	>200 CD4+ T-cells/ $\mu$ l Endogenous IFN- $\alpha$ < 3 U/ml, HAART	Approx. 40%	Fever, myalgia, depression
Pegylated IFN- $\alpha$ 2b*	50 $\mu$ g sc 1 x weekly	As for IFN- $\alpha$ (2a,b)	?	As for IFN- $\alpha$ (2a,b)
Liposomal Doxorubicin	20 mg/m <sup>2</sup> iv at biweekly intervals	KS stage T1, S0-1 (see Table 1, staging of KS)	Approx. 80%	Neutropenia, anemia Rarely: Flushing, dyspnea, back pain, palmo-plantar erythrodysesthesia
Liposomal Daunorubicin	40 mg/m <sup>2</sup> iv at biweekly intervals	T1, S0-1 (see Table 1, staging of KS)	Approx. 60%	Neutropenia, anemia Rarely: Flushing, dyspnea, back pain, palmo-plantar erythrodysesthesia
Paclitaxel	100 mg/m <sup>2</sup> iv at biweekly intervals	T1, S0-1 (see Table 1, staging of KS)	Approx. 60%	Neutropenia, thrombocytopenia, anemia, alopecia Rarely: Hypotension, ECG-changes

\*Pegylated IFN- $\alpha$  2b has only been licensed for treatment of chronic hepatitis C

## Immunotherapy

Interferons (IFN- $\alpha$  2a, IFN- $\alpha$  2b, IFN- $\beta$ ) are used successfully for classic, as well as sporadic and HIV-associated, epidemic Kaposi's sarcoma. Remission rates of 45-70% can be achieved. In addition to their well-known immunomodulatory activity, interferons induce apoptosis in tumor cells and lead to reduced  $\beta$ -FGF expression by inhibiting angiogenesis and therefore proliferation.

There are currently no standardized treatment regimens. In principle, high and low dose therapies can be distinguished. However, due to the considerable side effects, a high dose treatment (up to 30 million IU/day) is not commonly administered. Daily doses of 3-6 million IU sc are usually given. After remission (tumor growth stopped, tumors flattened, loss of purple color, change to brownish color), interferon dosing can be reduced to 3x/week. Complete remission can, at the earliest, be expected after 6-8 weeks of treatment (often significantly later). An initial study showed that interferon doses can be reduced even further when given with HAART, thereby decreasing interferon side effects (Krown 2002). Depression with suicidal tendencies does not seem to be a dose-related side effect of interferons.

There is almost no data on the use of the new, pegylated IFN- $\alpha$  2b for KS. It is depolymerized to IFN- $\alpha$  2b, the active substance, following subcutaneous application. It has been used successfully for the treatment of classical Kaposi's sarcoma (Thomas-Greber 2002) in a dose of 50 $\mu$ g/week subcutaneously. Whether higher doses or shorter treatment intervals are necessary for HIV-associated KS still remains to be investigated. Such studies have become more difficult to perform as a result of the significant decrease in both the incidence and prevalence of KS since the introduction of HAART. In principle, this new formulation should lead to a further improvement in the efficacy of interferon.

The efficacy of interferon treatment is dependent on the cellular immune status of the patient. In patients with more than 400 CD4+ T-cells/ $\mu$ l, remission rates are > 45%; with less than 200 CD4+ T-cells/ $\mu$ l they stand at only 7 %. The endogenous interferon levels are important prognostic indicators and are significantly elevated in the advanced stages of HIV infection which leads to reduced responses to exogenous interferon. The criteria for treatment with interferon in epidemic KS therefore include an early stage of HIV disease (CD4+ T-cells > 200/ $\mu$ l) and endogenous interferon levels < 3 U/ml. In the late stage of HIV disease, interferons should only be given in combination with an efficient HAART regimen. IFN- $\gamma$  leads to tumor progression and is contraindicated.

## Monitoring and follow-up care

In cases with isolated cutaneous and slowly progressive KS, HIV disease and HAART usually determine the necessary intervals for monitoring. However, even with a functional cellular immunity (CD4+ T-cells > 400/ $\mu$ l) and low viral load, tumor progression may be rapid with organ involvement in individual cases. Clinical examination of the skin, mucous membranes and lymph nodes is recommended at three-month intervals. The lungs and gastrointestinal tract should be monitored at 6-12 month intervals with appropriate diagnostic testing if indicated. However, evi-

dence-based data that tumor follow-up leads to improvement in the remission rates as a result of close monitoring is not yet available for Kaposi's sarcoma.

## References

1. Aoki Y, Tosato G. HIV-1 Tat enhances KSHV infectivity. *Blood*. 2004, 104: 810-4.
2. Andreoni M, Sarmati L, Nicastri E, et al. Primary human herpes virus 8 infection in immunocompetent children. *JAMA* 2002, 287:1295-300. <http://amedeo.com/lit.php?id=11886321>
3. Blagosklonny MV, Robey R, Sheikh MS, Fojo T. Paclitaxel-induced FasL-independent apoptosis and slow (non-apoptotic) cell death. *Cancer Biol Ther* 2002, 1:113-7. <http://amedeo.com/lit.php?id=12170770>
4. Bodsworth NJ, Bloch M, Bower M, Donnell D, Yocum R; International Panretin Gel KS Study Group. Phase III vehicle-controlled, multi-centered study of topical alitretinoin gel 0.1% in cutaneous AIDS-related Kaposi's sarcoma. *Am J Clin Dermatol*. 2001;2:77-87.
5. Bower M, Fox P, Fife K, Gill J, Nelson M, Gazzard B. HAART prolongs time to treatment failure in Kaposi's sarcoma. *AIDS* 1999, 13: 2105-2111. <http://amedeo.com/lit.php?id=10546864>
6. Bundow D, Aboulafia DM. Potential drug interaction with paclitaxel and highly active antiretroviral therapy in two patients with AIDS-associated Kaposi sarcoma. *Am J Clin Oncol*. 2004;27:81-4.
7. Chandra A, Demirhan I, Massambu C, Pyakurel P, Kaaya E et al. Cross-talk between human herpes virus 8 and the transactivator protein in the pathogenesis of Kaposi's sarcoma in HIV-infected patients. *Anticancer Res* 2003, 23:72-728.
8. Cheuk W, Wong KO, Wong CS, Dinkel JE, Ben-Dor D, Chan JK. Immunostaining for human herpes virus 8 latent nuclear antigen-1 helps distinguish Kaposi sarcoma from its mimickers. *Am J Clin Pathol*. 2004 , 121:335-42.
9. Cheung TW, Remick SC, Azarnia N, Proper JA, Barrueco JR, Dezube BJ. AIDS-related Kaposi's sarcoma: a phase II study of liposomal doxorubicin. The TLC D-99 Study Group. *Clin Cancer Res*. 1999;5:3432-7.
10. Dupont C, Vasseur E, Beauchet A, et al. Long-term efficacy on Kaposi's sarcoma of highly active antiretroviral therapy in a cohort of HIV-positive patients. *AIDS* 2000, 14:987-993. <http://amedeo.com/lit.php?id=10853980>
11. Duvic M, Friedman-Kien AE, Looney DJ, Miles SA, Myskowski PL, Scadden DT, Von Roenn J, Galpin JE, Groopman J, Loewen G, Stevens V, Truglia JA, Yocum RC. Topical treatment of cutaneous lesions of acquired immunodeficiency syndrome-related Kaposi sarcoma using alitretinoin gel: results of phase 1 and 2 trials. *Arch Dermatol*. 2000;136:1461-9.
12. Evans SR, Krown SE, Testa MA, Cooley TP, Von Roenn JH. Phase II evaluation of low-dose oral etoposide for the treatment of relapsed or progressive AIDS-related Kaposi's sarcoma: an AIDS Clinical Trials Group clinical study. *J Clin Oncol* 2002, 20:3236-41. <http://amedeo.com/lit.php?id=12149296>
13. Harrison M, Harrington KJ, Tomlinson DR, Stewart JS. Response and cosmetic outcome of two fractionation regimens for AIDS-related Kaposi's sarcoma. *Radiother Oncol*. 1998;46:23-8.
14. Kimball LE, Casper C, Koelle DM, Morrow R, Corey L, Vieira J. Reduced levels of neutralizing antibodies to kaposi sarcoma-associated herpesvirus in persons with a history of kaposi sarcoma. *J Infect Dis*. 2004, 189:2016-22.
15. Krown SE, Testa MA, Huang J. AIDS-related Kaposi's sarcoma prospective validation of the AIDS Clinical Trials Group staging classification. *J Clin Oncol* 1997, 15: 3085-92. <http://amedeo.com/lit.php?id=9294471>
16. Krown SE, Li P, Von Roenn JH, Paredes J, Huang J, Testa MA. Efficacy of low-dose interferon with antiretroviral therapy in Kaposi's sarcoma: a randomized phase II AIDS clinical trials group study. *J Interferon Cytokine Res* 2002, 22:295-303. <http://amedeo.com/lit.php?id=12034036>
17. Krown SE, Northfelt DW, Osoba D, Stewart JS. Use of liposomal anthracyclines in Kaposi's sarcoma. *Semin Oncol* 2004, 6, Suppl 13:36-52.
18. Lim ST, Tupule A, Espina BM, Levine AM. Weekly docetaxel is safe and effective in the treatment of advanced-stage acquired immunodeficiency syndrome-related Kaposi sarcoma. *Cancer* 2005, 103:417-21.
19. Lospalluti M, Mastrolonardo M, Loconsole F, Conte A, Rantuccio F. Classical Kaposi's sarcoma: a survey of 163 cases observed in Bari, South Italy. *Dermatology* 1995, 191:104-8. <http://amedeo.com/lit.php?id=8520054>
20. Martin-Carbonero L, Barrios A, Saballs P, et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. *AIDS* 2004, 18:1737-40.



21. Nasti G, Talamini R, Antinori A, Martellotta F et al. AIDS-related Kaposi's Sarcoma: evaluation of potential new prognostic factors and assessment of the AIDS Clinical Trial Group Staging System in the Haart Era. *J Clin Oncol*. 2003;21:2876-82.
22. Osoba D, Northfelt DW, Budd DW, Himmelberger D. Effect of treatment on health-related quality of life in AIDS-related Kaposi's sarcoma: a randomized trial of pegylated-liposomal doxorubicin versus doxorubicin, bleomycin, and vincristine. *Cancer Invest*. 2001;19:573-80.
23. Pati S, Pelsler CB, Dufraigne J, Bryant JL, Reitz MS Jr, Weichold FF. Antitumorigenic effects of HIV protease inhibitor ritonavir: inhibition of Kaposi sarcoma. *Blood* 2002, 99:3771-9. <http://amedeo.com/lit.php?id=11986235>
24. Pauk J, Huang ML, Brodie SJ, et al. Mucosal shedding of human herpesvirus 8 in men. *N Engl J Med*. 2000, 343:1369-77. <http://amedeo.com/lit.php?id=11070101>
25. Schöfer H. Kaposi-Sarkom. *Hautarzt* 1998, 48 Suppl 1:S39-45.
26. Sgadari C, Barillari G, Toschi E, et al. HIV protease inhibitors are potent anti-angiogenic molecules and promote regression of Kaposi sarcoma. *Nat Med* 2002, 8:225-32. <http://amedeo.com/lit.php?id=11875492>
27. Ramirez-Amador V, Esquivel-Pedraza L, Lozada-Nur F, et al. Intralesional vinblastine vs. 3% sodium tetradecyl sulfate for the treatment of oral Kaposi's sarcoma. A double blind, randomized clinical trial. *Oral Oncol* 2002, 38:460-7. <http://amedeo.com/lit.php?id=12110340>
28. Rosenthal E, Poizot-Martin I, Saint-Marc T, Spano JP, Cacoub P; DNX Study Group. Phase IV study of liposomal daunorubicine in AIDS-related Kaposi sarcoma. *Am J Clin Oncol*. 2002;25:57-9.
29. Schwartz RA (2004) Kaposi's sarcoma: an update. *J Surg Oncol* 87:146-51.
30. Tappero JW, Conant MA, Wolfe SF, et al. Kaposi's sarcoma: epidemiology, pathogenesis, histology, clinical spectrum, staging criteria and therapy. *J Am Acad Dermatol* 1993, 28: 371-95. <http://amedeo.com/lit.php?id=8445054>
31. Thoma-Greber E, Sander CA, Messer G, Röcken M. Pegyliertes Interferon- $\alpha$ 2b: Neue Therapie bei klassischem Kaposi-Sarkom. *Diaklinik Münchner Fortbildungswoche für Dermatologen* 2002, 52-4.
32. Triantos D, Horefti E, Paximadi E, et al. Presence of human herpes virus-8 in saliva and non-lesional oral mucosa in HIV-infected and oncologic immunocompromised patients. *Oral Microbiol Immunol*. 2004;19:201-4.
33. Tulpule A, Groopman J, Saville MW, et al. Multicenter trial of low-dose paclitaxel in patients with advanced AIDS-related Kaposi sarcoma. *Cancer* 2002, 95:147-54. <http://amedeo.com/lit.php?id=12115328>
34. Whitby D, Howard MR, Tenant-Flowers M, et al. Detection of Kaposi sarcoma associated herpesvirus in peripheral blood of HIV-infected individuals and progression to Kaposi's sarcoma. *Lancet* 1995, 346: 799-802. <http://amedeo.com/lit.php?id=7674745>
35. Yarchoan R. Therapy for Kaposi's sarcoma: recent advances and experimental approaches. *J Acquir Immune Defic Syndr* 1999, 21 Suppl 1: S66-73. <http://amedeo.com/lit.php?id=10430221>



## 14. Malignant Lymphomas

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Malignant lymphomas are neoplastic diseases of the lymphatic system that grow rapidly and aggressively, and lead to death within a few weeks or months if left untreated. Hodgkin's disease (HD) is distinguished from the large group of non-Hodgkin's lymphomas (NHL). In comparison to the normal population, HIV patients are affected significantly more frequently by all types of lymphoma (see Table 1). However, aggressive non-Hodgkin's lymphomas of B-cell origin are particularly frequent. The influence of HAART on the incidence of lymphomas is still the subject of controversy. In 2001, several studies indicated that a regression, if any, was by far not as impressive as with Kaposi's sarcoma or most opportunistic infections (Clarke 2001, Little 2001). In a more recent interim analysis (Kirk 2001), however, a moderate regression was demonstrated. This was shown to be particularly true for all the subtypes that mainly occur in severe immunodeficiency (see below). But, in comparison to other malignancies and opportunistic infections, the regression is much smaller, so that the relative proportion of AIDS-associated illnesses that are lymphomas is increasing. In some HIV cohorts, malignant lymphomas have already overtaken Kaposi's sarcoma as the most frequent malignancy. In the EuroSIDA study, the proportion of AIDS-defined illnesses that were malignant lymphomas increased from less than 4 % in 1994 to 16 % in 1998 (Mocroft 2000). In France, lymphomas accounted for 11 % of all deaths in HIV patients in 2000 (Bonnet 2004). In addition, in the HAART era, HIV patients are living much longer, so that the general risk of lymphoma is rising anyway (Stebbing 2004). Therefore, malignant lymphomas will be a significant morbidity and mortality factor in HIV patients in the future.

Table 1. Relative risk of different lymphomas in HIV patients in comparison to the normal population (adapted from Goedert 2000)

Malignant NHL total	165
High-grade malignancy NHL	348
Immunoblastic NHL	652
Burkitt's NHL	261
Not classifiable	580
Primary CNS lymphoma (PCNSL)	> 1,000
Low-grade malignancy NHL	14
Plasmocytoma	5
Hodgkin's disease	8

Malignant lymphomas in HIV-infected patients are also biologically very heterogeneous and differ in several aspects. For example, the association with EBV and other oncogenic viruses such as HHV-8 or SV40 is very variable. The extent of immunodeficiency also varies significantly. Burkitt's lymphoma and Hodgkin's disease

frequently occur even when the immune status is good. In contrast, immunoblastic and especially primary CNS lymphoma (PCNSL) are almost always associated with severe immunodeficiency. The frequency and extent of oncogenic mutations or cytokine dysregulation differ, as does the histogenetic origin of the malignant cells (Porcu 2000).

However, HIV-associated lymphomas – both NHL and HD – have numerous common clinical features. Characteristics include the usually aggressive growth, diagnosis in the advanced stages with frequent extranodal manifestations, poorer response to treatment, high relapse rates and an overall poor prognosis (Levine 2000).

Even in the HAART era, the treatment of malignant lymphoma remains problematic. Although aggressive chemotherapy is possible in many patients with existing immunodeficiency, it is complicated and requires a close cooperation between HIV clinicians and physicians with experience in hematology/oncology.

The following discusses systemic NHL, PCNSL and Hodgkin's lymphoma separately. Multicentric Castleman's disease will also be mentioned as a distinct entity, although it is not considered a malignant lymphoma. Low-grade (indolent) NHLs are very rare in HIV patients, and will therefore not be discussed here. As there are no data or even recommendations available, the treatment of such cases in the HAART era should follow the recommendations for HIV-negative patients.

## Systemic non-Hodgkin lymphomas (NHL)

A close association between systemic NHL and AIDS has been described for a long time – the first cases were published only about a year after the first description of AIDS and even before the discovery of HIV (Ziegler 1982). High-grade B-NHLs have been AIDS-defining since 1985.

90 % of HIV-associated NHLs are of B-cell origin. They are almost always of high-grade malignancy. Two main histological types dominate: according to the WHO classification these are Burkitt's lymphomas, which comprise 30-40 % of cases, and diffuse large-cell B cell lymphomas, comprising 40-60 %. However, a relatively large proportion of HIV-associated lymphomas (up to 30 %) cannot be classified even by reference laboratories. A small proportion of NHLs (1-3 %) are primary effusion or body cavity-based lymphomas and are considered as a distinct entity (see below).

The prognosis of patients with NHL was poor in the pre-HAART era, being between 6 and 9 months (Levine 2000). Since the advent of HAART, this seems to be changing. Whether the clinical and pathological spectrum of NHL is also changing, is still unclear.

## Signs and symptoms

The main symptom is lymph node enlargement. Lymphomas are firm, immobile or barely mobile and painless. A large proportion of patients have advanced-stage lymphoma at the time of diagnosis. Ann Arbor stages III-IV are almost always the rule, and B symptoms with fever, night sweats and/or weight loss are found in the majority of cases (60-80 %). General asthenia, significant malaise and rapid physical deterioration are also frequently seen. Extranodal involvement is common, and

may be to a grotesque extent. In our own cohort of 203 patients, 81 % had at least one extranodal focus (Hoffmann 2003). Whether the orbital cavity, testes, heart, breasts, bladder, kidneys, muscles, or bones – every conceivable region can be affected. However, the gastrointestinal tract, liver, and bone marrow are affected particularly frequently. Secondary CNS involvement can also occur. With extranodal disease, additional symptoms arise depending on the localization. These include, for example, abdominal pain from hepatosplenomegaly, hemorrhage or ileus symptoms due to intestinal involvement, bone pain with skeletal infiltration, or headache caused by brain disease.

## Diagnosis

Rapid histological diagnosis is important. If bone marrow biopsy cannot secure the diagnosis, a lymph node (e.g. cervical, axillary or inguinal) should be extirpated. Mere puncture biopsy of a lymph node is often not sufficient to secure a representative specimen. It is important to send the material to a specialized pathology laboratory with extensive experience in lymph node morphology. The basic pathological diagnosis should include information about the subtype (Burkitt?), the proliferation rate and the expression profile (definitely: CD20, and desirably: CD10, CD138, MUM-1) as these can influence the therapeutic consequences (see below).

All patients with suspected NHL should be staged according to the Ann-Arbor classification (Tables 2a, b).

Table 2a. Staging according to the updated Ann-Arbor classification

I	Involvement of a single lymph node region (I) or involvement of a single extralymphatic organ or site (IE)
II	Involvement of 2 or more lymph node regions on the same side of the diaphragm (II) or localized involvement of an extralymphatic organ or site plus its regional lymph nodes, with or without involvement of other lymph node regions on the same side of the diaphragm (IIE)
III	Involvement of lymph nodes regions on both sides of the diaphragm (III), can be accompanied by localized extralymphatic organ involvement (IIIE) or spleen involvement (IIIS) or both (IIIE+S)
IV	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement; or isolated involvement of an extralymphatic organ with involvement of distal (non-regional) lymph nodes.

Table 2b. Every stage is divided into categories A and B

A	Asymptomatic
B	General symptoms: a) unexplained weight loss of more than 10 % in the last six months, and/or b) unexplained persistent or recurring fever with temperatures above 38 °C, and/or c) drenching night sweats

Basic diagnostic tests for staging include chest radiography, abdominal ultrasound, bone marrow biopsy (aspiration alone is not enough!) and CT scans of the neck, thorax and abdomen. In addition to an updated immune status and viral load, the following should be determined at the very least: blood count, ESR, CRP, uric acid,

LDH, liver and kidney parameters and electrolytes. ECG and echocardiography are also important beforehand. The possible cardiotoxicity of chemotherapy (anthracyclines!) during the course of treatment can only be evaluated if these tests have been performed at the start! Pulmonary function should be tested before treatment with regimens containing bleomycin is initiated.

After two cycles of chemotherapy, a restaging should be performed to evaluate treatment success. This restaging should be oriented according to the original localization of lymphoma. After completion of the protocol, a complete restaging with bone marrow biopsy (if there was initial involvement) and all CT scans is necessary. With a complete remission, restaging is recommended initially at three-monthly intervals. These intervals can be prolonged to six months after one year and to twelve months after two years. Relapses after more than three years are rare.

In advanced stages of the disease (Ann Arbor III-IV), and particularly with ENT involvement, a diagnostic lumbar puncture is necessary before initiating systemic chemotherapy to exclude meningeal involvement. In such cases, 15 mg of methotrexate can be administered intrathecally as prophylaxis. Whether this (accepted by oncologists) action actually has any benefit or not, has never been shown in controlled studies.

For further details regarding the diagnosis and treatment of AIDS-associated lymphomas, the DAGNÄ recommendations and principles of treatment can also be consulted (<http://www.hiv.net/link.php?id=259>).

## Therapy

Due to extremely rapid generalization, even “early stages” are rarely limited. The real stage of the disease is often underestimated – every aggressive HIV-associated lymphoma should therefore be treated primarily with systemic chemotherapy with curative intent. Surgery or radiation therapy alone are not sufficient. Treatment must be started rapidly due to the aggressive nature of these lymphomas. In particular, time should not be wasted on staging. The necessary tests should be completed within a week.

In Europe, diffuse large-cell NHLs have been treated for many years with CHOP-based regimens (usually 4-6 cycles, see table). CHOP is the abbreviation used for the combination chemotherapy with the cytostatics cyclophosphamide, adriamycin (hydroxydoxorubicin), vincristine (Oncovin™) and prednisolone. To date, no other chemotherapy regimen has been shown to have better efficacy. CHOP can be administered in ambulatory care and is fairly well tolerated.

At least 4 cycles should be administered, and – as far as possible – 2 cycles after reaching complete remission (CR).

The standard three-week CHOP regimen (“CHOP-21”) is shown in Table 3. Following the success of “CHOP-14” in older HIV-negative patients (Pfreundschuh 2004), “CHOP-21” can also be condensed: in “CHOP-14” (one cycle every two weeks) the use of the growth hormone G-CSF (e.g. Filgastrim 30-48 million units or Neupogen™ 300/480 µg s.c. daily on days 4 to 13) reduces the duration of neutropenia. This approach not only decreases the phase of increased susceptibility to infections, but also increases the dose intensity of chemotherapy. However, there is no comparative data on this yet for HIV patients. So far, we have had fairly positive

experiences with this approach – in most HIV patients, it is possible to shorten the interval.

We recommend the administration of co-trimoxazole as an adjuvant therapy, up until one month after completion of the chemotherapy (960 mg three times weekly), independent of the CD4 cell count. Oral mucous membranes should be treated with mouthwashes and topical antimycotics such as amphotericin. Good compliance from the patients is an important factor. During chemotherapy, at least twice weekly monitoring of the patient's condition, blood count, liver and kidney parameters is necessary. Treatment is usually continued with the full dose according to protocol if leukocytes are above 3,000/ $\mu$ l again after nadir and platelets more than 80,000/ $\mu$ l on the planned day of treatment. Patients should be advised to carry out daily temperature monitoring and be told to present immediately in case of fever.

Table 3: CHOP regimen (4-6 cycles of 3 weeks each, repeat on Day 22) \*

Cyclophosphamide	Endoxan®	750 mg/m <sup>2</sup> i.v. Day 1
Doxorubicin	Doxo-Cell®, Adriblastin®	50 mg/m <sup>2</sup> i.v. Day 1
Vincristine	Vincristin®	1.4 mg/m <sup>2</sup> (maximum 2 mg) i.v. Day 1
Prednisolone	Decortin H®	2 tbl. à 50 mg qd p.o., Day 1-5
Mesna	Uromitexan®	20 % of cyclophosphamide dose at hours 0, 4, 8 (with reference to cyclophosphamide i.v. given as a short infusion or orally)

\* Standard CHOP regimen ("CHOP 21")

## Rituximab in HIV infection?

The introduction of the monoclonal CD20-antibody rituximab (MabThera™) was one of the biggest advances in oncology in recent years. In numerous lymphomas, this antibody, which binds highly specifically to CD20-positive B-cells (CD20 is expressed by most lymphoma cells), has markedly improved the effectiveness and length of response of conventional chemotherapy. A combination of CHOP and rituximab ("R-CHOP") is now standard in many lymphomas. Rituximab is usually well tolerated, but often leads to a longer lasting B-cell depletion, and occasionally to severe neutropenia (Voog 2003).

It is not clear whether rituximab has a similarly large clinical benefit for HIV patients as it has for HIV-negative patients with B-cell lymphoma. The results from AMC 010, a multicenter prospective and randomized US study, have at least raised doubts (Kaplan 2005). 143 patients with CD20-positive AIDS-NHL were randomized to CHOP or R-CHOP (rituximab in the usual dose of 375 mg/m<sup>2</sup> on day 1 with a monthly maintenance therapy for 3 months following chemotherapy). In addition to the chemotherapy, all patients also received G-CSF, a co-trimoxazole prophylaxis and an AZT-free HAART. Both groups had minimal differences at baseline. In the rituximab group, the CD4+ T-cell counts were slightly, but not significantly lower (128 vs 158/ $\mu$ l). With regard to other parameters, such as histology, stage of disease, etc., there were no significant differences. Even the planned CHOP cycles were carried out at the same intensity in both groups, and in both groups only slight dose reductions were necessary.

Essentially, with regard to the results: neither group differed significantly in the length of response, disease-free or total survival. However, neutropenia and incidence of (especially severe) infection were significantly higher in the rituximab group. Out of a total of 15 patients who died from an infection, 14 had received rituximab. The cause of death was usually septicemia from various bacteria – both gram-negative and gram-positive were identified. Death occurred in the majority (8/15) during the first two cycles, although 6 cases happened during the rituximab treatment at the end of the chemotherapy. Fatalities occurred in all centers and were therefore not due to a possible lack of expertise in any one location. A further risk factor for “death from infection” was a low baseline CD4+ T-cell count – 8/13 patients had less than 50 cells/ $\mu$ l. The cause of the high rate of severe infections is still unclear. Pathophysiologically, it is at least possible that in pre-existing T cell defects present in HIV patients, a long-lasting rituximab-induced B cell depletion or hypoglobulinemia has particularly negative effects (Miles 2005).

Following these data (which have to be examined), rituximab seems at first glance to have no significant beneficial effect on HIV patients with aggressive lymphomas, and if indeed there is one, this is cancelled by the increased risk of infection. In a further study from Italy, in which rituximab was given with CDE (cyclophosphamide, doxorubicin, etoposide), fatal infectious complications occurred in 8 % of patients (Spina 2005) – in the meantime, the effect of rituximab in HIV patients is now being carefully evaluated here too.

It is our opinion that in HIV patients, rituximab should only be used within clinical trials or on patients with low or hardly any immunosuppression. In addition, it is imperative that more data is obtained. For this reason, a multicentric cohort study has been set up for Germany starting in 2006, which should incorporate as many patients as possible.

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## **More intensive chemotherapy as standard CHOP**

After earlier studies showed that intensive chemotherapy led to a disproportionately high risk of infection and toxic complications (Kaplan 1997), the tendency for a long time was to withhold HIV patients from therapy and often to treat them with reduced-dose regimens. This seems to be changing in the age of HAART. Several prospective studies have shown that the tolerability of chemotherapy is improved through HAART (Powles 2002, Sparano 2004).

In the past few years, small pilot studies have been repeatedly published in which HIV patients have been treated with CHOP regimens. There are also studies in which doxorubicin has been given as liposomal Caelyx™ (Levine 2004) or where the dose of cyclophosphamide was increased (Costello 2004). In addition, CDE, a regimen which, when given for several days as infusions is supposed to overcome the potential chemotherapy resistance of lymphoma cells, is propagated again and again (Sparano 2004). The CR rates in these studies were between 50 and 75 %. In our experience, CR rates up to 70 % are also possible with HAART and standard CHOP. Whether these new attempts, which always cause a stir, are really better than CHOP, remains speculative. In our view, they are not ready for use outside of clinical trials.



Even stem cell transplantations are now possible in HIV patients – a scenario that was still unthinkable a few years ago. Very high doses of myeloablative chemotherapy in combination with HAART are well tolerated (Gabarre 2000 + 2004, Kang 2002, Re 2003, Krishnan 2005). In HIV patients with Burkitt's lymphoma, intensive protocols that were originally developed for HIV-negative patients are also being successfully employed (see below).

Today, the decisive question regarding more intensive chemotherapy in HIV patients is, therefore, not whether it can be used, but who actually needs it or will profit from an increased dose.

## HAART and classic risk factors

At first glance, the effect of HAART on the prognosis of HIV-associated NHL seems contradictory. At least four large cohort studies (Conti 2000, Levine 2000, Matthews 2000, Chow 2001) have shown sobering results. These data contradict numerous, mostly smaller, but more closely analyzed and prospective studies. These showed without exception that HAART significantly improved prognosis (Thiessard 2000, Antinori 2001, Besson 2001, Ratner 2001, Powles 2002, Vilchez 2002, Navarro 2003, Vaccher 2003, Sparano 2004). In addition to survival, some studies also showed improved disease-free survival, response rates and even improved tolerability of chemotherapy.

While the “classic” NHL risk factors for survival (including Ann Arbor stage, LDH, age, Karnofsky score) are already of lower significance in HIV patients than the HIV-relevant factors (CD4+ T-cells, history of AIDS), then the latter presumably lose relevance too when the impact of HAART is also considered (Hoffmann 2003, Lim 2005). In our own multicenter cohort with over 200 patients, the immunologic-virological success of HAART was an important and independent factor for the prognosis of patients (Hoffmann 2003). This was also true for patients who still had a relatively good immune status (> 200 CD4+ T-cells/ $\mu$ l at the time of lymphoma). The only additional clinical risk factors were extranodal disease and a history of AIDS, but had relatively weak predictive relevance. However, in a histological analysis, a post germinal centre profile was also associated with a worsened prognosis (Hoffmann 2003).

Thus, in an ART-naïve patient, the chances of complete remission are not necessarily poor even with an otherwise poor starting condition (advanced lymphoma or HIV). Whenever there is an opportunity for immune reconstitution with HAART and the general status of the patient allows, HAART should be started as rapidly as possible. Even with moderate immunodeficiency, maximum immune reconstruction should be the main goal of every treatment. Chemotherapy with curative intent should be chosen and, if possible, doses should not be reduced. In order to obtain more data, all patients in the German cohort studies should be included (see above for telephone/contact).

## Which HAART when?

Already existing, adequate HAART should be continued during chemotherapy if possible. In ART-naïve patients, the first one or two CHOP cycles can be completed before starting HAART. Some clinicians prefer to complete all six cycles out of concern for interactions and cumulative toxicities (Little 2003). In our opinion,

this is not necessary. The right choice of antiretroviral drugs is not easy, however. d4T, ddC and ddI have a high risk of polyneuropathy (vincristine!), but are less myelotoxic than AZT. Little is known of the possible interactions between PIs and NNRTIs with CHOP, and their influence on the metabolism of cyclophosphamide and other cytostatic agents. The effect on doxorubicin seems to be limited (Toffoli 2004).

In ART-naïve patients without pre-existing renal damage, a combination of tenofovir, 3TC/FTC and an NNRTI is possible. With a high viral load, however, this may rapidly lead to the development of resistance, which limits future options. Here we recommend the initial use of PI-containing combinations with regular measurements of plasma levels.

## Special entities of lymphoma

**Burkitt's or Burkitt-like lymphomas:** the particularly high proliferative capacity and aggressiveness of Burkitt's or Burkitt-like lymphomas is a problem even in HIV-negative patients. In this case, the CHOP regimen is insufficient (Trümper 2001). Although it is still unclear whether this is also true for HIV patients with Burkitt's lymphomas, many clinicians have in recent years tended to treat such patients more intensively. A modified dose-adapted protocol of the German multicenter study group for adult acute lymphoblastic leukemia (GMALL) is usually used for the treatment of HIV-negative cases of Burkitt-NHL/B-ALL, and consists of four to six short, intensive 5-day polychemotherapy cycles, alternating A and B cycles. A cytoreductive pretreatment with cyclophosphamide and prednisone, each for 5 days, was given before the first cycle. During cycle A, fractionated doses of ifosfamide for 5 days, intermediate- or high-dose methotrexate 500-3,000 mg/m<sup>2</sup>, VM26, cytarabine (ara-C), vincristine, and dexamethasone are given. During cycle B, ara-C, VM26 and ifosfamide are replaced by doxorubicin and cyclophosphamide (Hoelzer 1996).

The preliminary data show better responses than with CHOP (Hoffmann 2004) and rates comparative to those of HIV-negative patients (Oriol 2003). However, the GMALL protocol is a very intensive chemotherapy, which cannot be administered on an outpatient basis. Strict monitoring of patients in hospital for several weeks is very important. Centers without experience in this intensive protocol should not administer it to HIV-infected patients.

As well as the B-ALL-protocol, other intensive therapies have been reported, although they are hardly ever used in Germany (Fieschi 2001, Cortes 2002, Lichtman 2003, Wang 2003). A significant problem with most of the studies is that there is no control group. There is no randomized study. However, there is increasing evidence that conventionally treated patients with Burkitt's lymphoma also have a worse prognosis even in the age of HAART (Conti 2000, Lim 2005, Spina 2005). Although this has not been confirmed by all study teams (Bower 2005), intensive therapy should be considered for every patient with Burkitt's lymphoma. A poor immune status or the existence of a concurrent opportunistic infection does not necessarily have to be an obstruction (Lehmann 2005).

**Plasmablastic lymphomas:** are a relatively new entity in HIV patients. Plasmablastic lymphomas probably belong to the diffuse large-cell NHLs, but have a completely characteristic immunophenotype, which usually correlates to a post-

germinal center cell – markers for the B-cell antigen CD20 are negative, whereas the plasma-cell reactive antibodies VS38c and CD138 are positive (Brown 1998, Teruya-Feldstein 2004). The oral cavity is the site of involvement (Flaitz 2002, Gaidano 2002), although extra-oral manifestations do occur (Chetty 2003). There is a close association with an HHV-8 infection (Cioc 2004). Like Burkitt's lymphoma, plasmablastic lymphomas have a very high rate of proliferation and are extremely aggressive. More recent data shows that the earlier very poor prognosis is markedly improved by HAART (Teruya-Feldstein 2004, Lester 2004). In a study on 89 NHL, we were able to show that a post germinal center profile, as often occurs in plasmablastic lymphomas, is independently associated with a worse prognosis (Hoffmann 2005). It is our opinion that patients should therefore receive a more intensive treatment than CHOP-21.

**Primary effusion lymphoma (PEL):** a further therapeutic problem is the relatively rare entity of the so-called primary effusion lymphoma which is also termed body cavity lymphoma (Carbone 1997, 2000). These lymphomas are often very difficult to diagnose histologically. A visible tumor mass is usually absent, so that malignant cells can only be found in body cavities (e.g. pleural, pericardial, peritoneal). There are histological similarities to immunoblastic and anaplastic cells with a non-B-, non-T phenotype. Every pleural or pericardial effusion occurring in an HIV patient and containing malignant cells, is suspicious of PEL. The involved pathologist should always be informed about this suspicion.

There is a characteristic close association with the herpes virus HHV-8, which can be detected in the malignant cells, and which provides a relatively typical gene expression profile (Simonelli 2005, Fan 2005). Recently, a solitary variant has been reported, which is neither morphologically nor immunophenotypically distinguishable from the classical PEL types (Chadburn 2004). The response to CHOP is usually poor and poorer than that of centroblastic NHL (Simonelli 2003). Case studies with complete remission on HAART alone have been described (Boulanger 2001, Hocqueloux 2001). We have, however, seen two PEL patients who have also died of progression despite CHOP and HAART after only a few months.

Recently, a combined chemotherapy with high dose methotrexate has been reported, with which, in at least 3/7 patients, a lasting complete remission could be achieved – a notable achievement in view of the otherwise poor prognosis, and an approach that should be followed up (Boulanger 2003). On the other hand, there are reports in which even intensive treatment regimens were unsuccessful (Waddington 2004).

## Relapse therapy, stem cell transplantation

At the moment, no general recommendations for relapse therapy of NHL can be given. The prognosis of NHL relapse is poor overall, anyway. A team from the USA reported their positive experiences using the ESHAP protocol (etoposide, methylprednisolone, ara-C and cisplatin) – DHAP appears to have no effect in this case (Bi 2001). The EPOCH-regimen may also be effective. Other salvage monotherapies with mitoguazon or liposomal daunorubicin are well tolerated, but purely palliative (Levine 1997, Tulpule 2001).

It should always be checked whether the affected patient with a relapse of lymphoma qualifies in principle for an autologous stem cell transplant (ASCT). In

ASCT, the intensity of the chemotherapy can be markedly increased by the preceding gain of pluripotential stem cells (own cells: autologous; foreign cells: allogenic). Following the myeloablative chemotherapy, the patients are re-infused with the stem cells.

Over 70 cases have been described so far worldwide (Gabarre 2000 + 2004, Re 2003, Krishnan 2003 + 2005, Serrano 2005), including even a few allogenic SCT (Kang 2002). In Germany, experience with ASCT has been gained on approximately 5-10 HIV patients, and we have recently published the first case (Hoffmann 2006). The critical problem in many hematological centers is above all a logistical one, namely the complicated storage of stem cells, which has to conform to strict safety regulations. The storage of potentially infectious HIV material together with stem cells from non-infected patients in the normal cooling tanks is not allowed – an extra (expensive) tank is required.

## References

1. Antinori A, Cingolani A, Alba L, et al. Better response to chemotherapy and prolonged survival in AIDS-related lymphomas responding to HAART. *AIDS* 2001, 15:1483-91. <http://amedeo.com/lit.php?id=11504980>
2. Berenguer J, Miralles P, Serrano D, Carrión R, López JC, Cosin J, Pineda AG, Buño I, Martín J. Autologous hematopoietic stem cell transplantation for AIDS-related lymphoma. Abstract 806, 10th CROI 2003, Boston, USA. <http://www.retroconference.org/Archive/Posters/Retro10/806.pdf>
3. Besson C, Goubar A, Gabarre J, et al. Changes in AIDS-related lymphoma since the era of HAART. *Blood* 2001, 98:2339-44. <http://amedeo.com/lit.php?id=11588028>
4. Bi J, Espina BM, Tulpule A, Boswell W, Levine AM. High-dose cytosine-arabinoside and cisplatin regimens as salvage therapy for refractory or relapsed AIDS-related non-Hodgkin's lymphoma. *J AIDS* 2001, 28:416-21. <http://amedeo.com/lit.php?id=11744828>
5. Bonnet F, Lewden C, May T, et al. Malignancy-related causes of death in HIV-infected patients in the era of HAART. *Cancer* 2004, 101:317-24. <http://amedeo.com/lit.php?id=15241829>
6. Boue F, Gabarre J, Gisselbrecht C, et al. CHOP chemotherapy plus rituximab in HIV patients with high grade lymphoma – results of an ANRS trial. Abstract 1824, 44<sup>th</sup> ASH 2002, Philadelphia, USA.
7. Boulanger E, Agbalika F, Maarek O, et al. A clinical, molecular and cytogenetic study of 12 cases of human herpesvirus 8 associated primary effusion lymphoma in HIV-infected patients. *Hematol J* 2001, 2:172-9. <http://amedeo.com/lit.php?id=11920242>
8. Boulanger E, Daniel MT, Agbalika F, Oksenhendler E. Combined chemotherapy including high-dose methotrexate in KSHV/HHV8-associated primary effusion lymphoma. *Am J Hematol* 2003, 73: 143-8. Abstract: <http://amedeo.com/p2.php?id=12827649&s=hiv>
9. Brown RS, Campbell C, Lishman SC, et al. Plasmablastic lymphoma: a new subcategory of HIV-related non-Hodgkin's lymphoma. *Clin Oncol* 1998;10:327-9. <http://amedeo.com/lit.php?id=9848336>
10. Carbone A, Cilia AM, Gloghini A, et al. Primary effusion lymphoma cell lines harbouring human herpesvirus type-8. *Leuk Lymphoma*. 2000;36:447-56.
11. Carbone A, Gaidano G. HHV-8-positive body-cavity-based lymphoma: a novel lymphoma entity. *Br J Haematol* 1997, 97: 515-522.
12. Chadburn A, Hyjek E, Mathew S, et al. KSHV-positive solid lymphomas represent an extra-cavitary variant of primary effusion lymphoma. *Am J Surg Pathol* 2004, 28:1401-16. <http://amedeo.com/lit.php?id=15489644>
13. Chetty R, Hlatswayo N, Muc R, et al. Plasmablastic lymphoma in HIV+ patients: an expanding spectrum. *Histopathology* 2003;42:605-9. <http://amedeo.com/lit.php?id=12786898>
14. Chow KU, Mitrou PS, Geduldig K, Helm EB, Hoelzer D, Brodt HR. Changing incidence and survival in patients with AIDS-related non-Hodgkin's lymphomas in the era of HAART. *Leuk Lymphoma* 2001, 41:105-116. <http://amedeo.com/lit.php?id=11342362>
15. Cioc AM, Allen C, Kalmr JR, et al. Oral plasmablastic lymphomas in AIDS patients are associated with human herpesvirus 8. *Am J Surg Pathol* 2004, 28:41-6. <http://amedeo.com/lit.php?id=14707862>
16. Clarke CA, Glaser SL. Epidemiologic trends in HIV-associated lymphomas. *Curr Opin Oncol* 2001, 13:354-359. <http://amedeo.com/lit.php?id=11932904>

17. Conti S, Masocco M, Pezzotti P et al. Differential impact of combined antiretroviral therapy on the survival of Italian patients with specific AIDS-defining illnesses. *J Acquir Immune Defic Syndr* 2000, 25:451-458. <http://amedeo.com/lit.php?id=11141245>
18. Cortes J, Thomas D, Rios A, et al. Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone and highly active antiretroviral therapy for patients with AIDS-related Burkitt lymphoma/leukemia. *Cancer* 2002, 94:1492-9.
19. Costello RT, Zerazhi H, Charbonnier A, et al. Intensive sequential chemotherapy with hematopoietic growth factor support for non-Hodgkin lymphoma in patients infected with the human immunodeficiency virus. *Cancer* 2004, 100:667-76. <http://amedeo.com/lit.php?id=14770420>
20. Ellent DP, Rowley SD, Goldberg SL, et al. Autologous hematopoietic stem cell transplantation for the treatment of HIV-infected patients on HAART with non-Hodgkin's lymphoma. Abstract 2413, 39th ASCO 2003, Chicago, IL/USA.
21. Fieschi C, Boulanger E, Galicier L, et al. Intensive chemotherapy (LMB 86) regimen for HIV-associated stage IV Burkitt's lymphoma/leukemia. Abstract 592, 8th CROI 2001, Chicago, IL
22. Flaitz CM, Nichols CM, Walling DM, Hicks MJ. Plasmablastic lymphoma: an HIV-associated entity with primary oral manifestations. *Oral Oncol* 2002;38:96-102. <http://amedeo.com/lit.php?id=11755827>
23. Gabarre J, Azar N, Autran B, Katlama C, Leblond V. High-dose therapy and autologous haematopoietic stem-cell transplantation for HIV-1-associated lymphoma. *Lancet* 2000, 355:1071-2. <http://amedeo.com/lit.php?id=10744095>
24. Gabarre J, Choquet S, Azar N, et al. High dose chemotherapy with autologous stem cell transplantation for HIV-associated lymphoma: a single center report on 14 patients. Abstract 2092, 43th ASH 2001, Orlando, USA.
25. Gabarre J, Marcelin AG, Azar N, et al. High-dose therapy plus autologous hematopoietic stem cell transplantation for human immunodeficiency virus (HIV)-related lymphoma: results and impact on HIV disease. *Haematologica* 2004, 89:1100-8. <http://amedeo.com/lit.php?id=15377471>
26. Gaidano G, Cerri M, Capello D, et al. Molecular histogenesis of plasmablastic lymphoma of the oral cavity. *Br J Haematol* 2002; 119: 622-628. <http://amedeo.com/lit.php?id=12437635> <http://amedeo.com/p2.php?id=12437635&s=hiv>
27. Goedert JJ. The epidemiology of AIDS malignancies. *Semin Oncol* 2000, 27:390-401. <http://amedeo.com/lit.php?id=10950365>
28. Hocqueloux L, Agbalika F, Oksenhendler E, Molina JM. Long-term remission of an AIDS-related primary effusion lymphoma with antiviral therapy. *AIDS* 2001, 15:280-2.
29. Hoffmann C, Wolf E, Fatkenheuer G, et al. Response to highly active antiretroviral therapy strongly predicts outcome in patients with AIDS-related lymphoma. *AIDS* 2003, 17:1521-9. <http://amedeo.com/lit.php?id=12824790>
30. Hoffmann C, Wolf E, Faetkenheuer G, et al. The short and intensive B-ALL protocol is a highly effective regimen in patients with AIDS-associated Burkitt or Burkitt-like lymphoma. Abstract 787, 11th CROI 2004, San Francisco.
31. Kang EM, de Witte M, Malech H, et al. Nonmyeloablative conditioning followed by transplantation of genetically modified HLA-matched peripheral blood progenitor cells for hematologic malignancies in patients with AIDS. *Blood* 2002, 99:698-701. <http://amedeo.com/lit.php?id=11781257>
32. Kaplan L. No benefit from Rituximab in a randomized phase III trial of CHOP with or without rituximab for patients with HIV-associated Non-Hodgkin's Lymphoma: AIDS Malignancies Consortium Study 010. Abstract S17, 7th AMC 2003, Bethesda, Maryland, USA.
33. Kaplan LD, Straus DJ, Testa MA, et al. Low-dose compared with standard-dose m-BACOD chemotherapy for non-Hodgkin's lymphoma associated with HIV infection. *N Engl J Med* 1997, 336:1641-8. <http://www.amedeo.com/lit.php?id=9171066>
34. Kirk O, Pedersen C, Cozzi-Lepri A, et al. Non-Hodgkin lymphoma in HIV-infected patients in the era of HAART. *Blood* 2001, 98: 3406-3412. <http://amedeo.com/lit.php?id=11719381>
35. Kneba M, Dreger P, Pantel K. *Antikörpertherapie in der Hämatologie und Onkologie*. UNI-MED Verlag, Bremen, 1. Auflage, 2001.
36. Krishnan A, Molina A, Zaia J, et al. Autologous stem cell transplantation for HIV-associated lymphoma. *Blood* 2001, 98:3857-3859. <http://amedeo.com/lit.php?id=11739198>
37. Krishnan A, Molina A, Zaia J, et al. Durable remissions with autologous stem cell transplantation for high risk HIV-associated lymphomas. *Blood* 2004, Epub ahead of print. <http://amedeo.com/lit.php?id=15388574>
38. Krishnan A, Zaia J, Forman SJ. Should HIV-positive patients with lymphoma be offered stem cell transplants? *Bone Marrow Transplant* 2003;32:741-8. <http://amedeo.com/lit.php?id=14520416>
39. Lester R, Li C, Galbraith P, et al. Improved outcome of human immunodeficiency virus-associated plasmablastic lymphoma of the oral cavity in the era of highly active antiretroviral therapy: a report of two cases. *Leuk Lymphoma* 2004, 45:1881-5. <http://amedeo.com/lit.php?id=15223650>

## 502 Malignant Lymphomas

40. Levine AM, Seneviratne L, Espina BM, et al. Evolving characteristics of AIDS-related lymphoma. *Blood* 2000, 96: 4084-4090. <http://amedeo.com/lit.php?id=11110677>
41. Levine AM, Tulpule A, Espina B, et al. Liposome-encapsulated doxorubicin in combination with standard agents (cyclophosphamide, vincristine, prednisone) in patients with newly diagnosed AIDS-related non-Hodgkin's lymphoma: results of therapy and correlates of response. *J Clin Oncol* 2004; 22:2662-70. <http://amedeo.com/lit.php?id=15226333>
42. Levine AM, Tulpule A, Tessman D, et al. Mitoguazone therapy in patients with refractory or relapsed AIDS-related lymphoma: results from a multicenter phase II trial. *J Clin Oncol*. 1997;15:1094-103.
43. Levine AM. AIDS-related lymphoma: clinical aspects. *Semin Oncol* 2000, 27:442-53. <http://amedeo.com/lit.php?id=10950371>
44. Lewden C, Hérigret L, Bonnet F, et al. Causes of death in HIV-infected adults in the era of HAART, the French Survey "Mortalite 2000". Abstract 753, 9th CROI 2002, Seattle, USA. <http://www.retroconference.org/2002/Abstract/13298.htm>
45. Lichtman SM, Calderon N. Alternating CODOX-M and IVAC in HIV positive patients with burkitt's lymphoma. Abstract 2471, ASCO 2003, Chicago, Illinois.
46. Little RF, Gutierrez M, Jaffe ES, et al. HIV-Associated non-Hodgkin lymphoma: incidence, presentation, and prognosis. *JAMA* 2001, 285:1880-1885. <http://amedeo.com/lit.php?id=11308402>
47. Little RF, Pittaluga S, Grant N, et al. Highly effective treatment of AIDS-related lymphoma with dose-adjusted EPOCH: impact of antiretroviral therapy suspension and tumor biology. *Blood* 2003;101:4653-9. <http://amedeo.com/p2.php?id=12609827&s=hiv>
48. Matthews GV, Bower M, Mandalia S, et al. Changes in AIDS-related lymphoma since the introduction of HAART. *Blood* 2000, 96:2730-2734. <http://amedeo.com/lit.php?id=11023505>
49. Mocroft A, Katlama C, Johnson AM, et al. AIDS across Europe, 1994-1998: the EuroSIDA study. *Lancet* 2000, 356:291-296. <http://amedeo.com/lit.php?id=11071184>
50. Navarro JT, Ribera JM, Oriol A, et al. Improved outcome of AIDS-related lymphoma in patients with virologic response to highly active antiretroviral therapy. *J AIDS* 2003,; 32: 347-8.
51. Oriol A, Ribera JM, Esteve J, et al. Lack of influence of human immunodeficiency virus infection status in the response to therapy and survival of adult patients with mature B-cell lymphoma or leukemia. Results of the PETHEMA-LAL3/97 study. *Haematologica* 2003,; 88:445-53.
52. Pfreundschuh M, Trumper L, Kloess M, et al. Two-weekly or 3-weekly CHOP chemotherapy with or without etoposide for the treatment of elderly patients with aggressive lymphomas: results of the NHL-B2 trial of the DSHNHL. *Blood* 2004, 104:634-41. <http://amedeo.com/lit.php?id=15016643>
53. Porcu P, Caligiuri MA. AIDS-related lymphomas: future directions. *Semin Oncology* 2000, 4:454-62. <http://amedeo.com/lit.php?id=10950372>
54. Powles T, Imami N, Nelson M, Gazzard BG, Bower M. Effects of combination chemotherapy and HAART on immune parameters in HIV-1 associated lymphoma. *AIDS* 2002, 16:531-6. <http://amedeo.com/lit.php?id=11872995>
55. Ratner L, Lee J, Tang S et al. Chemotherapy for HIV-associated non-Hodgkin's lymphoma in combination with HAART. *J Clin Oncol* 2001, 19: 2171-8. <http://amedeo.com/lit.php?id=11304769>
56. Re A, Cattaneo C, Michieli M, et al. High-dose therapy and autologous peripheral-blood stem-cell transplantation as salvage treatment for HIV-associated lymphoma in patients receiving highly active antiretroviral therapy HAART. *JCO Clin Oncol* 2003, ;21:4423-7. <http://amedeo.com/lit.php?id=14581441><http://amedeo.com/p2.php?id=14581441&s=hiv>
57. Simonelli C, Spina M, Cinelli R, et al. Clinical features and outcome of primary effusion lymphoma in HIV-infected patients: a single-institution study. *J Clin Oncol* 2003;21:3948-54. <http://amedeo.com/lit.php?id=14581418>
58. Sparano JA, Lee S, Chen MG, et al. Phase II trial of infusional cyclophosphamide, doxorubicin, and etoposide in patients with HIV-associated non-Hodgkin's lymphoma: an Eastern Cooperative Oncology Group Trial (E1494). *J Clin Oncol* 2004, 22:1491-500. <http://amedeo.com/lit.php?id=15084622>
59. Spina M, Jaeger U, Sparano JA, et al. Rituximab plus infusional cyclophosphamide, doxorubicin and etoposide (R-CDE) in HIV-associated non-Hodgkin's lymphoma: pooled results from three phase II trials. *Blood* 2004, ahead of print <http://amedeo.com/lit.php?id=15550484>
60. Spina M, Simonelli C, Vaccher E, et al. Rituximab and infusional cyclophosphamide, doxorubicin, and etoposide (CDE) in combination with HAART: a safe and highly active regimen in HIV-related Non-Hodgkin's lymphomas (NHL). Abstract F9/1, 9th EACS 2003, Warsaw, Poland.
61. Stebbing J, Gazzard B, Mandalia S, et al. Antiretroviral treatment regimens and immune parameters in the prevention of systemic AIDS-related non-Hodgkin's lymphoma. *J Clin Oncol* 2004, 22:2177-83. <http://amedeo.com/lit.php?id=15169806>
62. Teruya-Feldstein J, Chiao E, Filippa DA, et al. CD20-negative large-cell lymphoma with plasmablastic features: a clinically heterogeneous spectrum in both HIV-positive and -negative patients. *Ann Oncol* 2004, 15:1673-9. <http://amedeo.com/lit.php?id=15520070>

63. Thiessard F, Morlat P, Marimoutou C et al. Prognostic factors after non-Hodgkin lymphoma in patients infected with the HIV: Aquitaine cohort, France, 1986-1997. *Cancer* 2000, 88:1696-1702. <http://amedeo.com/lit.php?id=10738229>
64. Tirelli U, Spina M, Jaeger U, et al. Infusional CDE with rituximab for the treatment of HIV-associated non-Hodgkin's lymphoma: preliminary results of a phase I/II study. *Recent Results Cancer Res* 2002, 59:149-53. <http://amedeo.com/lit.php?id=11785839>
65. Toffoli G, Corona G, Cattarossi G, et al. Effect of highly active antiretroviral therapy (HAART) on pharmacokinetics and pharmacodynamics of doxorubicin in patients with HIV-associated non-Hodgkin's lymphoma. *Ann Oncol* 2004, 15:1805-9. <http://amedeo.com/lit.php?id=15550586>
66. Trümper L, Möller P, Neubauer A. Non-Hodgkin-Lymphome. *Lehrbuch der Klinischen Onkologie* (Hrsg. Hiddemann W, Bartram C, Huber H), Springer Verlag. Original-Artikel: <http://hiv.net/link.php?id=188>
67. Tulpule A, Rarick MU, Kolitz J, et al. Liposomal daunorubicin in the treatment of relapsed or refractory non-Hodgkin's lymphoma. *Ann Oncol* 2001;12:457-62.
68. Vaccher E, Spina M, Talamini R, et al. improvement of systemic human immunodeficiency virus-related non-hodgkin lymphoma outcome in the era of highly active antiretroviral therapy. *Clin Infect Dis* 2003; 37: 1556-1564.
69. Vilchez RA, Jorgensen JL, Kroll MH. Systemic non-Hodgkin lymphoma in HIV-infected patients in the era of highly active antiretroviral therapy. *Blood* 2002; 99: 4250-1.
70. Voog E, Morschhauser F, Solal-Celigny P. Neutropenia in patients treated with rituximab. *N Engl J Med* 2003; ;348:2691-4.
71. Waddington TW, Aboulafia DM. Failure to eradicate AIDS-associated primary effusion lymphoma with high-dose chemotherapy and autologous stem cell reinfusion: case report and literature review. *AIDS Patient Care STDS* 2004, 18:67-73. <http://amedeo.com/lit.php?id=15006181>
72. Wang ES, Straus DJ, Teruya-Feldstein J, et al. Intensive chemotherapy with cyclophosphamide, doxorubicin, high-dose methotrexate/ifosfamide, etoposide, and high-dose cytarabine (CODOX-M/IVAC) for HIV-associated Burkitt lymphoma. *Cancer* 2003; 98: 1196-205. <http://amedeo.com/lit.php?id=12973843>
73. Ziegler JL, Drew WL, Miner RC, et al. Outbreak of Burkitt's-like lymphoma in homosexual men. *Lancet* 1982, 2:631-3. <http://amedeo.com/lit.php?id=6125777>

## Primary CNS lymphoma

Primary CNS lymphomas (PCNSL) are a late complication of HIV infection and used to occur in up to 10 % of AIDS patients. Large autopsy series in the 1990s showed even higher prevalence rates. The incidence of PCNSL seems to have decreased significantly in the last years in comparison to systemic lymphomas.

PCNSL are EBV-associated in almost 100 % of cases (Camilleri-Broet 1997). Histologically, findings are almost always consistent with diffuse large-cell non-Hodgkin's lymphomas. In these patients, the CD4 T cells are almost always below 50/ $\mu$ l at the time of diagnosis. In the pre-HAART era, PCNSL had the poorest prognosis of all the AIDS-defining illnesses, with a median survival of less than three months (Fine and Maher 1993). In the last years, this bleak picture, often characterized by therapeutic nihilism, has changed significantly. In the HAART-era, survival may be several years and even complete remission has become possible (Hoffmann 2001).

## Signs and symptoms

Different neurological deficits occur depending on the localization. Epileptic seizures may be the first manifestation of disease. Personality changes, changes in vigilance, headache and focal deficits such as paresis are also frequent. Fever is

usually absent. As patients are almost always severely immunocompromised, constitutional symptoms may mask the actual problem.

## Diagnosis

Cranial CT or (better) MRT scan should be performed rapidly. The most important differential diagnosis is cerebral toxoplasmosis. A solitary mass is usually more indicative of PCNSL. However, 2-4 lesions may be present, which are usually fairly large (more than 2 cm in diameter). More than four lesions of a PCNSL are rarely found.

In addition to an updated toxoplasmosis serology, which – if negative – makes toxoplasmosis very unlikely, a recent CD4+ T-cell count should be available. The better the immune status, the less likely the diagnosis of PCNSL. In our own cohort, less than 20 % of patients had more than 50 CD4+ T-cells/ $\mu$ l at the time of diagnosis. At over 100 cells/ $\mu$ l, however, cerebral toxoplasmosis is also less likely.

In addition to the physical examination, a minimal diagnostic program (chest radiography, abdominal ultrasound) should clarify whether the CNS involvement is secondary to systemic lymphoma. This should always include fundoscopy to exclude ocular involvement (up to 20 %).

Besides cerebral toxoplasmosis, differential diagnoses include abscesses, glioblastoma and cerebral metastasis of solid tumors. In the absence of increased intracranial pressure, lumbar puncture is advised. If steroids have already been administered, however, the probability of finding malignant cells is diminished. In our experience, EBV-PCR of CSF that has been propagated by some groups has not been helpful.

In most cases, a treatment attempt for toxoplasmosis can be made initially. If this is unsuccessful, PCNSL is more likely. In such cases, stereotactic brain biopsy is essential to secure the diagnosis.

## Treatment

For many years, cranial radiation therapy has been the only option for patients with PCNSL, independent of the HIV status. In HIV-negative patients, using the combination of radiation therapy and steroids, a remission of 12-18 months duration is usually achieved. In HIV patients in the pre-HAART era, radiation only improved survival from 0.9 to 3.0 months (Fine 1993). Survival of more than one year was rare.

The prognosis for HIV-negative patients has improved in the last years due to the combination of methotrexate-based (MTX) chemotherapies and radiation. Smaller studies have indicated that monotherapy with high doses of MTX could be effective, thereby reserving radiation therapy for relapses (De Angelis 2001). Whether these results will be applicable in HIV patients is not clear. In addition, the incidence of PCNSL is now diminishing to such an extent that convincing data on therapy efficacy can hardly be expected in the near future. A clear recommendation for treatment can therefore not be made at this time.

Many clinicians favor cranial radiation therapy alone in HIV-infected patients (fractionated, 40 Gy total dose). In our experience, a treatment attempt with intravenous MTX is justified (3 g/m<sup>2</sup> every 14 days with leucovorin rescue) – also in



order to avoid possible neurological damage from radiation. A small study in HIV patients has shown that this approach is practical (Jacomet 1997).

However, the decisive factor in all cases – independent of the specific therapy chosen – is the best possible immune reconstitution. Under HAART, survival of several years has become realistic. Complete remissions have even been described after treatment with HAART alone (McGowan 1998, Corales 2000). In our own cohort of 29 patients with histologically diagnosed PCNSL, all four patients who experienced an increase in CD4 T cells survived longer than 18 months. Three out of four patients reached complete remission. One patient has now lived for over six years without evidence of relapse (Hoffmann 2001). In a multivariate analysis, HAART was shown to be the only factor associated with a prolonged survival in addition to cranial radiation therapy. Two of these patients, however, died after about three years of a progressive neurological syndrome, which was probably a long-term sequela of radiation therapy in both cases. In view of the better prognosis for patients today, radiation toxicity should therefore be considered more than in the past. Three further studies from France, the USA and Australia have since shown a survival of several years due to HAART (Rigolet 2001, Skiest 2003, Newell 2004).

All patients with PCNSL should therefore be treated intensively with HAART, to achieve the best possible immune reconstitution. If only a moderate immune reconstitution is possible, additional immunomodulatory or antiviral therapies should be evaluated. The partially very positive reports about ganciclovir and interleukin-2 (Raez 1999, Aboulafia 2002) or hydroxyurea (Slobod 2000) should, however, be interpreted with care. “Between the lines” of these publications, in which either individual or hardly more than 2-4 patients were described, HAART was almost always a factor.

In all cases with signs of raised intracranial pressure, rapid administration of steroids (e.g. dexamethasone 8 mg tid, decreasing the dose rapidly after resolution of edema) is indicated, even if diagnostic testing is more difficult as a result.

## References

1. Aboulafia DM. Interleukin-2, ganciclovir, and high-dose zidovudine for the treatment of AIDS-associated primary central nervous system lymphoma. *Clin Infect Dis* 2002, 34: 1660-2.
2. Camilleri-Broet S, Davi F, Feuillard J, et al. AIDS-related primary brain lymphomas: histopathologic and immunohistochemical study of 51 cases. *Hum Pathol* 1997, 28:367-74. <http://amedeo.com/lit.php?id=9042803>
3. Corales R, Taege A, Rehm S, Schmitt S. Regression of AIDS-related CNS Lymphoma with HAART. XIII International AIDS-Conference, Durban, South Africa, 2000, Abstract MoPpB1086.
4. DeAngelis LM. Primary central nervous system lymphomas. *Curr Treat Options Oncol*. 2001, 2:309-18. <http://amedeo.com/lit.php?id=12057111>
5. Fine HA, Mayer RJ. Primary central nervous lymphoma. *Ann Intern Med* 1993, 119:1093-1104. <http://amedeo.com/lit.php?id=8239229>
6. Hoffmann C, Tabrizian S, Wolf E et al. Survival of AIDS patients with primary central nervous system lymphoma is dramatically improved by HAART-induced immune recovery. *AIDS* 2001, 15:2119-2127. <http://amedeo.com/lit.php?id=11684931>
7. Jacomet C, Girard PM, Lebrette MG, Farese VL, Monfort L, Rozenbaum W. Intravenous methotrexate for primary central nervous system non-Hodgkin's lymphoma in AIDS. *AIDS* 1997, 11:1725-30. <http://amedeo.com/lit.php?id=9386807>
8. Levine AM. AIDS-related lymphoma: clinical aspects. *Semin Oncol* 2000, 27:442-53. <http://amedeo.com/lit.php?id=10950371>
9. McGowan JP, Shah S. Long-term remission of AIDS-related PCNSL associated with HAART. *AIDS* 1998, 952-954.

10. Newell ME, Hoy JF, Cooper SG, et al. HIV-related primary central nervous system lymphoma: factors influencing survival in 111 patients. *Cancer* 2004, 100:2627-36. <http://amedeo.com/lit.php?id=15197806>
11. Raez L, Cabral L, Cai JP, et al. Treatment of AIDS-related primary central nervous system lymphoma with zidovudine, ganciclovir, and interleukin 2. *AIDS Res Hum Retroviruses* 1999, 15:713-9. <http://amedeo.com/lit.php?id=10357467>
12. Rigolet A, Bossi P, Caumes E, et al. Epidemiological features and incidence trends of primary cerebral lymphomas observed in 80 HIV-infected patients from 1983 to 1999. *Pathol Biol (Paris)* 2001, 49:572-5. <http://amedeo.com/lit.php?id=11642021>
13. Skiest DJ, Crosby C. Survival is prolonged by highly active antiretroviral therapy in AIDS patients with primary central nervous system lymphoma. *AIDS* 2003, 17:1787-93.
14. Slobod KS, Taylor GH, Sandlund JT, Furth P, Helton KJ, Sixbey JW. Epstein-Barr virus-targeted therapy for AIDS-related primary lymphoma of the central nervous system. *Lancet* 2000, 356:1493-94.

## Hodgkin's disease (HD)

The incidence of HD is elevated in HIV-infected patients by a factor of 5-10 compared to the HIV-negative population. For particular subtypes, such as lymphocyte-depleted and mixed-cellularity HD, the relative risk is presumably much higher (Frisch 2001). Despite this and the growing realization that these subtypes at least are clearly associated with immunodeficiency, HIV-HD is not included as an AIDS-defining illness.

An advanced stage of disease at diagnosis is typical, as is frequent extranodal involvement and a trend towards prognostically poorer subtypes (Tirelli 1995, Rapezzi 2001, Thompson 2004). Mediastinal disease is significantly less frequent than in HIV-negative patients. A further difference to HD in seronegative patients is the predominance of cases with Reed-Sternberg cells, as well as the clear association with EBV infection, which is 80-100 %, depending on the study. EBV infection is therefore seen as an important etiologic factor for development of HIV-HD.

In comparison to HIV-negative HD, which is a highly treatable tumor, the prognosis of HIV-HD is poor. In nearly all cohorts with more than 20 patients from the pre-HAART era, the median survival was only between 15-20 months, respectively (Andrieu 1993, Errante 1999, Levine 2000, Tirelli 1995). The response to chemotherapy was also moderate compared to the normal population. Complete remission rates were between 40-80 %, and hematological and infectious complications were frequent.

Even if there are initial indications that this is changing in the era of HAART, as with NHL, there is little data so far. In our own multicenter cohort of 56 patients, the median survival was 40 months. In patients with adequate HAART, the two-year survival rate was 84 %, which is encouraging (Hoffmann 2004). In the meantime, other groups have also reported better prognoses with HAART (Ribera 2002, Gérard 2003).

## Signs and symptoms

B symptoms occur in the majority of cases. Extranodal and advanced stages are almost always the rule. Lymphomas are firm, immobile or hardly mobile and pain-

less, and the distinction from HIV lymphadenopathy or tuberculous lymphadenitis is not always possible.

## Diagnosis

Staging is necessary as for non-Hodgkin lymphomas (see relevant section). Diagnostic lymph node extirpation is even more important here than with NHL, as puncture only rarely allows diagnosis of Hodgkin's disease. Single accurate diagnostics are better than half-heartedly bothering the patient with repeated punctures and losing time unnecessarily! Surgical extirpation is possible as an outpatient in many centers. As with NHL, specimens should be sent to reference laboratories if possible.

Since bleomycin will be administered, a lung function test should always precede the first chemotherapy.

## Treatment

Many clinicians still favor the classical ABVD regimen (four double cycles) for HIV patients. ABVD is the abbreviation for the combination chemotherapy with the cytostatics adriamycin, bleomycin, vinblastine and DTIC (dacarbazine). Ambulatory treatment is possible. It should be contemplated, however, whether this therapy is still sufficient in the HAART era, particularly for advanced stages of the disease.

Table 4: ABVD regimen (4 double cycles, repeat on Day 29)\*

Adriamycin (= doxorubicin)	Doxo-Cell <sup>®</sup> , Adriblastin <sup>®</sup>	25 mg/m <sup>2</sup> i.v. Day 1 + 15
Bleomycin	Bleomycin Hexal <sup>®</sup> , Bleo-Cell <sup>®</sup>	10 mg/m <sup>2</sup> i.v. Day 1 + 15
Vinblastine	Velbe <sup>®</sup> , Vinblastin Hexal <sup>®</sup>	6 mg/m <sup>2</sup> i.v. Day 1 + 15
Dacarbazine (DTIC)	Detimedac <sup>®</sup>	375 mg/m <sup>2</sup> i.v. Day 1 + 15

\* ABVD regimen. Due to strong emetogenicity of dacarbazine, 5HT<sub>3</sub>-receptor blocker antiemetics should always be administered, e.g. granisetron, tropisetron or ondansetron.

In HIV-negative patients with advanced stages (as is almost always the case for HIV-HD) the BEACOPP regimen of the German Hodgkin Study Group has been used in the last years, mainly with escalated dosing. This has proven to be significantly more effective, both with regard to response rates and long-term survival. However, the BEACOPP regimen is more toxic. Whether these positive results can be seen in HIV-HD is still not clear. However, based on initial reports and our own experience, BEACOPP seems to be possible (Hartmann 2003). There is also growing experience to date with the Stanford V protocol, for which there have recently been promising reports (Spina 2002).

## References

1. Andrieu JM, Roithmann S, Tourani JM, et al. Hodgkin's disease during HIV-1 infection: the French registry experience. French Registry of HIV-associated Tumors. *Ann Oncol* 1993, 4:635-41. <http://amedeo.com/lit.php?id=8240994>
2. Errante D, Gabarre J, Ridolfo AL, et al. Hodgkin's disease in 35 patients with HIV infection: an experience with epirubicin, bleomycin, vinblastine and prednisone chemotherapy in combination with antiretroviral therapy and primary use of G-CSF. *Ann Oncol* 1999, 10:189-95. <http://amedeo.com/lit.php?id=10093688>

3. Frisch M, Biggar R, et al. Association of Cancer with AIDS-related immunosuppression in Adults. *JAMA* 2001, 1736-1745. <http://amedeo.com/lit.php?id=11277828>
4. Gérard L, Galicier L, Boulanger E, et al. Improved survival in HIV-related Hodgkin's lymphoma since the introduction of HAART. *AIDS* 2003;17:81-7. <http://amedeo.com/lit.php?id=12478072>
5. Hartmann P, Rehwald U, Salzberger B, Franzen C, Sieber M, Wohrmann A, Diehl V. BEACOPP therapeutic regimen for patients with Hodgkin's disease and HIV infection. *Ann Oncol* 2003;14:1562-9. <http://amedeo.com/lit.php?id=14504059>
6. Hoffmann C, Chow KU, Wolf E, et al. HIV-associated Hodgkin's Disease in the era of HAART – is there an improvement in survival? Abstract 504, DGHO München 2002.
7. Levine AM, Li P, Cheung T, et al. Chemotherapy consisting of doxorubicin, bleomycin, vinblastine, and dacarbazine with granulocyte-colony-stimulating factor in HIV-infected patients with newly diagnosed Hodgkin's disease: a prospective, multi-institutional ACTG study (149). *JAIDS* 2000, 24:444-50. <http://amedeo.com/lit.php?id=11035615>
8. Powles T, Bower M. HIV-associated Hodgkin's disease. *Int J STD AIDS* 2000, 11:492-4. <http://amedeo.com/lit.php?id=10990330>
9. Rapezzi D, Ugolini D, Ferraris AM, Racchi O, Gaetani GF. Histological subtypes of Hodgkin's disease in the setting of HIV infection. *Ann Hematol* 2001, 80:340-4. <http://amedeo.com/lit.php?id=11475147>
10. Re A, Casari S, Cattaneo C, et al. Hodgkin disease developing in patients infected by HIV results in clinical features and a prognosis similar to those in patients with HIV-related non-Hodgkin lymphoma. *Cancer* 2001, 92:2739-45. <http://amedeo.com/lit.php?id=11753946>
11. Ribera JM, Navarro JT, Oriol A, et al. Prognostic impact of highly active antiretroviral therapy in HIV-related Hodgkin's disease. *AIDS* 2002, 16: 1973-6.
12. Spina M, Gabarre J, Rossi G, et al. Stanford V regimen and concomitant HAART in 59 patients with Hodgkin disease and HIV infection. *Blood* 2002, 100:1984-8. <http://amedeo.com/lit.php?id=12200356>
13. Spina M, Vaccher E, Nasti G, Tirelli U. HIV-associated Hodgkin's disease. *Semin Oncol* 2000, 27:480-8. <http://amedeo.com/lit.php?id=10950375>
14. Thompson LD, Fisher SI, Chu WS, Nelson A, Abbondanzo SL. HIV-associated Hodgkin lymphoma: a clinicopathologic and immunophenotypic study of 45 cases. *Am J Clin Pathol.* 2004, 121:727-38. <http://amedeo.com/lit.php?id=15151213>
15. Tirelli U, Errante D, Dolcetti R, et al. Hodgkin's disease and HIV infection: clinicopathologic and virologic features of 114 patients from the Italian Cooperative Group on AIDS and Tumors. *J Clin Oncol* 1995, 13:1758-67. <http://amedeo.com/lit.php?id=7541452>

## Multicentric Castleman's Disease (MCD)

Although rare, multicentric Castleman's disease is a highly problematic illness for the affected patients – not only due to the (in HIV infection) poor prognosis, but also because many clinicians and pathologists are not very familiar with this entity. The usually severely ill patients are often subjected to diverse diagnostic and therapeutic procedures. In comparison to the benign, localized hyperplasia of lymphatic tissue, first described by Castleman in 1956, HHV-8-associated multicentric Castleman's disease, as it occurs in HIV infection, is a malignant lymphoproliferative disease (Oksenhendler 1996). Although multicentric Castleman's disease in HIV is not classified as a lymphoma or AIDS-defining illness, prognosis is poor. In a prospective study, the median survival was 14 months (Oksenhendler 1996).

The pathogenesis of the disease is not well understood. There is a close association to HHV-8, and as a result about half of the patients also have Kaposi's sarcoma. Cytokine dysregulation seems to play an important role – in particular IL-6 and IL-10 are elevated with close association to the HHV-8 viral load (Oksenhendler 2000). The extent of immunodeficiency varies significantly. We have seen an MCD patient with a normal immune status and low viral load. Progression to malignant lymphoma (often HHV-8-associated entities such as PEL) is frequent. In by far the

largest prospective study to date with 60 MCD cases, 14 patients developed malignant lymphoma after a median observation period of 20 months (Oksenhendler 2002).

## Signs and symptoms

The main signs are the often significant lymph node enlargements, which are almost always combined with considerable B symptoms including fever, night sweats and weight loss. Patients complain of weakness and malaise. There is always massive splenomegaly. Hepatomegaly (70 %), respiratory symptoms (65 %) and edema with hypoalbuminemia (55 %) are also seen in the majority of cases. The extent of symptoms is very variable and may fluctuate considerably. Some patients have Castleman “episodes”. Lymph nodes, which may be anything from very soft (as with tuberculosis) to rock hard (as with lymphoma) on palpation, can normalize or relapse within weeks without any intervention.

## Diagnosis

Ultrasound reveals hepatosplenomegaly. Laboratory tests show constantly elevated CRP, hypergammaglobulinemia and hypoalbuminemia. There is often significant anemia (may be hemolytic, often reflecting pancytopenia).

The diagnosis is made histologically after lymph node extirpation – providing that the pathologist knows what HIV-associated multicentric Castleman’s disease looks like. Clinicians should explicitly indicate their suspicion. It is possible that a significant proportion of cases are never correctly diagnosed. In the case of the symptoms described above, the pathological diagnosis of HIV-associated lymphadenopathy should not be accepted too easily. HIV alone rarely causes such severe illness! The germinal centers of affected lymph nodes have an onion-skin appearance with vascular proliferation. Hyaline-vascular and plasma cell types of Castleman’s disease can be distinguished.

## Treatment

At present, there is no clear recommendation for a specific treatment for MCD. HAART should always be given, although it doesn’t always help (Dupin 1997, Lanzafame 2000, Aaron 2002, de Jong 2003, Sprinz 2004). Some cases have even been described to occur after starting HAART, leading to the suspicion that the inflammatory component of MCD may be increased by immune reconstitution (Zietz 1999). Apart from HAART, there are numerous, very diverse forms of therapy, which unfortunately means that so far none of them is particularly convincing. The problem lies also within the countless case reports, where a probable positive “publication bias” has to be taken into account. On the other hand, something has to be done quickly in HIV patients with MCD: the course of disease can be extremely fulminant. In our experience, CRP is a useful parameter aside from symptoms and signs, for measuring the course of disease and observing the effectiveness of MCD treatment.

**Immunomodulation** – because of the association with HHV-8, several antiviral substances have been tried, including ganciclovir, which was successful on at least one patient (Caspar 2003). However, in other cases, antiviral therapy with foscarnet

or didofovir had no benefit (Coty 2003, Senanayake 2003, Berezne 2004). For interferon, there are positive as well as negative examples (Coty 2003, Nord 2003). In HIV-negative patients, some very optimistic data from Japan has been published, in which 7 patients were successfully treated with anti-IL-6 receptor antibodies (Nishimoto 2000). Another new approach, supported by an encouraging number of case studies, is thalidomide, which is believed to inhibit cytokine dysregulation as well as the inflammatory component of MCD (Lee 2003, Jung 2004). In contrast, steroids have no effect on MCD.

**Immunochemotherapy** – well-tolerated chemotherapies such as vincristine (2 mg i.v. as a bolus at 14-day intervals) or oral etoposide (50 mg daily) have proven effective according to several reports as well as our own experience (Scott 2001). Even CHOP chemotherapy can help, but does not seem to significantly prolong survival. Rituximab, a monoclonal antibody against CD20-expressing cells, which is also used in B cell lymphomas (see above), is being tried in several patients (Corbellino 2001, Marcelin 2003, Marrache 2003, Kofteridis 2004). In a study on 5 HIV patients with MCD, remission was achieved in 3 (Marcelin 2003). However, there are also reports in which rituximab has no effect (Casquero 2005, Neuville 2005).

**Splenectomy** – in severe cases, splenectomy may be appropriate. In a series of 40 patients, the median survival following splenectomy was 28 versus 12 months (Oksenhendler 2002). According to a US team, the symptoms were improved in 10/10 patients following splenectomy (Coty 2003). Why this should occur, is currently unclear. It is speculated that IL-6 production is reduced and that a large reservoir of HHV-8 is removed through the splenectomy.

## References

1. Aaron L, Lidove O, Yousry C, Roudiere L, Dupont B, Viard JP. Human herpesvirus 8-positive castleman disease in HIV-infected patients: the impact of HAART. *Clin Infect Dis* 2002, 35:880-2. <http://amedeo.com/lit.php?id=12228826>
2. Berezne A, Agbalika F, Oksenhendler E. Failure of didofovir in HIV-associated multicentric Castleman disease. *Blood* 2004, 103:4368-9.
3. Casper C, Nichols WG, Huang ML, Corey L, Wald A. Remission of HHV-8 and HIV-associated multicentric Castleman's disease with ganciclovir treatment. *Blood* 2003; Nov 13 [Epub ahead of print]. <http://amedeo.com/lit.php?id=14615380>
4. Castleman B, Iverson L, Menendez VP. Localized mediastinal lymph-node hyperplasia resembling lymphoma. *Cancer* 1956, 9: 822-830.
5. Corbellino M, Bestetti G, Scalomogna C, et al. Long-term remission of Kaposi sarcoma-associated herpesvirus-related multicentric Castleman disease with anti-CD20 monoclonal antibody therapy. *Blood* 2001;98:3473-5.
6. Coty PC, Astrow A, Gallinson D, et al. A single institution's experience treating castlemans disease in HIV positive patients. Abstract 2485, 39<sup>th</sup> ASCO 2003, Chicago, IL/USA
7. de Jong RB, Kluin PM, Rosati S, et al. Sustained high levels of serum HHV-8 DNA years before multicentric Castleman's disease despite full suppression of HIV with highly active antiretroviral therapy. *AIDS* 2003; 17:1407-8.
8. Dupin N, Krivine A, Calvez V, et al. No effect of protease inhibitor on clinical and virological evolution of Castleman's disease in an HIV-1-infected patient. *AIDS* 1997;11:1400-1.
9. Jung CP, Emmerich B, Goebel FD, Bogner JR. Successful treatment of a patient with HIV-associated multicentric Castleman disease (MCD) with thalidomide. *Am J Hematol* 2004, 75:176-7.
10. Kofteridis DP, Tzagarakis N, Mixaki I, et al. Multicentric Castleman's disease: prolonged remission with anti CD-20 monoclonal antibody in an HIV-infected patient. *AIDS* 2004, 18:585-6.
11. Lanzafame M, Carretta G, Trevenzoli M, et al. Successful treatment of Castleman's disease with HAART in two HIV-infected patients. *J Infect* 2000, 40:90-1. <http://amedeo.com/lit.php?id=10762119>

12. Lee FC, Merchant SH. Alleviation of systemic manifestations of multicentric Castleman's disease by thalidomide. *Am J Hematol* 2003; 73: 48-53. <http://amedeo.com/p2.php?id=12701121&s=hiv>
13. Marcelin AG, Aaron L, Mateus C, et al. Rituximab therapy for HIV-associated Castleman's disease. *Blood* 2003, 102:2786-8. <http://amedeo.com/p2.php?id=12842986&s=hiv>
14. Marrache F, Larroche C, Memain N, et al. Prolonged remission of HIV-associated multicentric Castleman's disease with an anti-CD20 monoclonal antibody as primary therapy. *AIDS* 2003;17:1409-10.
15. Nishimoto N, Sasai M, Shima Y, et al. Improvement in Castleman's disease by humanized anti-interleukin-6 receptor antibody therapy. *Blood* 2000;95:56-61. <http://amedeo.com/lit.php?id=10607684>
16. Nord JA, Karter D. Low dose interferon-alpha therapy for HIV-associated multicentric Castleman's disease. *Int J STD AIDS* 2003;14:61-2.
17. Oksenhendler E, Boulanger E, Galicier L, et al. High incidence of Kaposi sarcoma-associated herpesvirus-related non-Hodgkin lymphoma in patients with HIV infection and multicentric Castleman disease. *Blood* 2002, 99:2331-6. <http://amedeo.com/lit.php?id=11895764>
18. Oksenhendler E, Carcelain G, Aoki Y, et al. High levels of human herpesvirus 8 viral load, human interleukin-6, interleukin-10, and C reactive protein correlate with exacerbation of multicentric castleman disease in HIV-infected patients. *Blood* 2000, 96:2069-73. <http://amedeo.com/lit.php?id=10979949>
19. Oksenhendler E, Duarte M, Soulier J, et al. Multicentric Castleman's disease in HIV infection: a clinical and pathological study of 20 patients. *AIDS* 1996, 10:61-7. <http://amedeo.com/lit.php?id=8924253>
20. Scott D, Cabral L, Harrington WJ Jr. Treatment of HIV-associated multicentric Castleman's disease with oral etoposide. *Am J Hematol* 2001, 66:148-50. <http://amedeo.com/lit.php?id=11421297>
21. Senanayake S, Kelly J, Lloyd A, et al. Multicentric Castleman's disease treated with antivirals and immunosuppressants. *J Med Virol* 2003; 71: 399-403. <http://amedeo.com/p2.php?id=12966545&s=hiv>
22. Sprinz E, Jeffman M, Liedke P, et al. Successful treatment of AIDS-related Castleman's disease following the administration of highly active antiretroviral therapy (HAART). *Ann Oncol* 2004, 15:356-8.
23. Zietz C, Bogner JR, Goebel FD, Lohrs U. An unusual cluster of cases of Castleman's disease during HAART for AIDS. *N Engl J Med* 1999, 340:1923-4.





Part 5

## Special Chapters



## 15. The New HIV Patient

Sven Philip Aries, Bernhard Schaaf

### The initial interview

Can and should be spread over several appointments at short intervals.

### What the patient should know afterwards

- In general terms, how the virus causes illness.
- The difference between being HIV-infected and suffering from AIDS.
- The importance of CD4+ T-cells and virus load.
- How other people can become infected and how this can be avoided with a great degree of certainty.
- That additional venereal diseases should be avoided, as these can worsen the course of HIV infection; and that it is, at least in theory, possible to become infected with another more pathogenic or resistant strain of HIV.
- Where HIV therapy comes in and how good it can be.
- A healthy balanced diet and regular physical exercise can help improve the prognosis.
- Smoking increases the risk of a number of complications.
- Where to find further information.
- The self-help groups and facilities available in the area for the support of HIV-infected patients.
- What further tests are planned and their usefulness for future treatment.

### What the doctor should know afterwards

#### Infection and risk

- When, where and why was the positive HIV test performed? Was there a negative test prior to this? What risks has the patient taken in the meantime? The question regarding risks can help in the assessment of potential dangers for the patient in further treatment. In the case of a patient without recognizable risk, the test result may be held in doubt until confirmation is given (see also “Laboratory”).
- Where has the patient been recently? This is important because certain germs, which are dangerous for the immunodeficient patient, occur in specific regions. For example, someone who has lived in Hollywood for a lengthy period has a relevant risk of histoplasmosis (which is very rare in Europe).
- What drugs are consumed? Large amounts of alcohol are not only toxic to the liver, but also make adherence more difficult due to loss of control. For smok-

ers, the cardiovascular complications of lipodystrophy during therapy are more threatening.

- Family history of diabetes.
- Tuberculosis among contacts of the patient.

### Concomitant illnesses

- What previous illnesses, what concomitant illnesses?
- Former treated or untreated infections and STDs, including syphilis and hepatitis B/C?
- What medications are taken regularly/occasionally?

### Social

- What is the social background of the patient? What does he do professionally? What duties does he have to fulfill? What are his priorities? Who knows about his infection? Who will help him when he becomes ill? Who does he talk to about his problems? Does he have any friends who are also infected? Is he interested in getting in touch with social workers or self-help groups?

## The laboratory

- The HIV test is checked in a cooperating laboratory. Western blot is only positive if gp41+120/160 or p24+120/160 react. Cross-reactive antibodies, for example in the case of collagenosis, lymphoma or recent vaccination can lead to false-positive test results.
- Complete blood count: 30-40 % of all HIV patients suffer from anemia, neutropenia or thrombopenia. Check-up at least every 3-6 months, asymptomatic patients included.
- CD4+ T-cell count at the beginning and every 3-4 months thereafter. Allow for variations (dependent on time of day, particularly low at midday, particularly high in the evening; percentage with less fluctuation; HTLV-1 co-infection leads to higher counts despite existing immunodeficit).
- Electrolytes, creatinine, GOT, GPT,  $\gamma$ GT, AP, LDH, lipase.
- Blood sugar determination in order to assess the probability of metabolic side-effects when undergoing antiretroviral therapy.
- Lipid profile, as a baseline determination to check the course of metabolic side-effects when undergoing antiretroviral therapy.
- Urine status (proteinuria is often a sign of HIV-associated nephropathy).
- Hepatitis serology: A and B, in order to identify vaccination candidates; C, in order to possibly administer HCV therapy prior to ART; perhaps also G, since this coinfection seems to have a positive effect on the course of HIV infection.
- TPHA test.
- Toxoplasmosis serology IgG. If negative: important for differential diagnosis, if CD4+ T-cells  $<150/\mu\text{l}$  – prevention of infection (no raw meat). If positive: medical prophylaxis if necessary.

- CMV serology (IgG). For the identification of CMV-negative patients. If negative: important for differential diagnosis, then information about prevention (safe sex). In cases of severe anemia, transfusion of CMV-negative blood only. If positive: prophylaxis if necessary.
- Varicella serology (IgG). If negative: in principle, active vaccination with attenuated pathogens is contraindicated, but at  $> 400$  CD4+ T-cells/ $\mu$ l it is probably safe and perhaps useful.

## The examination

- Physical diagnosis, including an exploratory neurological examination (incl. vibration sensitivity and mini-mental test).
- Tuberculin skin test according to Mendel Mantoux with 10IE (not Tine stamp test as sensitivity is too low). Positive if greater than 5 mm: give prophylaxis (3 months rifampicin and pyrazinamide is probably best); if negative: repeat examination annually.
- Chest X-ray. Contradictory recommendations, probably only makes sense in case of positive tuberculin skin test or clinical indications of disease of the thoracic organs.
- Sonographic scan of the abdomen. A harmless, informative examination as a baseline finding, but not mentioned in the standard guidelines.
- ECG and pulmonary function test. Simple tests to rule out any cardiovascular and pulmonary disease.
- For women, a PAP smear upon initial diagnosis, after 6 months and then, if negative, once a year. Important because of the approx. 1.7-fold increase in the risk of cervical carcinoma.
- For homosexually active males, an anal PAP smear is recommended every 3 years (due to approx. 80-fold increase in risk of anal carcinoma).
- Especially at low CD4+ T-cell counts (e.g.  $<200/\mu$ l) funduscopy (ophthalmological consultancy!) in order to rule out active CMV retinitis or scars. Advisable in cases of good immune status also (photographic documentation as a baseline).
- Nutritional advice and/or treatment of malnutrition.
- Verifying vaccinations (see chapter on vaccinations).
- Checking the necessity of OI prophylaxis.
- Checking the indication for an antiretroviral therapy.



## 16. Vaccinations and HIV

Dirk Albrecht and Thomas Weitzel

### General considerations

The increased morbidity and mortality of infectious diseases is a key feature of HIV infection. Vaccination and immunoprophylaxis can make an important contribution to their prevention. In this chapter, we discuss the potential benefits and risks of vaccinating HIV patients, and provide an overview of available vaccines and post-exposure prophylactic measures and their proper use.

Vaccination recommendations should always take into account the national guidelines, which reflect the strategies for preventing infectious diseases that differ sometimes from country to country. Also, the availability of vaccines may vary. This chapter is, to a certain extent, based on the German standards and the vaccines marketed in Germany.

### Assessing potential benefits of a vaccination

**What is the current status of protection?** Is a prior infection documented or likely? Are prior vaccinations documented? Depending on their immune status, a poorer response to previous vaccines and an accelerated decline of protective immunity over time must be expected in HIV patients. Antibody titer controls should be considered more frequently than in healthy individuals.

**What is the individual risk of acquiring a specific infection?** Amongst other things, the medical history should include sexual behavior, contact to people carrying a particular infection, travel, and contact with children.

**What are the chances of developing protective immunity after vaccination?** Poor immune status at the time of vaccination decreases the likelihood of developing a protective response. As a general rule, CD4+ T-cell counts  $< 300/\mu\text{l}$  may result in a reduced response to immunization; at  $< 100/\mu\text{l}$  significant immunization effects are improbable (Castelli & Patroni 2000). ART-mediated immune reconstitution effects require a dynamic approach to vaccination strategies. Consequently, vaccinations should be reconsidered if CD4+ T-cells rise to  $> 200/\mu\text{l}$  in patients on ART. Nevertheless, recent data shows that even after immune reconstitution, the CD4+ T-cell nadir might influence the effectiveness of vaccination (Lederman 2003). On the other hand, ART might have a positive effect on the success of vaccination.

### Assessing the risk of a vaccination

In 1992, the first report of an increased viral load following vaccination was published (Ho 1992). This effect, which reflects the stimulation of cellular immunity, is not apparent in vaccine non-responders, however, it has been observed following various vaccinations including tetanus, pneumococci, influenza, and hepatitis B. Vaccination provoked viral replication peaks one to three weeks later; thus, a rou-

tine viral load should not be performed within four weeks of vaccination. Numerous studies demonstrated that these viral load elevations are transient, and immunologically and clinically irrelevant. Nevertheless, activated replication carries the increased risk of viral mutation. In a study in influenza vaccinees, this theoretical concern was confirmed in 2 out of 34 patients whose HIV strains developed new RT- or protease-gene mutations (Kolber 2002). This risk of developing resistant strains might need to be considered in patients with limited therapeutic options. Furthermore, elevations of viral load might lead to an increased risk of maternal-fetal transmission during pregnancy.

Adverse effects of inactivated vaccines are not increased in HIV patients. In live vaccines, however, the rate of severe infection caused by the vaccine strain itself is increased: life-threatening and fatal complications have been reported following live vaccines, including those for smallpox, tuberculosis, measles, and yellow fever. Consequently, live vaccines were contraindicated in HIV patients. Nowadays, however, this rule does not need to be strictly applied, since the patient's immune status as well as the potential for severe side effects of the particular live vaccine must be considered.

## **Vaccination of contacts**

Whenever HIV patients are susceptible to vaccine-preventable infections, particular care should be taken to vaccinate close contacts, who, after gaining protective immunity, will not transmit the disease. However, if contacts are vaccinated with certain live vaccines (e.g. oral polio vaccine), the HIV patient is at risk of acquiring vaccine-associated illness. Thus, oral polio vaccination of contact persons is contraindicated and the inactivated vaccine should be used. Secondary transmission of MMR or varicella following vaccination is very unlikely. But, if contacts develop vaccine-associated varicella, the HIV patient should receive acyclovir prophylaxis.

## **Summary**

The indications and optimal timing for a vaccination depend on individual factors such as the stage of HIV infection and the exposure risk to the particular infectious disease. Patients in the early stages of HIV should be vaccinated as soon as possible. In patients with severe immunodeficiency, active vaccinations rarely generate protective immunity and some are even contraindicated. These patients should be informed about how to avoid exposure, and contacts should be vaccinated. For some agents, passive immunization or post-exposure antibiotic prophylaxis are available. When antiretroviral therapy leads to a sustained rise in CD4 counts, vaccinations should be reconsidered and/or repeated.

## **Vaccinations in HIV-infected children**

HIV-infected children should be vaccinated according to national children vaccination schedules, with the following exceptions:



- (1) In children with severe immunodeficiency, as defined by CD4+ T-cell counts < 750/ $\mu$ l (0-12 months old), < 500/ $\mu$ l (1-5 years old), and < 200/ $\mu$ l (> 5 years old), or by relative CD4 counts < 15 %, MMR vaccination is contraindicated.
- (2) In children with a detectable immune deficit, as defined by relative CD4+ T-cell counts < 25 %, varicella vaccination is contraindicated.

A possible strategy to avoid unnecessary live vaccines is to predict their probability of success by measuring the response to other inactivated vaccines: if there is no measurable response to diphtheria/tetanus booster, a benefit from live vaccines such as MMR or varicella is unlikely, even if CD4+ T-cell counts are higher than the above mentioned limits (Tim Niehues, pers. comm.). In these cases, immunoglobulin prophylaxis might be useful.

HIV-infected children should receive a series of the 7-valent pneumococcal conjugate vaccine, starting in the third month of life, and supplemented by the 23-valent-polysaccharide vaccine after the second year of life.

## Postexposure prophylaxis

In susceptible individuals, the risk of infection and/or disease severity can be reduced by postexposure prophylactic measures. These include active and passive immunizations as well as chemoprophylaxes. Usually, the time between exposure and beginning prophylactic measures is crucial and should be minimized. Table 2 provides an overview of reasonable postexposure prophylaxis regimens in HIV patients.

## Practical approach to vaccinations

### Informed consent

HIV patients should be circumstantially informed regarding the benefits and risks of vaccines, with particular attention to HIV-related vaccine problems. The obligation to inform vaccinees follows national recommendations and has been recently summarized in Germany (STIKO 2004).

Some countries might require written information material and/or a written informed consent. Vaccine information statements in different languages are available via the Internet (e.g. [www.immunize.org](http://www.immunize.org)).

### Timing of a vaccination

Vaccination should be postponed in the presence of a moderate to severe acute infection; a mild infection might be ignored. Live vaccines such as MMR, varicella or yellow fever have to be given either simultaneously or at least four weeks apart from one another. After a dose of immunoglobulin, live vaccines should not be administered within the following three months.

At times when exact viral load measurements are crucial for decisions on ART, all vaccinations should be postponed as they can influence viral replication.

## Primary vaccination series or booster

A primary vaccination schedule is only necessary when no prior vaccination is reported or documented. A past incomplete primary series should be completed, but not repeated. In view of the insufficient data, the monitoring of immune protection by antibody tests should be performed more liberally in HIV patients than in the general population.

## Route of application

Vaccination routes are recommended by the manufacturer of each vaccine. High immunogenicity and few complications make intramuscular injections the preferable route of application for the majority of vaccines. The most recommended site is the deltoid muscle, in infants the anterolateral thigh. Many water-soluble vaccines can also be administered subcutaneously. In hemophiliacs, subcutaneous vaccination followed by thorough compression of the injection site for > 2 minutes usually allows vaccination without the coadministration of clotting factors. Only a few vaccines require subcutaneous injection, including meningococcal polysaccharide, Japanese encephalitis, yellow fever, and varicella vaccines. Intradermal rabies vaccination, which is licensed in some countries, should not be performed in HIV patients due to reduced immunogenicity.

## Side effects

The most common side effects after injection of a vaccine are transient and mild. They include reddening, swelling and pain at the injection site. Occasionally, hours to days after the vaccination, elevated body temperature, headache and malaise are reported. Severe vaccination side effects should be reported to health authorities and/or the vaccine manufacturers.

## Combining vaccines

For both primary vaccination series and booster doses it is recommendable to combine vaccines to minimize patient discomfort as well as cost. With some variations between countries, due to differing licensing status, a growing number of vaccines are available in fixed combinations.

## Documentation

Vaccinations should be documented in the patient's medical records as well as in a vaccination card to be kept by the patient. For the latter, a World Health Organization-recommended form can be ordered either through the WHO or national providers. Full documentation includes brand, manufacturer, and lot number of the vaccine.

## Details on individual vaccines

**Tetanus/Diphtheria:** Following a primary series during childhood, lifelong protection should be maintained by boosting at regular intervals. Depending on their CD4+ T-cell count, HIV patients have a reduced booster response and an accelerated antibody waning (Moss 2003). According to a Danish study (Kurtzhals 1992)

and our own experiences in Germany, adult HIV patients frequently have insufficient protection against diphtheria. Whenever possible, tetanus-diphtheria combination vaccines should be used, which, in Germany, are also available in combination with polio and/or pertussis. In the context of a rising incidence of pertussis in adolescents and adults, boosting with acellular pertussis vaccine in adolescents has recently been recommended, and is under discussion for adults (Halperin 2005). Since the adult pertussis booster vaccines are exclusively available in the above-mentioned combinations in Germany as well as in other countries, their use should be considered when tetanus/diphtheria vaccines are given.

**Pneumococcal:** HIV patients have an increased risk of invasive pneumococcal infections (Hirschtick 1995). However, in patients with CD4+ T-cell counts  $< 500/\mu\text{l}$ , the response to pneumococcal polysaccharide vaccine was decreased (Weiss 1995), and a double-dose booster did not induce a better response (Rodriguez-Barradas 1996). Similar observations were made with the conjugate vaccine in HIV-infected adults and children (Ahmed 1996, Mahdi 2005). However, the pneumococcal vaccine seems to protect from invasive infections (Breiman 2000, Grau 2005).

Confusing data arose from a prospective randomized study on 1,392 HIV patients in Uganda, which reported an increased incidence of pneumococcal infections in the vaccine group (French 2000). Selective destruction of activated B-cell clones, hypothesized to be the underlying mechanism, could not be verified by further investigations (French 2004). Remarkably, long-term follow-up of the initial patient collective showed reduced mortality in the vaccine group, making the assessment of the effects of pneumococcal vaccination in an African setting on patients without ART even more difficult (Watera 2004).

According to current recommendations, HIV patients with CD4+ T-cells  $> 200/\mu\text{l}$  should receive pneumococcal vaccination as early as possible after their HIV diagnosis. In patients with CD4+ T-cell counts  $< 200/\mu\text{l}$ , the effectivity of the vaccine is uncertain, but vaccination should be considered. If, in the course of ART, CD4+ T-cells rise to a stable count of  $> 200/\mu\text{l}$ , pneumococcal vaccination should be repeated. Infants from 3 months to 2 years of age should be vaccinated with the 7-valent conjugate vaccine, supplemented by the 23-valent polysaccharide vaccine at age  $> 2$  years. An interval of  $> 2$  months should be kept between the two vaccines.

**Influenza:** Among HIV patients, an increased incidence of influenza has not been found, but complications and severe courses are more common and increased mortality has been observed (Lin & Nichol 2001). Several studies documented a good tolerability of the vaccine in HIV patients (Zanetti 2002). Thus, yearly vaccination at the beginning of the influenza season is recommended for all HIV patients older than six months. In children under ten years of age, the first vaccination should include two doses at a 4-week interval. When CD4+ T-cells are  $< 100/\mu\text{l}$ , a response is rarely measurable, and it is unclear whether the benefit outweighs the cost (Rose 1993). The intranasal live vaccine is contraindicated in HIV patients.

**Hepatitis B:** HIV/HBV coinfection is a common problem with dual adverse effects since both the risk of chronic HBV infection and the risk of severe HIV-related complications are increased. Thus, all HIV patients seronegative to HBV should be vaccinated (Laurence 2005). The vaccination response rate and durability, being

generally reduced in HIV patients, correlate with CD4+ T-cell counts. Vaccination should thus be performed early following the diagnosis of HIV, and possibly be repeated following immune reconstitution caused by ART. The immune response should be monitored by anti-HBs levels 4-8 weeks after the last dose: anti-HBs levels  $> 100$  IE/l indicate protective immunity; a booster should be performed after ten years. With levels  $< 100$  IE/l, the response is inadequate and an immediate booster should be performed followed by another antibody control. Persistent non-responders should be vaccinated with higher doses of antigen, which are recommended for dialysis patients and other forms of immunosuppression (Poland 2004). High dose hepatitis B vaccines might be useful as first-line vaccines in HIV patients (Fonseca 2005), but more studies are needed for general recommendations.

**Hepatitis A:** This infection is common among HIV patients, but HIV usually causes little aggravation of its course. In a French HIV cohort, 5.8 % acquired acute hepatitis A per year (Fonquernie 2001). The vaccine is indicated in patients with chronic liver disease or increased risk of exposure, e.g. MSM, hemophiliacs, travelers to high-prevalence regions. Routine pre-vaccination serology (HAV IgG) is not generally recommended, but can be considered in patients with possible prior exposure (e.g. Germans born before 1950). A combination with HBV is available and reduces costs.

**Measles:** As measles can cause severe disease in HIV patients, susceptible patients should be vaccinated whenever possible. The status of protection should be checked prior to trips in endemic areas. Unless two vaccinations are documented, a serological test should be performed. In the US, persons born before 1957 are considered immune. The MMR vaccine is used in Germany, but this is contraindicated in symptomatic HIV infection and/or with CD4+ T-cell counts  $< 200/\mu\text{l}$  or  $< 14$  % (in children: age-specific thresholds). For susceptible patients, post-exposure immunoglobulin is indicated in certain high-risk situations even prior to exposure.

**Yellow fever:** Information on the effectivity and safety of yellow fever vaccine in HIV patients is only available from  $< 50$  patients, all with CD4+ T-cell counts  $> 200/\mu\text{l}$  (Goujon 1995, Receveur 2000, Tattevin 2004). These limited data indicate good tolerability, but reduced rates of seroconversion. One case report describes fatal encephalitis in a patient with a low CD4+ T-cell count, who was asymptomatic at the time of vaccination (Kengsakul 2002). International recommendations state that vaccination is possible in asymptomatic HIV patients with CD4+ T-cell counts  $> 200/\mu\text{l}$ . Due to reduced response rates, titer controls might be useful. We recommend the documentation of seroconversion in a paired serum sample (before, and 2-3 weeks after vaccination). If vaccination is contraindicated, a medical waiver should be issued to patients traveling to countries where yellow fever vaccination is mandatory. However, if there is a substantial risk of exposure, unvaccinated patients should be advised to abandon the journey.

**Table 1: Vaccines and their indications<sup>1</sup>**

Vaccine type	Schedule <sup>2</sup>	Indication <sup>2</sup>	Comments
<b>Cholera<sup>3</sup></b> inactivated + toxoid	primary: 2x (d 0, wk 1-6) protection: 2 y	travelers with high risk of exposure <sup>5</sup>	also limited protection against some forms of travelers' diarrhea
<b>Diphtheria</b> toxoid	primary: 3x (d 0, wk 4-8, mth 6-12) boost every 10 y	generally recommended	reduced dose after 6 <sup>th</sup> year of life
<b><i>Hemophilus influenzae b</i> (HiB)</b> polysaccharide	primary: according to childhood schedule	generally recommended in childhood booster: not routine	Incidence of HiB infections in HIV patients low
<b>Hepatitis A</b> inactivated	primary: 2x (d 0, mth 6) boost after 10 y	chronic liver disease increased risk of exposure (e.g. MSM, hemophilia, travel to endemic area)	
<b>Hepatitis B</b> recombinant antigen	primary: 3x (d 0, wk 4, mth 6) boost after 10 y or according to antibody level	generally recommended in childhood generally recommended in HIV patients	
<b>Influenza<sup>3</sup></b> inactivated/fractionated antigen	1x per year	generally recommended in HIV patients	year-specific antigen combination according to WHO
<b>Japanese encephalitis</b> inactivated	primary: 3x protection: 3 y	travelers with high risk of exposure <sup>5</sup>	
<b>Measles</b> live attenuated	children: 2x adults: 1x	generally recommended in childhood susceptible HIV-patients <sup>5</sup> travelers to endemic area	recommended only in asymptomatic HIV-infection and CD4 > 200/μl (> 14 %)
<b>Meningococcal (groups A, C, W135, Y)</b> I. 4-valent polysaccharide II. 4-valent conjugate	1x	immunodeficiency (e.g. complement deficiencies, asplenia) travelers with high risk of exposure <sup>5</sup>	no protection against serotype B (high prevalence in Europe and Brazil) mandatory for pilgrims to Saudi-Arabia some countries: recommended for children, students
<b>Mumps</b> live attenuated	children: 2x adults: 1x	generally recommended in childhood susceptible persons <sup>5</sup> with frequent contact to children	HIV: recommended only in asymptomatic HIV infection and CD4 > 200/μl (> 14 %)

**Table 1: Vaccines and their indications<sup>1</sup>**

Vaccine type	Schedule <sup>2</sup>	Indication <sup>2</sup>	Comments
<b>Pertussis</b> purified acellular antigens	primary: according to childhood schedule boost: 1x in 11 <sup>th</sup> to 18 <sup>th</sup> year of life	generally recommended in childhood increased risk of exposure (e.g. hospital personnel, childcare facilities): boost every 10y	some countries may change their strategy to general recommendation for lifelong booster
<b>Pneumococcal</b> I. 23-valent polysaccharide II. 7-valent conjugate	I: primary: 1x boost every 6 y II: in children only 1x – 4x depending on age	general recommendation for HIV patients I: 2 years and older II: 2 months and older; no advantages to I in adults	protection only against subset of the naturally occurring strains
<b>Poliomyelitis<sup>3</sup></b> inactivated	primary: 4x (according to childhood schedule) boost: 1x in 11 <sup>th</sup> to 18 <sup>th</sup> year of life	children: generally recommended adults: increased risk of exposure (e.g. health care, travel to endemic areas): boost after 10 y	avoid live vaccine (OPV) in HIV patients and their contacts
<b>Rabies</b> inactivated	primary: see manufacturer protection: 3-5 y	occupational risk of animal contact travelers with high risk of exposure <sup>4</sup>	HIV: often poor response, serological testing recommended, no intradermal vaccination
<b>Rubella</b> live attenuated	children: 2x adults: 1x	generally recommended in childhood susceptible persons <sup>5</sup> with frequent children contact women of child-bearing age	HIV: recommended only in asymptomatic HIV infection and CD4 > 200/μl (> 14 %)
<b>Smallpox</b> live attenuated	Controversial	HIV infection is contraindication for prophylactic vaccination	HIV patients should avoid contact with vaccinees for 2 weeks (risk of transmission of vaccine strain)
<b>Tetanus</b> toxoid	primary: 3x (d 0, wk 4-8, mth 6-12) boost every 10 y	generally recommended	
<b>Tick-borne encephalitis</b> inactivated	primary: 3x (d 0, mth 1-3, mth 9-12) (accelerated: d 0, d 7, d 21) boost according to manufacturer	inhabitants of/travelers to endemic regions with risk of tick exposure	consider regional distribution profile European TBE vaccine is probably protective against RSSE (Hayasaka D 2001)
<b>Tuberculosis</b> live BCG-strain	1x in newborns	not recommended in Germany	HIV is a contraindication
<b>Typhoid fever<sup>3</sup></b> polysaccharide	1x	travelers with high risk of exposure <sup>4</sup>	

**Table 1: Vaccines and their indications<sup>1</sup>**

Vaccine type	Schedule <sup>2</sup>	Indication <sup>2</sup>	Comments
<b>Varicella</b> live attenuated	age 11 mths- 12 y: 1x age > 12 y: 2x (> 6 wks apart)	generally recommended in childhood/adolescence susceptible persons <sup>5</sup> with frequent contact to children or immunosuppressed patients women (child-bearing age)	HIV: not licensed for HIV patients; vaccination can be considered in asymptomatic patients with CD4 > 25 %
<b>Yellow fever</b> live attenuated	1x (> 10 d prior to possible exposure) protection: 10 y	travelers to endemic areas travel requirements in some countries!	vaccination only in authorized institutions HIV: asymptomatic HIV-infection and CD4 > 200/ $\mu$ l

**Notes**

d = day, wk = week, mth = month, y = year

- Also observe national vaccination guidelines and manufacturer's recommendations
- Schedules and indications mainly adapted to standards and available vaccines in Germany. Strategies in other countries may vary.
- Live vaccine also available, but not recommended in HIV patients
- Disease specific definitions. If in doubt, seek travel advice.
- Susceptible*: No documented history of the disease, no prior vaccination, no specific antibodies in serological test.

**Table 2: Postexposure vaccines and chemoprophylaxes**

Disease	type of prophylaxis	Indication	Comments
<b>Diphtheria</b>	I. active immunization II. chemoproph.	close / face-to-face contact with a case patient I. if last vaccination > 5 y II. independent of immunization status	II: e.g. erythromycin 4x 500 mg/d x 7-10 d
<b><i>Hemophilus influenzae b</i></b>	chemoproph.	patients with immunosuppression or persons from their close environment after close contact with a case patient	rifampicin 1x 600 mg/d x 4 d
<b>Hepatitis A</b>	I. active immunization II. simultaneous immunoglobulin	I: every exposure of a susceptible <sup>1</sup> person II: additionally in patients at risk of severe course (e.g. HBV- or HCV-infection)	
<b>Hepatitis B</b>	I. active immunization/booster II. simultaneous immunoglobulin <sup>5</sup>	protection status after percutaneous exposure <sup>2</sup> : insufficient: I+II partial: I complete: not needed	

**Table 2: Postexposure vaccines and chemoprophylaxes**

<b>Disease</b>	<b>type of prophylaxis</b>	<b>Indication</b>	<b>Comments</b>
<b>Influenza</b>	I. active immunization II. chemoproph.	I: community outbreak with strain covered by vaccine II: direct exposure of any unvaccinated HIV patient; in patients with severe immunodepression independent of their immunization status	II: Influenza A: amantadine 2x 100 mg/d (> 65 years: 1x 100 mg/d) Influenza A or B: oseltamivir: 1x 75 mg/d for details see ACIP (Harper 2005)
<b>Measles</b>	I. active immunization/booster II. (simultaneous) immunoglobulin <sup>5</sup>	I: exposure of a susceptible <sup>1</sup> person II: exposure of a susceptible <sup>1</sup> person with more than mild immunosuppression, when response to active immunization is unlikely or immunization is contraindicated	active immunization within 72 hours of exposure consider contraindications for vaccination!
<b>Meningococcal</b>	I. active immunization II. chemoproph.	following an index case: I: according to health authorities II: all household members; persons in contact with oropharyngeal secretions; close contacts in child-care centers, dormitories	II: rifampicin 2x 600 mg/d x 2 d or ciprofloxacin 1x 500 mg or ceftriaxone 1x 250 mg i.m.
<b>Mumps</b>	active immunization	exposure of a susceptible <sup>1</sup> person	active immunization within 3 (-5) days of exposure consider contraindications for vaccination!
<b>Pertussis</b>	I. active immunization II. chemoproph.	I: exposure and incomplete immunization II: close contacts, e.g. household contacts	chemoprophylaxis within 7 days of exposure erythromycin 4x 500 mg/d x 14 d (alternatively: clarithromycin, cotrimoxazole)
<b>Polio</b>	I. active immunization	any exposure independent of immunization status	avoid delays!
<b>Rabies</b>	I. active immunization/booster II. simultaneous immunoglobulin <sup>5</sup>	according to national or local recommendations	HIV: consider double dose of active vaccine on day 0, consider immunoglobulin more liberally in immunosuppressed patients
<b>Rubella</b>	active immunization	exposure of a susceptible <sup>1</sup> person	active immunization is indicated within 5 days of exposure consider contraindications for vaccination!



**Table 2: Postexposure vaccines and chemoprophylaxes**

Disease	type of prophylaxis	Indication	Comments
<b>Tetanus</b>	I. active immunization/booster II. simultaneous immunoglobulin <sup>5</sup>	I: vaccine status unknown, incomplete primary series or last booster > 5 years ago II: unknown, 0 or 1 dose of primary series or 2 doses of primary series and > 24 hours between injury and booster	after minor, clean wounds: booster only if last is > 10 years ago; simultaneous immunoglobulin not needed
<b>Tuberculosis</b>	chemoproph.	HIV patient after contact with open TB case	treat in analogy to latent TB (see TB chapter)
<b>Varicella</b>	I: active immunization II: simultaneous immunoglobulin <sup>5</sup> III: chemoproph.	I: chickenpox exposure <sup>3</sup> of a susceptible <sup>1</sup> patient; zoster exposure <sup>4</sup> of a susceptible <sup>1</sup> patient II: exposure <sup>3,4</sup> of a susceptible <sup>1</sup> patient with more than mild immunosuppression < 96 hours after exposure III: exposure <sup>3,4</sup> of a susceptible <sup>1</sup> patient with more than mild immunosuppression > 96 hours after exposure	I: up to 5 days after exposure or 3 days after beginning of exanthema; consider contraindications! III: limited data on prophylactic acyclovir (see Hambleton 2005)

**Notes**

- susceptible*: No documented history of the disease, no prior vaccination, no specific antibodies on serological testing.
- hepatitis b* protection status: (if available within 48 hrs, test anti-HBs titer)  
*complete*: good responder and last dose < 5 years ago; or anti-HBs > 100 IE/ml within the last 12 months  
*partial*: good responder and last dose > 5, but < 10 years ago; or current anti-HBs documented > 10 (but < 100) IE/ml  
*insufficient*: anything less than partial or complete protection  
*good responder*: anti-HBs documented > 100 IE/ml after primary series
- chickenpox exposure*: face-to-face contact, household contact, > 1 hour in the same room.
- zoster exposure*: direct contact with skin lesions or their secretions. The indication for immunoprophylaxis following zoster exposure is unclear due to insufficient data; stated is the personal opinion of the authors.
- specific hyperimmunoglobulin available in some countries

**References**

- Ahmed F, Steinhoff MC, Rodriguez-Barradas MC, Hamilton RG, Musher DM, Nelson KE. Effect of human immunodeficiency virus type 1 infection on the antibody response to a glycoprotein conjugate pneumococcal vaccine: results from a randomized trial. *J Infect Dis* 1996; 173: 83-90.
- Breiman RF, Keller DW, Phelan MA, Sniadack DH, Stephens DS, Rimland D. Evaluation of effectiveness of the 23-valent pneumococcal capsular polysaccharide vaccine for HIV-infected patients. *Arch Intern Med* 2000; 160:2633-8.

## 530 Vaccinations and HIV

3. Castelli F, Patroni A. The human immunodeficiency virus-infected traveler. *Clin Infect Dis* 2000; 31: 1403-8.
4. Center for Disease Control and Prevention. Influenza Antiviral Medications: 2004-05 Interim Chemoprophylaxis and Treatment Guidelines. October 18, 2004. siehe <http://www.cdc.gov/flu/professionals/treatment/0405antiviralguide.htm>
5. Fonquernie L, Meynard JL, Charrois A, Delamare C, Meyohas MC, Frottier J. Occurrence of acute hepatitis A in patients infected with human immunodeficiency virus. *Clin Infect Dis* 2001; 32: 297-9.
6. Fonseca MO, Pang LW, de Paula Cavalheiro N, Barone AA, Heloisa Lopes M. Randomized trial of recombinant hepatitis B vaccine in HIV-infected adult patients comparing a standard dose to a double dose. *Vaccine* 2005; 23: 2902-8.
7. French N, Nakiyingi J, Carpenter LM, Lugada E, Watera C, Moi K. 23-Valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults: double-blind, randomised and placebo controlled trial. *Lancet* 2000; 355: 2106-11.
8. French N, Moore M, Haikala R, Kaythy H, Gilks CF. A case-control study to investigate serological correlates of clinical failure of 23-valent pneumococcal polysaccharide vaccine in HIV-1-infected Ugandan adults. *J Infect Dis* 2004; 190:707-12.
9. Goujon C, Tohr M, Feuille V, Coulaud JP, Dupont B, San-Sonetti P. Good tolerance and efficacy of yellow fever vaccine among subjects carriers of HIV. 4th Int Conf Travel Med, Acapulco, 1995, Abstract 32.
10. Grau I, Pallares R, Tubau F et al. Epidemiologic changes in bacteremic pneumococcal disease in patients with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Arch Intern Med* 2005; 165: 1533-40.
11. Halperin SA. Pertussis- a disease and vaccine for all ages. *N Engl J Med* 2005; 353: 1615-7.
12. Hambleton S, Gershon AA. Preventing varicella-zoster disease. *Clin Microbiol Rev*. 2005 Jan;18(1):70-80
13. Harper SA, Fukuda K, Uyeki TM, et al. Prevention and control of influenza. Recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2005; 54: 1-40.
14. Hayasaka D, Goto A, Yoshii K, Mizutani T, Kariwa H, Takashima I. Evaluation of European tick-borne encephalitis virus vaccine against recent Siberian and far-eastern subtype strains. *Vaccine*. 2001 Sep 14;19(32):4774-9.
15. Hirschtick RE, Glassroth J, Jordan MC, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. *N Engl J Med* 1995; 333: 845-51.
16. Ho DD. HIV-1 viraemia and influenza. *Lancet* 1992; 339:1549.
17. Kengsakul K, Sathirapongsasuti K, Punyagupta S. Fatal myeloencephalitis following yellow fever vaccination in a case with HIV infection. *J Med Assoc Thai* 2002; 85: 131-4.
18. Kolber MA, Gabr AH, De La Rosa A, et al. Genotypic analysis of plasma HIV-1 RNA after influenza vaccination of patients with previously undetectable viral loads. *AIDS* 2002; 16: 537-42
19. Kurtzhals JA, Kjeldsen K, Heron I, Skinhoj P. Immunity against diphtheria and tetanus in human immunodeficiency virus-infected Danish men born 1950-59. *APMIS* 1992; 100: 803-8.
20. Laurence JC. Hepatitis A and B immunizations of individuals infected with human immunodeficiency virus. *Am J Med* 2005; 118(Suppl 10A): 75S-83S.
21. Lederman HM, Williams PL, Wu JW, et al. Incomplete immune reconstitution after initiation of HAART in HIV-infected patients with severe CD4+ cell depletion. *J Infect Dis* 2003; 188: 1794-803.
22. Lin JC, Nichol KL. Excess mortality due to pneumonia or influenza during influenza seasons among persons with acquired immunodeficiency syndrome. *Arch Intern Med* 2001;161: 441-6.
23. Madhi SA, Kuwanda L, Cutland C, Holm A, Kaythy H, Klugman KP. Quantitative and qualitative antibody response to pneumococcal conjugate vaccine among African HIV-infected and uninfected children. *Pediatr Infect Dis J* 2005; 24: 410-6.
24. Moss WJ, Clements CJ, Halsey NA. Immunization of children at risk of infection with human immunodeficiency virus. *Bull World Health Organ* 2003; 81: 61-70.
25. Poland GA, Jacobson RM. Clinical practice: prevention of hepatitis B with the hepatitis B vaccine. *N Engl J Med* 2004; 351: 2832-8.
26. Receveur MC, Thiebaut R, Vedy S, Malvy D, Mercie P, Bras ML. Yellow fever vaccination of human immunodeficiency virus-infected patients: report of 2 cases. *Clin Infect Dis* 2000; 31: E7-8.
27. Rodriguez-Barradas MC, Groover JE, Lacke CE, et al. IgG antibody to pneumococcal capsular polysaccharide in HIV-infected subjects: persistence of antibody in responders, revaccination in nonresponders, and relationship of immunoglobulin allotype to response. *JID* 1996; 173: 1347-53.
28. Rose DN, Schechter CB, Sacks HS. Influenza and pneumococcal vaccination of HIV-infected patients: a policy analysis. *Am J Med* 1993; 94: 160-8.

29. STIKO. Hinweise für Ärzte zum Aufklärungsbedarf bei Schutzimpfungen. *Epidemiologisches Bulletin* 2004; Nr.6: 33-52.
30. Tettevin P, Depatureaux AG, Chapplain JM, et al. Yellow fever vaccine is safe and effective in HIV-infected patients. *AIDS* 2004; 18: 825-7.
31. Watera C, Nakiyingi J, Miro G, et al. 23-Valent pneumococcal polysaccharide vaccine in HIV-infected Ugandan adults: 6-year follow-up of a clinical trial cohort. *AIDS* 2004; 18:1210-3.
32. Weiss PJ, Wallace MR, Oldfield EC, et al. Response of recent HIV seroconverters to the pneumococcal polysaccharide vaccine and *Haemophilus influenzae* type b conjugate vaccine. *J Infect Dis* 1995; 171: 1217-22.
33. Zanetti AR, Amendola A, Besana S, Boschini A, Tanzi E. Safety and immunogenicity of influenza vaccination in individuals infected with HIV. *Vaccine* 2002; 20 (Suppl 5): B29-32.



## 17. Traveling with HIV

Thomas Weitzel

HIV patients are fond of traveling. In 1995, an American study revealed that 20 % of HIV patients had traveled in the previous two years, with 60 % of those having visited developing countries (Kemper 1995). In a 1996 study from the Netherlands, 20 % of the HIV patients reported traveling abroad within the past year (Simons 1999). Ever since, increasing expectancy and quality of life have caused a further rise in the travel activities of HIV patients.

### Travel preparations

Depending on their immune status, HIV patients bear an increased risk of travel-associated complications. In particular, if CD4+ T-cell counts are below 200/ $\mu$ l, there is a substantial threat of severe gastrointestinal and other opportunistic infections, which can be acquired while traveling. Furthermore, the effectiveness of vaccinations in this group of patients is reduced.

Therefore, HIV-infected individuals should carefully plan their travel. According to the destination and style of travel, the latest travel advice should be observed. A general overview of travel recommendations can be accessed through different Internet sites (Frädrieh 2000). Especially before traveling to tropical or subtropical countries, it is recommended to obtain additional information from travel medicine specialists. Long-term travelers should, in advance, clarify the treatment possibilities of HIV-related problems at their destination.

A first-aid kit for HIV-infected travelers should contain, besides the usual drugs (local antihistaminics, disinfectants, sun protection, analgesics, antipyretics, antiemetics, and antidiarrheals), an antibiotic for the empirical treatment of acute diarrhea (see below).

### Antiretroviral therapy (ART)

A newly started antiretroviral regimen should be proven to be effective and well tolerated for at least three months before long-term traveling takes place. Depending on the destination and the activities planned, interruption of therapy can be considered. If ART is being continued during traveling, the following aspects should be considered:

- A sufficient amount of antiretroviral drugs should be packed, preferably in the hand luggage (suitcases can get lost...).
- The availability of the ART at destination should be checked beforehand. When necessary, prescriptions and a medical letter in English should be taken along.
- For some countries it may be useful to pack antiretroviral drugs in neutral packages because of entry regulations (see below).

- Storage requirements for the drugs (refrigeration, etc.) must be checked in advance – especially when traveling over long distances.
- Steps to cope with an unplanned therapy interruption during travel should be discussed with the patient in advance.

## General precautions

The higher risk of gastrointestinal infections for HIV patients demands the adherence to the principles of food and water hygiene (see links below). The following food and drink are to be avoided:

- Raw fruit or vegetables that are not peeled
- Raw or undercooked meat or fish dishes
- Tap water
- Ice cubes made from tap water
- Unpasteurized milk or milk products
- Food prepared or distributed under insecure hygienic circumstances (e.g. street vendors)

Even brushing teeth or swimming carries the risk of swallowing small amounts of potentially contaminated water. In the lack of hygienic beverages, tap water should be boiled. In areas up to 2,000 meters above sea level, a boiling time of one minute kills all potential pathogens; at higher altitudes, the boiling time should be prolonged to three minutes. Chemical or filtration methods of water treatment are less reliable.

Certain vector-transmitted infections, e.g. leishmaniasis, pose a special risk to HIV-infected patients (see below). Repellents are helpful in avoiding those threats. Products containing at least 24 % DEET are internationally recommended. Sun protection has to be applied before repellent. Sleeping areas should be mosquito safe (a mosquito net is the best repellent!). Impregnation of clothes and mosquito nets with permethrin offers additional safety. Outdoors, long and bright clothes should be worn and outdoor stays during dawn or night ought to be avoided (see links).

Since condoms and lubricants abroad are not always of reliable quality, a sufficient amount of these products should be brought, to guarantee safe sex during the holiday.

Because of possible *Strongyloides stercoralis* infection (see below), direct skin contact to fecally contaminated soil should be avoided. It is wise to wear closed shoes and place a towel underneath when lying on the ground.

Precautions against zoonotic infections such as salmonellosis or cryptosporidiosis include proper hand washing following animal contact.

## Vaccinations

A travel medicine consultation is an opportunity to check and complete routinely recommended immunizations such as tetanus/diphtheria, pneumococcal, influenza, and hepatitis B vaccinations. It has to be kept in mind that the southern hemisphere influenza season is from April to September, while in the tropics influenza can oc-

cur all year long. Additional immunizations have to be considered according to travel style, duration, and destination. Open immunization questions usually require the consultation of a specialized institution (see links). Further details on this issue can be seen in the chapter on vaccinations in this book.

## Malaria prophylaxis

The interactions between antiretroviral drugs and drugs available for malaria prophylaxis, such as chloroquine, mefloquine, doxycycline, and Malarone™ (atovaquone/proguanil), are inadequately evaluated.

In healthy volunteers taking mefloquine (Lariam™) together with ritonavir, a 30 % reduction of the steady-state plasma level of ritonavir was reported; however, mefloquine did not change the ritonavir level after a single dose of ritonavir (Khaliq 2001). The explanation is probably a reduced bile production caused by mefloquine. No relevant interactions seem to occur if mefloquine is coadministered with nelfinavir or indinavir (Schippers 2000).

Chloroquine is metabolized by CYP2D6, but is also significantly excreted by the kidneys; explicit data on interactions of chloroquine with HIV drugs are lacking. In vitro, chloroquine inhibits HIV replication and shows synergistic effects together with protease inhibitors (Savarino 2001 and 2004). On the other hand, PIs display an inhibitory effect on plasmodia (Parikh 2005). Whether these observations could have an impact on the clinical management of HIV infection or malaria is still uncertain.

Clinical data on the interactions of atovaquone and proguanil with HIV drugs are missing. In vitro data indicate that ritonavir causes a reduced level of atovaquone and an increased level of proguanil. Atovaquone decreases the indinavir level by 20 % and increases the acyclovir level by 30 %.

Doxycycline is not metabolized by the cytochrome p450 system. Thus, relevant interactions with HIV drugs are not anticipated.

Available data and clinical experience indicate that mefloquine as well as doxycycline and chloroquine can be safely and effectively used in patients taking antiretroviral therapy. Although clinical studies are lacking, the same applies for Malarone™. Thus, recommendations for malaria prophylaxis are not limited by concomitant HIV medication.

Common drugs for malaria stand-by treatment are chloroquine, mefloquine, Malarone™, and Riamet™ (artemether/lumefantrine). Both components of Riamet™ are substrates of CPY3A4; due to incalculable increases in drug exposure, Riamet™ is contraindicated with protease inhibitors (see Riamet™ product information). With this exception, HIV patients should follow the same recommendations as healthy travelers. However, mefloquine is often unfavorable because of frequent neurological comorbidity in HIV patients.

## Entry regulations and travel insurance

Although contentious as a measure of health policy and not recommended by the WHO, more than 150 countries, including the USA, refuse entry to HIV infected individuals. This particularly affects long-term stays in connection with work or

study. To avoid problems, information on entry regulations should be obtained beforehand. Peter Wiessner and Karl Lemmen's brochure "Schnellfinder" provides an excellent and comprehensive overview on entry policies. In cooperation with David Haerry of the Swiss Aids Info Docu, a regularly updated version of this databank is available online (see links).

The American foreign ministry also publishes a list of countries with HIV-specific entry restrictions (see links). Under certain circumstances, e.g. visits to conferences, family members, or business travel, journeys to the USA are possible for HIV patients if they apply for a "visa waiver". However, the procedure is time consuming and the passport endorsement can complicate further travel to the USA or other countries.

Travel insurances usually exclude existing illnesses and often refuse HIV patients explicitly. For that reason, special HIV travel insurances have been made available in the UK and USA (see links).

## Special risks

### Enteric infections

Reduced immunological defense and diminished gastric acid production increase the risk for gastrointestinal infections in HIV patients. Furthermore, bacterial enteric infections such as salmonellosis, shigellosis, and *Campylobacter* infections bear a high risk of bacteremia and relapse. Infections caused by *Cryptosporidium sp.*, *Isospora belli* and microsporidia are dangerous due to chronicity. Therefore, HIV-infected patients must strictly observe proper water and food hygiene (Hayes 2003).

Prophylactic use of antibiotics, although reducing the prevalence of travel-associated diarrhea, is not generally recommended in HIV patients. In individual situations, e.g. HIV patients with advanced immunodeficiency traveling under poor hygienic conditions, prophylaxis with ciprofloxacin (500 mg per day) could be considered. In Southeast Asia, an increasing rate of quinolone resistance makes azithromycin a useful alternative. Because of widespread bacterial resistance, cotrimoxazole and doxycycline are not sufficient.

Travel-associated diarrheal diseases should be empirically self-treated for five to seven days with ciprofloxacin (500 mg per day) or alternatively azithromycin (400 mg per day). In afebrile episodes of non-bloody diarrhea, short-term use of loperamide is justified. Adequate oral rehydration has to be maintained.

### Malaria

Malaria does not behave like an opportunistic infection. However, the details on the interaction between HIV and malaria are widely unknown. Malaria seems to increase HIV replication through proinflammatory cytokines. HIV-infected pregnant women appear to have a higher malaria risk. Malaria-HIV coinfection in pregnancy is associated with increased parasitemia and a higher incidence of prematurity as well as low birth weight (Ayisi 2003, ter Kuile 2004). Until recently, the clinical influence of HIV infection on malaria was considered to be small except for the above mentioned problems in pregnancy. However, new data on HIV-infected ma-



alaria patients demonstrated a negative influence of the HIV infection on the clinical course of malaria (Grimwade 2004), a higher risk for severe malaria in patients with low CD4+ T-cell counts, and a high frequency of atypical malaria manifestation, e.g. respiratory or intestinal symptoms (Cohen 2005).

The efficacy of antimalarial prophylaxis and therapy is not influenced by HIV. Accordingly, recommendations for malaria therapy are generally applicable to HIV patients. As described above, drug interactions of antimalarial and HIV drugs are insufficiently established. The treatment of complicated malaria is especially problematic since the indicated drugs, quinine, quinidine, or artemisinin derivatives, are all metabolized by CYP3A4. The coadministration of these drugs with CYP3A4 inhibitors, especially protease inhibitors, efavirenz, and delavirdine, requires intensive care monitoring and, when possible, drug level monitoring.

## Measles

Measles, considered on a global level, is a common infection. In 2002, more than 200 million measles cases with about 600,000 deaths were reported worldwide (WHO, 2004). In HIV-infected patients, measles often runs a severe course. American studies showed a mortality rate of 40 %, mostly due to giant-cell pneumonitis (Kaplan, 1996). Non-immune HIV patients should therefore consider active or passive immunization before traveling to areas with a high prevalence of measles.

## Leishmaniasis

Visceral leishmaniasis (kala azar), caused by parasites of the *Leishmania donovani* complex, is a life-threatening opportunistic infection with limited therapeutic options. An analysis of imported cases in Germany showed that most cases of visceral leishmaniasis were acquired in European Mediterranean countries, long-term travelers were affected in particular, and HIV patients had a higher infection risk than healthy travelers (Weitzel 2005). Most frequently, HIV patients with CD4+ T-cell counts below 200/ $\mu$ l are affected (Kaplan 1996). Due to the infection's potentially extended latency period, symptoms can occur long after exposure in endemic areas. Diagnosis is challenging, mostly requiring cooperation with a specialized center. Cutaneous leishmaniasis does not seem to occur more frequently in HIV patients. Severely immunocompromised HIV patients must be informed of the risk of leishmaniasis even when traveling to Mediterranean countries. Preventive measures against mosquito bites should be followed in order to avoid leishmanial infections (see above); because of the vector's small size, the use of an impregnated mosquito net of small mesh size is advisable.

## Tuberculosis

Globally, tuberculosis is the most prevalent HIV-associated opportunistic infection. Before and after long-term travel to countries of high tuberculosis endemicity, a tuberculin skin test should be performed. Patients with a positive tuberculin skin reaction or with a known high risk exposure should receive a course of treatment for latent tuberculosis (see chapter "Tuberculosis"). HIV-infected individuals should avoid risk areas such as hospitals, prisons or homeless-shelters or wear adequate facemasks.

## Endemic mycoses

Endemic mycoses are rare infections. Nevertheless, they are able to cause life-threatening opportunistic infections in HIV patients even years after stays in endemic areas. Most agents of endemic mycoses are thought to enter the pulmonary tract after inhalation of infective spores. In areas endemic for *Penicillium marneffei* (South East Asia, Southern China) and *Coccidioides immitis* (south-west parts of the USA, parts of Central and South America), increased exposure to dust or soil should be avoided (e.g. construction sites, agriculture, garden work, excavations, storms). *Histoplasma capsulatum* is prevalent worldwide in soil contaminated with bird and bat droppings. Exposure might happen during eco or adventure tourism and should be avoided by HIV-infected persons. In individual cases, e.g. severely immunocompromised HIV patients with a foreseeable contact to agents of endemic mycoses, primary prophylaxis can be considered. Depending on the expected pathogen, either fluconazole or itraconazole should be prescribed.

Another fungus causing severe infections in HIV patients is *Sporothrix schenckii*. This pathogen, which occurs worldwide, enters the body through cutaneous lesions. Wearing gloves while working with plants, hay, or peat moss can reduce the sporotrichosis risk.

## Sexually transmitted diseases

A recent study reported the high sexual activity and frequency of risk behavior (unprotected sex) in young British tourists (Bellis 2004). In Germany, an estimated 5 to 10 % of HIV infections are acquired during holidays. HIV-positive travelers should be aware of the special risks that sexually transmitted diseases and HIV reinfection present to them.

## Other parasites

Due to hygienic and climatic circumstances, the following parasitic pathogens are more frequently found in developing countries and carry the risk of severe infection in HIV patients:

- *Strongyloides stercoralis* is prevalent in most tropical and subtropical areas. The parasite is transmitted by cutaneous larval invasion after skin contact with contaminated soil. In HIV patients, there is the risk of a “hyperinfection syndrome” with a high fatality rate (Gompels 1991). Besides HIV infection, corticosteroid use seems to be an additional risk factor, as these drugs seem able to increase larval maturation triggering a cycle of massive autoinfection.
- *Trypanosoma cruzi* is endemic in large parts of Latin America. This protozoan causes Chagas disease and is transmitted by triatomine bugs. Chagas disease, which often persists asymptotically for many years, can reactivate in severely immunocompromised HIV patients. In these cases, lesions radiologically resembling cerebral toxoplasmosis are often found in the central nervous system (Rocha 1994).
- *Babesia sp.*, prevalent worldwide, are able to cause infections in a broad spectrum of vertebrates and are transmitted by ticks. Severe infections, clinically mimicking malaria or manifesting as fever of unknown origin, mainly occur in

patients after splenectomy, but have also been reported in severely immunocompromised HIV patients (Falagas et Klempner 1996).

- Free-living amoeba (*Acanthamoeba sp.* and *Balamuthia mandrillaris*) are ubiquitous, living in soil and water. In HIV-infected and other immunocompromised patients, these organisms are capable of causing severe infections of the central nervous system (granulomatous encephalitis), as well as local infections of the skin and cornea (Sison 1995).

## Medical problems after traveling

The threat presented by the diseases discussed in this chapter makes it imperative that any symptom occurring after travel be checked. Because most tropical diseases are quite rare in temperate countries, diagnosis is often delayed. An analysis of imported visceral leishmaniasis revealed a median time span of 85 days until the diagnosis was established (Weitzel 2005). Furthermore, tropical diseases often manifest atypically in HIV patients (Karp et Neva 1999). In any event, differential diagnosis of febrile syndromes in HIV-infected individuals is very broad; after traveling abroad the clinical situation can become even more complex needing close cooperation of HIV and Tropical Medicine specialists.

## References

1. Ayisi JG, van Eijk AM, ter Kuile FO, et al. The effect of dual infection with HIV and malaria on pregnancy outcome in western Kenya. *AIDS* 2003; 17: 585-94.
2. Bellis MA, Hughes K, Thomson R, Bennett A. Sexual behaviour of young people in international tourist resorts. *Sex Transm Infect* 2004; 80: 43-7.
3. Cohen C, Karstaedt A, Freaun J, et al. Increased prevalence of severe malaria in HIV-infected adults in South Africa. *Clin Infect Dis* 2005; 41: 1631-7.
4. Falagas ME, Klempner MS. Babesiosis in patients with AIDS: a chronic infection presenting as fever of unknown origin. *Clin Infect Dis* 1996; 22: 809-12.
5. Frädriich A. Reisemedizinische Informationen im Internet: Cook it, peel it or leave it. *Deutsches Ärzteblatt* 2000; 97 (Supplement: Praxis Computer): 26-8. (Accessed November 11, 2004, at <http://www.aerzteblatt.de/v4/archiv/artikel.asp?id=23275>)
6. Gompels MM, Todd J, Peters BS, Main J, Pinching AJ. Disseminated strongyloidiasis in AIDS: uncommon but important. *AIDS* 1991; 5: 329-32.
7. Grimwade K, French N, Mbatha DD, Zungu DD, Dedicoat M, Gilks CF. HIV infection as a cofactor for severe falciparum malaria in adults living in a region of unstable malaria transmission in South Africa. *AIDS* 2004; 18: 547-54.
8. Hayes C, Elliot E, Krales E, Downer G. Food and water safety for persons infected with human immunodeficiency virus. *Clin Infect Dis* 2003; 36 (Suppl 2): S106-9.
9. Kaplan JE, Hu DJ, Holmes KK, Jaffe HW, Masur H, De Cock KM. Preventing opportunistic infections in HIV-infected persons: implications for the developing world. *Am J Trop Med Hyg* 1996; 55: 1-11.
10. Karp CL, Neva FA. Tropical infectious diseases in human immunodeficiency virus-infected patients. *Clin Infect Dis* 1999; 28: 947-63.
11. Khaliq Y, Gallicano K, Tisdale C, Carignan G, Cooper C, McCarthy A. Pharmacokinetic interaction between mefloquine and ritonavir in healthy volunteers. *Br J Clin Pharmacol* 2001; 51: 591-600.
12. Kemper CA, Linett A, Kane C, Deresinski SC. Frequency of Travel of Adults Infected with HIV. *J Travel Med* 1995; 2: 85-8.
13. Parikh S, Gut J, Istvan E, et al. Antimalarial activity of human immunodeficiency virus type 1 protease inhibitors. *Antimicrob Agents Chemother* 2005; 49: 2983-5.
14. Rocha A, de Meneses AC, da Silva AM, et al. Pathology of patients with Chagas' disease and acquired immunodeficiency syndrome. *Am J Trop Med Hyg* 1994; 50: 261-8.
15. Savarino A, Gennero L, Chen HC, et al. Anti-HIV effects of chloroquine: mechanisms of inhibition and spectrum of activity. *AIDS* 2001; 15: 2221-9.

## 540 Traveling with HIV

16. Savarino A, Lucia MB, Rastrelli E, et al. Anti-HIV effects of chloroquine: inhibition of viral particle glycosylation and synergism with protease inhibitors. *J Acquir Immune Defic Syndr* 2004; 35: 223-32.
17. Schippers EF, Hugten PW, den Hartigh J, et al. No drug-drug interaction between neftinavir or indinavir and mefloquine in HIV-1-infected patients. *AIDS* 2000; 14: 2794-5.
18. Simons FM, Cobelens FG, Danner SA. Common health problems in HIV-infected travelers to the (sub)tropics. *J Travel Med* 1999; 6: 71-5.
19. Sison JP, Kemper CA, Loveless M, McShane D, Visvesvara GS, Deresinski SC. Disseminated acanthamoeba infection in patients with AIDS: case reports and review. *Clin Infect Dis* 1995; 20: 1207-16.
20. ter Kuile FO, Parise ME, Verhoeff FH, et al. The burden of co-infection with human immunodeficiency virus type 1 and malaria in pregnant women in sub-saharan Africa. *Am J Trop Med Hyg* 2004; 71: 41-54.
21. Weitzel T, Mühlberger N, Jelinek T, et al. Imported Leishmaniasis in Germany 2001-2004: data of the SIMPID surveillance network. *Eur J Clin Microbiol Infect Dis* 2005; 24: 471-6.
22. The world health report 2004 - changing history. Geneva: World Health Organisation, 2004. (Accessed November 11, 2004, at <http://whqlibdoc.who.int/whr/2004/924156265X.pdf>)

## Links

- Travel Medicine  
<http://www.cdc.gov/travel/>  
<http://www.who.int/ith/>  
<http://www.crm.de/>
- Tropical Medicine institutions in Germany  
<http://dtg.org/98.html>
- German recommendations for malaria prophylaxis and therapy  
<http://dtg.org/malaria.html>
- Entry regulations and HIV-associated restrictions  
<http://www.aidsnet.ch/linkto/immigration/>  
<http://travel.state.gov/travel/HIVtestingreqs.html>
- Travel insurance and HIV infection  
<http://www.nat.org.uk/>  
<http://www.gay.com/travel/article.html?sernum=8580>
- Drinking water & mosquito protection  
<http://www2.ncid.cdc.gov/travel/yb/utills/ybGet.asp?section=reecs&obj=food-drink-risks.htm&cssNav=browsecyb>  
<http://www2.ncid.cdc.gov/travel/yb/utills/ybGet.asp?section=reecs&obj=bugs.htm&cssNav=browsecyb>

## 18. HIV and HBV/HCV Coinfections

Jan-Christian Wasmuth and Juergen Rockstroh

### HIV and HCV Coinfection

#### Epidemiology and transmission

Coinfection with HIV and HCV occurs frequently, due to the fact that both are transmitted via the same pathways (parenteral, sexual, vertical). 240,000 people (30 % of HIV-infected individuals) are estimated to be infected with both viruses in the USA.

Several European countries have even higher rates of coinfection. In Spain, at least 50 % of the 130,000 HIV-infected patients are also HCV-positive as a result of the high incidence of i.v. drug users. More than 90 % of coinfecting individuals are positive for HCV RNA, i.e. have chronic hepatitis C.

As HCV is ten times more infectious than HIV on blood-to-blood contact, intravenous drug users and recipients of blood products are particularly susceptible to coinfection. For example, on routine testing of blood products from HIV-infected hemophiliacs treated before the discovery of HCV in the early nineties, HCV antibodies and HCV RNA were detected in the serum of over 90 % of patients. The probability of transmission from needlestick injuries after exposure to HCV-contaminated blood is 2–8 %, compared to only 0.3 % after exposure to HIV-contaminated blood.

In contrast, sexual transmission of HCV occurs significantly less frequently than HBV or HIV. As a result, HCV is rare in homosexual men and coinfection is more seldom in this group. However, recently there have been reported clusters of cases of acute hepatitis C among homosexual HIV-positive men, clearly indicating that HCV can be sexually transmitted. The risk of transmission probably depends on the number of sexual partners and the performance of sexual practices that are prone to injuries. In total, about 4–8 % of all HIV-infected homosexuals are also infected with HCV.

Perinatal transmission of hepatitis C is rare in immunocompetent individuals (<1 %). The transmission rate rises with increasing immunosuppression in HIV-positive mothers, and is estimated to be as high as 20 %. On the other hand, HIV-positive mothers treated effectively with HAART do not appear to have an increased risk for materno-fetal transmission of the hepatitis C virus (in combination with cesarean section; Pembrey 2005).

#### Clinical course and pathogenesis

##### Course of hepatitis C in HIV/HCV-coinfecting patients

The clinical course of hepatitis C and HIV coinfection is determined by the HIV-associated immunosuppression. Progression of immunosuppression accelerates the course of hepatitis C. This was first shown in data from the American Multicenter

Hemophilia Cohort Study (MHCS), in which 10 % of adult hemophiliacs with HCV coinfections developed hepatic failure after a latent period of 10–20 years, even before the onset of AIDS-defining opportunistic infections or neoplasms (Eyster 1993). Rapid progression of liver disease was found particularly in patients with CD4+ T-cell counts below 100/μl. In the group of HIV-negative but HCV-positive patients, there was not a single case of liver failure during the same period of observation. In this group, the latent period until liver failure or hepatocellular carcinoma develop is estimated to be 30–40 years. Several studies, some of which included histological analyses, have confirmed the accelerated course of hepatitis C with concurrent HIV infection.

The improved treatment options for HIV infection have increased the likelihood of patients actually living to experience the development of liver failure. The associated decrease in mortality with HIV infection has resulted in a relative increase in hepatitis-associated mortality. In some centers, liver failure is now the most frequent cause of death in HIV-infected patients. This, together with the accelerated course of hepatitis C with HIV coinfection, has led many experts to regard hepatitis C as an opportunistic infection.

### **Course of HIV infection in HIV/HCV-coinfected patients**

Studies, that determined the influence of hepatitis C on HIV infection, yielded contradictory results at first. The Swiss Cohort Study identified hepatitis C as an independent risk factor for the more rapid progression of HIV infection to AIDS and death. This phenomenon could not be explained by less frequent use or poorer tolerability of HAART, but was due to a diminished rise in CD4+ T-cells in HIV patients with concurrent hepatitis C. However, long-term follow-up could not certify this difference further. In other studies (e.g. Johns Hopkins Cohort, EuroSIDA), hepatitis C did not influence the probability of progression of HIV infection, especially after correction for the use of and response to HAART (Rockstroh 2005). Taken together, extended follow-up of different cohorts could not show a significant influence of hepatitis C on the course of HIV infection.

### **Course of hepatitis C with HAART**

The unfavorable course of hepatitis C in HIV infection can be improved by treatment of HIV infection with HAART. In addition, the development of liver failure can be delayed by the improved immune function under HAART. This is particularly true for patients who achieve a good immune recovery.

On the other hand, hepatitis C infection can aggravate the potential hepatotoxicity of several HAART regimens. Up to 10 % of patients have to discontinue HAART due to severe hepatotoxicity. This risk is associated especially with the so-called “d-nucleosides” (ddI, ddC, d4T). These substances should be avoided in coinfecting patients. Nevirapine and tipranavir should be used with caution.

In some coinfecting patients, a temporary increase in transaminases is observed after initiation of HAART. This most likely corresponds to an increased inflammatory activity of hepatitis C as a result of the improved immune status. Nevertheless, long-term follow-up has shown that HAART improves the course of hepatitis C. Indications for HAART, according to current treatment guidelines, should be carefully checked in all coinfecting patients.

## Diagnosis

The diagnostic tests used in coinfecting patients are no different from those used in patients with HCV monoinfection. Detection of HCV antibodies (anti-HCV) proves exposure to HCV, but does not distinguish between resolved and chronic hepatitis C. Chronic hepatitis C is diagnosed by the detection of HCV viremia (i.e. HCV RNA). It should be noted that HCV antibodies might be lost during the course of HIV infection as a result of the underlying immunosuppression, although nowadays this phenomenon has become rare, probably due to improved test kits. It may therefore be useful to determine HCV RNA levels, even if the anti-HCV test is negative, if there is clinical suspicion or advanced immunodeficiency. Similarly, determination of HCV RNA levels is indicated in cases of suspected acute (primary) HCV infection, as HCV antibodies usually only become detectable one to five months after infection.

Patients with HIV/HCV coinfection have significantly higher levels of HCV viremia than patients with HCV monoinfection (about 1 log). In parallel to an ongoing rise in viremia, the risk of perinatal or sexual transmission increases. However, the level of viremia does not have a prognostic value for the course of hepatitis C. Accordingly, regular testing of HCV-RNA as a routine clinical procedure is not necessary. However, it should be noted that some patients might lose HCV-RNA in parallel to progression of immune deficiency, but experience a flare up of hepatitis C together with clinical symptoms following immune reconstitution under HAART. Therefore, regular testing around the initiation of HAART seems to be prudent.

It is possible to predict a response to treatment from the level of the HCV viremia: if the concentration of HCV RNA is below 800,000 IU /ml, the probability of treatment success is significantly higher than at levels above 800,000 IU /ml (800,000 IU/ml equals about 2 million copies/ml dependent on the test used).

When considering the treatment of hepatitis C, genotyping is necessary before starting. Six genotypes with numerous subtypes are known to date, and are seen to have different regional distributions: genotypes 1 and 3 are predominantly found in Europe, whereas genotypes 4 and 5 are found in Africa, and genotype 6 in Asia. They are mainly of prognostic value with regard to the response to treatment. Genotypes 2 and 3 in particular are associated with significantly better responses to interferon therapy. Coinfection with several genotypes is possible.

Transaminases, the parameters of cholestasis, and markers of the synthetic capacity of the liver (CHE, albumin, total protein, and coagulation factors) should be determined. They provide the same indication and interpretation indices as in patients without HIV infection.

The importance of taking liver biopsies before the initiation of HCV therapy is controversial, and there are no consistent recommendations based on results from clinical studies. On the one hand, it is thought that HCV therapy should only be administered if there is a histologically confirmed "absolute" indication for treatment, as it may be associated with numerous side effects, possible interactions with HAART and relatively low efficacy. On the other hand, it must be assumed that HCV therapy is almost always justifiable in coinfecting patients, as the course of hepatitis C is accelerated and past studies have shown that progression to fibrosis or cirrhosis occurs in approximately half of all patients. In addition, liver biopsies need

to be repeated every 2 to 3 years due to the accelerated course of disease, and not all patients are prepared to go through with this. If a liver biopsy is not available, current consensus recommendations suggest treatment of hepatitis in case of genotypes 2+3, or genotype 1 and low HCV viremia. If a liver biopsy has been performed that shows no significant fibrosis, immediate treatment is usually not required regardless of the underlying genotype.

There are several histological classifications used. In Europe the METAVIR-Score is used most often. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = significant septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). Treatment is recommended for grades F2-F4; it may be deferred for grades F0+F1.

Before performing a liver biopsy, contraindications must be carefully considered. This is particularly important for hemophiliacs, who often cannot be biopsied (risk of hemorrhage!).

Several methods for non-invasive assessment of liver fibrosis have become available and are being used increasingly. Of special interest is the Fibroscan<sup>®</sup> device that measures liver stiffness directly correlated to the degree of fibrosis with a novel technique (transient elastography). Scientific data and clinical experiences have so far been very promising. Recommendations on the need for liver biopsy will probably change in the near future.

If there is clinical suspicion requiring the detection or exclusion of extrahepatic manifestations (vasculitis, glomerulonephritis, systemic cryoglobulinemia), appropriate investigations may be necessary (skin biopsy, urine tests, kidney biopsy, detection of serum cryoglobulins).

The recommendations for autoantibody testing to exclude autoimmune disease vary and test results are difficult to interpret: up to 60 % of all patients with hepatitis C have autoantibodies such as ANA, RF, anticardiolipin, SMA, and LKM1 antibodies as an accompanying autoimmune phenomenon without any clinical relevance. If the titers of these autoantibodies increase or appear for the first time during interferon therapy, treatment does not usually have to be discontinued, and so the need for routine testing of autoantibodies is arguable. In order to exclude autoimmune hepatitis, however, ANA, SMA, ANCA, and LKM1 antibodies should be determined before interferon therapy is initiated. Patients with positive results should be monitored closely for deterioration of liver function on interferon therapy as a sign of active autoimmune hepatitis. If liver function worsens, interferon should be discontinued. The need for immunosuppressive therapy can only be decided on a case-by-case basis.

Before treatment with interferon, TSH levels should always be determined to exclude thyroid disease. With normal thyroid function, it is sufficient to monitor TSH at 12-weekly intervals. In cases of hypothyroidism, substitution with levothyroxine is recommended, and thyreostatic treatment is similarly recommended for hyperthyroidism before initiation of interferon therapy. After adequate treatment, interferon therapy can usually be administered under close monitoring of TSH (every 4 weeks). Approximately 5 % of patients develop thyroid dysfunction on interferon therapy. This generally manifests within the first 3 months of treatment. If hypothy-



roidism is induced, interferon therapy can usually be continued in combination with substituted levothyroxine. The first manifestation of hyperthyroidism is enough cause for most authors to discontinue treatment, although even here it may be possible to continue interferon therapy in certain cases. In the majority of patients, thyroid dysfunction resolves after discontinuation of interferon. However, it may also persist, and therefore cases need to be considered individually.

Up to 12 % of patients with hepatitis C have thyroid autoantibodies before treatment with interferon (antibodies against thyroid peroxidase = anti-TPO, anti-thyroglobulin antibodies and TSH receptor antibodies). In these patients, the risk of a deterioration in thyroid function on interferon is significantly higher than in patients without these antibodies. If possible, autoantibodies should be determined in all patients before beginning treatment, but at the very least in those patients with abnormal TSH levels, in order to have a baseline value to allow subsequent monitoring.

## Therapy

The goal of hepatitis C treatment is to achieve permanently negative HCV RNA levels. This is generally referred to as a sustained response. It is defined as a negative HCV RNA six months after completion of treatment.

Negative HCV RNA at the end of the treatment period is described as an end of treatment response. If transaminases have normalized, this is referred to as a biochemical response. However, the latter does not correlate with the further clinical course of hepatitis C and is therefore no longer used today. Failure to respond to treatment is referred to as a non-response.

In the following text, response rates always refer to sustained responses. This is because only sustained responses have been clearly associated with the resolution of liver fibrosis and extrahepatic manifestations, as well as with the prevention of further transmission.

When HCV RNA becomes detectable again after having been negative, it is referred to as a relapse. The probability of a relapse is highest within the first months following completion of treatment and decreases steadily afterwards. Therefore, the success of therapy is usually determined and evaluated six months after the end of treatment. In individual cases, relapses may occur at later time points, sometimes after years. Therefore, regular monitoring is advisable even following successful treatment (monitoring of transaminases; HCV RNA if there is reason to suspect a relapse).

Hepatitis C is treated with interferons and nucleoside analogs. Interferons are glycoproteins that protect cells from viral infection by inhibiting viral mRNA translation and reducing viral penetration and release. In addition, the immune reaction is influenced via modulation of cytokine profiles. The guanosine analog ribavirin is used as a nucleoside analog. Liver transplantation may be a possible option for patients who have cirrhosis and cannot be treated with interferon therapy.

The treatment of hepatitis C in HIV-infected patients differs in two main points from the treatment of hepatitis C in monoinfected patients: the response rates are lower due to the underlying immunodeficiency, and discontinuation of treatment as a result of side effects is more frequent.

Interferon monotherapy and combination treatment with standard interferon- $\alpha$  and ribavirin are no longer relevant. Response rates varying from 13 to 40 % and discontinuation of treatment in approximately 30 % of cases due to side effects were not satisfactory. Pegylated interferons henceforth have replaced standard interferons. These are bound to polyethylene glycol (PEG), in contrast to conventional interferons (i.e. interferon- $\alpha$  2a or interferon- $\alpha$  2b). Pegylation shields the interferon- $\alpha$  protein from enzymatic degradation, and thereby considerably lengthens its half-life. As a result, absorption of interferon is slower (producing less peak concentrations, which are associated with side effects) and a consistently high plasma level (with less low trough levels, during which efficacy could be reduced). Pegylated interferons can therefore be administered only once instead of three times weekly.

The combination of pegylated interferon with ribavirin is regarded as standard therapy in coinfecting patients. Initial encouraging results have been found by the APRICOT study (AIDS Pegasys™ Ribavirin International Coinfection Trial), which is the largest published study in HIV/HCV-coinfecting patients to date (Torriani 2004). A sustained response was achieved in 40 % after a treatment period of 48 weeks. Only 12 % of participants had to discontinue therapy due to adverse events. Particularly genotype 1, which is associated with a poor prognosis, showed a better response to this treatment (29 %) compared to the conventional interferon/ribavirin therapy. The more favorable genotypes 2 and 3 reached response rates of 62 %. Overall response rates, as well as response rates according to different genotypes, were significantly better than in the other two treatment arms: standard interferon-2 $\alpha$  plus ribavirin (total: 12 %, genotype 1: 7 %, genotypes 2+3: 20 %) or pegylated interferon with placebo (total: 20 %, genotype 1: 14%, genotypes 2+3: 36 %). All patients were treated over a period of 48 weeks regardless of the genotype. Of special interest is the finding that the relapse rate at week 72 was only 2 % for genotypes 2+3, whereas relapse-rates of up to 50 % were associated with the former treatment period of 24 weeks. Therefore, genotypes 2+3 should also be treated for 48 weeks.

The superiority of PEG-interferon/ribavirin was confirmed in subsequent trials with even better response rates (e.g. PRESCO). Currently, several trials are addressing the question of whether shorter treatment periods are possible in HIV-coinfecting patients if early treatment response is achieved at week 4.

Detailed information on interferon, PEG-interferon and ribavirin can be found in the section on Drug Profiles.

Concerns that interferon treatment could have a negative effect on HIV infection have not been confirmed in any study. In fact, there is further suppression of detectable HIV viremia in the majority of patients as a result of the antiviral effect of interferon. Absolute CD4+ T-cell counts may drop slightly due to temporary leukopenia, but percentage values usually rise. No treatment study to date has shown a significant deterioration of HIV infection (Soriano 2002).

The treatment options remain inadequate for patients with a non-response or relapse. In patients treated earlier with interferon monotherapy, an attempt can be made using a combination of PEG-interferon and ribavirin. There are currently no standard recommendations for treatment of patients after failed PEG-interferon therapy. In single patients, a triple combination of PEG-interferon, ribavirin and amantadine (2 x 100 mg/day) has been used successfully, although reliable data are

not available. HCV-specific protease inhibitors and polymerase inhibitors, as well as other new substances, will add new options in the next years.

The management of acute hepatitis C also remains unclear. In patients with HCV monoinfection, early treatment with interferon  $\alpha$ -2b within the first six months has shown excellent response rates (98 %!) (Jaeckel 2001), although subsequent analyses found lower response rates (approx. 80 %). Retrospective analyses in HIV-infected patients revealed response rates of more than 80 % (Vogel 2005). These data support early treatment even in the presence of HIV coinfection. At the moment, we treat patients with asymptomatic acute hepatitis C immediately, whereas patients with symptomatic hepatitis are followed for 12 weeks in order to await possible spontaneous clearance. If not cleared, we recommend treatment for a period of 24 weeks with peg-interferon alone for genotypes 2+3, and peg-interferon plus ribavirin for genotypes 1+4. However, the optimal strategy is unclear at the moment. If possible, patients should be treated within prospective clinical studies.

## Practical tips for management of treatment

The following treatment recommendations have been compiled for HIV coinfection:

### Indications and contraindications

As HIV coinfection accelerates the course of hepatitis C and increases the risk of hepatotoxicity after initiation of HAART, the indication for treatment should be determined in **every** patient with diagnosed HIV/HCV coinfection. The algorithm in Figure 1 (see below) can be used as a guide.

In particular, treatment should be discussed for cases with a bioptically confirmed fibrosis of grade F2-F4. Extra-hepatic manifestations of hepatitis C are also an indication for treatment (vasculitis, glomerulonephritis, systemic cryoglobulinemia). The following factors are associated with a more favorable response to treatment:

- HCV RNA < 800,000 IU/ml (+ genotype 1)
- HCV genotype 2+3
- Age < 50 years
- Histologically, low grade of fibrosis
- Normal  $\gamma$ -GT
- Stable HIV infection
- Female sex (currently being discussed; possibly insufficient dose adjustment for weight in heavier men)

In addition, contraindications should be evaluated. The most important are:

- Decompensated liver cirrhosis or history of decompensation (but not compensated cirrhosis, i.e. CHILD A cirrhosis!)
- Leukopenia (<1,500/ $\mu$ l)
- Thrombocytopenia (< 50,000/ $\mu$ l)
- Anemia (< 10 g/dl)

## 548 HIV and HBV/HCV Coinfections

- Severe, as yet untreated thyroid dysfunction
- CD4+ T-cell count < 200/ $\mu$ l (relative contraindication, see below)
- Severe psychiatric illnesses
- Symptomatic cardiac disease
- Active opportunistic infections
- Active drug or alcohol abuse
- HIV treatment with ddI (AZT and d4T should be avoided too)

Methadone or polamidone substitution is **not** a contraindication if good monitoring can be ensured during the treatment phase. However, patients with active drug or alcohol abuse should first be introduced to the appropriate programs.

In addition, the immune status of the patient and current antiretroviral therapy must be considered (see below).

If possible, HCV should be treated before HIV. Reasons for this include the increased hepatotoxicity of HAART with concurrent hepatitis C; possibly, impaired immune reconstitution resulting from hepatitis C; better compliance; and finally, prevention of drug interactions. The following scheme is suggested:

### **Patients without HAART**

If the CD4+ T-cell count is above 350/ $\mu$ l, treatment of hepatitis C can be started. It is unclear whether a high viral load (> 50,000/ml) requires initiation of HAART.

If the CD4+ T-cell count is between 200 and 350/ $\mu$ l, the patient might benefit from treatment of hepatitis C if HIV RNA is below 5,000 copies/ml. If it is higher, initiation of HAART should be considered.

A CD4+ T-cell count below 200/ $\mu$ l is a relative contraindication. HAART should be initiated first. When there is an adequate increase in the CD4 count, interferon therapy can be reconsidered.

### **Patients on HAART**

If CD4+ T-cells are above 350/ $\mu$ l under stable HAART and the viral load is below the level of detection, treatment can be started.

If CD4+ T-cells are between 200 and 350/ $\mu$ l and the viral load is stable below the limit of detection, the decision should be dependent on the overall situation (with consideration of severity of hepatitis, HCV genotype and status of HIV infection).

A CD4+ T-cell count below 200/ $\mu$ l is a relative contraindication. It is a judgement call to decide whether to take the risk of a treatment attempt with interferon (with the likelihood of a poor response and the danger of a further decline in the CD4+ T-cell count as a result of interferon treatment).

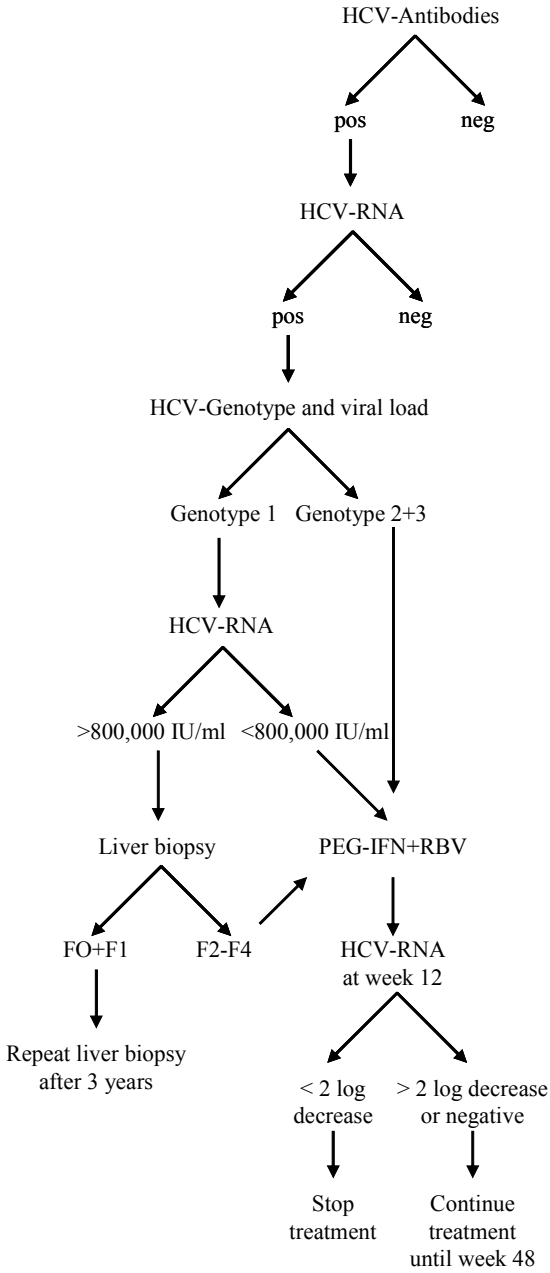


Figure 1: Hepatitis C treatment algorithm

ALT, alanine aminotransferase; PEG-IFN, pegylated interferon; RBV, ribavirin; modified after Soriano 2002 and Rockstroh 2004

If necessary, antiretroviral treatment should ideally be modified several weeks before HCV therapy is initiated. ddI is contraindicated with concurrent HCV therapy (as it can lead to pancreatitis, mitochondrial toxicity, and more cases of liver decompensation). AZT and d4T should also be avoided if possible, in order to prevent additive toxicities (zidovudine: anemia and leukopenia; stavudine: mitochondrial toxicity). Before modifying HAART, it should be insured that the treatment success of HIV therapy is not going to be compromised. In such cases, HCV treatment should only be started if the overall clinical situation is stable, i.e. good viral suppression has been achieved and side effects have been evaluated or treated.

To detect a hepatocellular carcinoma (HCC), alpha-Fetoprotein (AFP) and sonography of the liver should be performed every 6-12 months in all patients with chronic hepatitis C. This is particularly relevant for patients with F3/F4-fibrosis. Some experts recommend shorter intervals that are not yet feasible in most circumstances. There is no urgent need to monitor HCV-RNA at every visit, as it has no prognostic value.

### **Treatment practice**

The combination of PEG-interferon with ribavirin over a period of 48 weeks is recommended as the standard therapy (Soriano 2004) regardless of the genotype (Rockstroh 2004, Alberti 2005).

Two interferons are currently available as PEG-interferons: PEG-Intron™ and Pegasys™. PEG-Intron™ is administered subcutaneously and the dose is based on body weight at 1.5 µg/kg. Pegasys™ is injected subcutaneously at a fixed dose of 180 µg. Both substances are administered once a week, and must be kept refrigerated.

The dosage of ribavirin should be 800 mg daily for genotypes 2 and 3, whereas genotypes 1 and 4 need to be treated with 1,000-1,200 mg daily according to current consensus recommendations. The capsules can be taken once daily, or spread over the day.

Patients should be counseled extensively on the expected side effects before beginning treatment. Three main aspects should be explicitly addressed:

Almost all patients experience influenza-like symptoms or malaise when beginning treatment. As the severity of symptoms cannot be predicted beforehand, treatment should be initiated at a time when there are no important private or professional events pending (e.g. before a weekend). The administering physician should be readily available during the first days of treatment. In addition, paracetamol should be prescribed (dosage has to be adjusted individually; single dose = 1,000 mg). Symptoms usually improve within the first two to four weeks. A decision to stop treatment should therefore not be made before the end of the first month if possible.

Most patients tolerate treatment quite well and can continue their daily activities normally. However, it is possible that particularly in the initial stages of treatment, they may be unable to work for several days. In rare cases, the side effects may be so grave that patients are unable to work for the entire duration of treatment. This also needs to be discussed with the patient in advance.

Patients must be made aware of the fact that both interferon and ribavirin are potentially teratogenic. A reliable method of contraception for at least six months after treatment is therefore important.

All patients require regular clinical monitoring. This should initially take place every 2 weeks; later at least every 4 weeks. Laboratory monitoring should include:

- A complete blood count and transaminases every 2-4 weeks
- Thyroid function tests every 12 weeks (more frequently with pre-existing dysfunction)
- Immune status every 12 weeks
- Lactate levels every four weeks in patients on stavudine comedication

HCV RNA is the most important parameter for measuring the treatment response and is determined after 12 weeks to decide on the duration of treatment. In practice, it is often already determined after four or eight weeks - partly because it is a motivation for further treatment if there is a treatment response.

The evaluation of psychological side effects is made at every clinic visit. Observations made by others, such as family members, may also be very helpful.

The management of possible side effects is often the decisive factor for the success of treatment. A high discontinuation rate in numerous (older) clinical studies is likely also to have been due to a lack of experience with combination therapy. Proper management of side effects probably results in significantly better treatment success rates. It is often helpful to indicate to patients that side effects are reversible after stopping therapy.

Ribavirin causes hemolytic anemia in up to 20 % of patients. This can be treated with epoetin alfa. Dose recommendations differ: usually approximately 100 IE/kg body weight are injected subcutaneously three times a week. 40,000 IE once a week also significantly improve ribavirin-induced anemia (Sulkowski 2005). Alternatively, halving the dose (hemoglobin below 10 g/dl) or discontinuing ribavirin altogether (hemoglobin below 8.5 g/dl) are possible options. However, dose reductions, frequently used in the past, should only be made if epoetin does not help. Newer studies have shown that the correct dosing of ribavirin is associated with a better treatment response. A daily 5 mg dose of folic acid is recommended to reduce hematotoxicity.

Treatment with granulocyte colony stimulation factor (G-CSF) may ameliorate an interferon-induced leukopenia. Clinical experience is very limited so far. However, so that the required dose of interferon can be maintained in case of severe leukopenia (neutrophil count below 500/ $\mu$ l), this recommendation seems to be justified. Doses have to be adjusted individually. In most instances low doses are adequate, as hematopoiesis itself is not impaired (e.g. Filgrastim 30 Mio IE once a week).

Mild depression whilst on interferon can be treated with well-tolerated antidepressants (e.g. paroxetine 20 mg daily). Therapy should be stopped immediately in cases of severe depression or on development of suicidal thoughts.

The frequent occurrence of weight loss can be lessened with dietary counseling. It is important to ensure a regular diet that is tailored to the patient's wishes (e.g. inpatients with drug addiction). It is possible that the weight loss is a form of lipomat-

rophy, and therefore nucleoside analogs with a lower risk for development of lipodystrophy should be used if possible.

Thyroid dysfunction may develop during treatment with interferon (see above), which might necessitate discontinuation of interferon therapy.

The duration of treatment depends on the treatment response. If HCV RNA is still positive after 12 weeks, treatment is discontinued irrespective of genotype, as a treatment response is unlikely even if therapy is continued. Earlier recommendations were to wait until week 24 because of delayed elimination kinetics in HIV patients compared to HCV-monoinfected patients. However, it is now possible to reach a decision after just 12 weeks, even in HIV patients.

If HCV RNA has dropped by at least 2 logs or is negative, treatment should be continued for another 36 weeks in patients with all genotypes. Earlier recommendations were to stop therapy after week 24 in patients with genotype 2 or 3. However, recent data from the APRICOT study showed a very low relapse rate after 48 weeks of treatment, whereas prior studies revealed relapse rates of up to 50 % if patients were treated for only 24 weeks. Therefore, patients with all genotypes should receive treatment for at least 48 weeks. Continuation of treatment beyond this time point, especially in patients with genotypes 1 and 4, could possibly reduce relapse rates further.

Recommendations for treatment of hepatitis C are constantly evolving. Therefore an experienced treatment center should always be contacted if clarifications are needed.

Due to the complexities of HIV/HCV coinfection, patients should be treated within clinical studies wherever possible.

## References

1. Alberti A, Clumeck N, Collins S, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005; 42:615-624. <http://amedeo.com/lit.php?id=15916745>
2. Eyster ME, Diamondstone LS, Lien JM, et al. Natural history of Hepatitis C virus infection in multi-transfused hemophiliacs. Effect of coinfection with HIV. *J AIDS* 1993; 6:602-10. <http://amedeo.com/lit.php?id=8098752>
3. Greub G, Ledergerber B, Battegay M, et al. Clinical progression, survival and immune recovery during antiretroviral therapy in patients with HIV-1 and Hepatitis C virus coinfection. *Lancet* 2000; 356:1800-1805. <http://amedeo.com/lit.php?id=11117912>
4. Jaeckel E, Cornberg M, Wedemeyer H, et al. Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; 345:1452-7. <http://amedeo.com/lit.php?id=11794193>
5. Manns MP, McHutchison JG, Gordon SC, et al. Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; 358:958-65. <http://amedeo.com/lit.php?id=11583749>
6. Nelson M, Matthews G, Brook MG, et al. BHIVA guidelines on HIV and chronic hepatitis: coinfection with HIV and hepatitis C virus infection. *HIV Med* 2005; Suppl 2:96-106. <http://amedeo.com/lit.php?id=16011539>
7. Pembrey L, Newella ML, Tovob PA, EPHN Collaborators. The management of HCV infected pregnant women and their children European paediatric HCV network. *J Hepatol* 2005; 43:515-25. <http://amedeo.com/lit.php?id=16144064>
8. Rockstroh JK, Spengler U, Sudhop T, et al. Immunosuppression may lead to progression of Hepatitis C virus associated liver disease in hemophiliacs coinfecting with HIV. *Am J Gastroenterol* 1996; 91:2563-68. <http://amedeo.com/lit.php?id=8946987>
9. Rockstroh JK. Management of hepatitis B and C in HIV co-infected patients. *J AIDS* 2003; 34 Suppl 1:S59-65. <http://amedeo.com/lit.php?id=14562859>



10. Rockstroh JK and Spengler U. HIV and hepatitis C virus co-infection. *Lancet Infect Dis* 2004; 4:437-44. <http://amedeo.com/lit.php?id=15219554>
11. Rockstroh JK, Mocroft A, Soriano V, et al. Influence of hepatitis C virus infection on HIV-1 disease progression and response to highly active antiretroviral therapy. *J Infect Dis* 2005; 192:992-1002. <http://amedeo.com/lit.php?id=16107951>
12. Sulkowski MS, Mast EE, Seeff LB, Thomas DL. Hepatitis C virus infection as an opportunistic disease in persons infected with HIV. *Clin Infect Dis* 2000, 30 (Suppl 1):S77-S84. <http://amedeo.com/lit.php?id=10770916>
13. Sulkowski MS, Dieterich DT, Bini EJ, et al. Epoetin alfa once weekly improves anemia in HIV/Hepatitis C virus-coinfected patients treated with interferon/ribavirin: a randomized controlled trial. *J Acquir Immune Defic Syndr* 2005; 39:504-506. <http://amedeo.com/lit.php?id=16010180>
14. Soriano V, Sulkowski M, Bergin C, et al. Care of patients with chronic Hepatitis C and HIV co-infection: recommendations from the HIV-HCV International Panel. *AIDS* 2002, 16:813-28. <http://amedeo.com/lit.php?id=11919483>
15. Soriano V, Puoti M, Sulkowski M, et al. Care of patients with Hepatitis C and HIV co-infection. *AIDS* 2004, 18:1-12. <http://amedeo.com/lit.php?id=15090824>
16. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004, 351:438-50. <http://amedeo.com/lit.php?id=15282351>
17. Vogel M, Biniek B, Jessen H, et al. Treatment of acute hepatitis C infection in HIV-infected patients: a retrospective analysis of eleven cases. *J Viral Hepat* 2005; 12:207-211. <http://amedeo.com/lit.php?id=15720537>

## HIV and HBV coinfection

### Introduction

The hepatitis B virus is one of the most common human pathogens worldwide. Up to 95 % of all HIV-infected patients have been infected with hepatitis B, and approximately 10-15 % have chronic hepatitis B, with considerable variation among geographical regions and risk groups. It is estimated that around 100,000 HIV-infected patients in the USA suffer from chronic hepatitis B. Sexual transmission is the most frequent route of contraction. Transmission via the bloodstream is more probable than for HIV: following a needlestick injury contaminated with HBV-infected blood, the risk of infection is around 30% (HCV approx. 2-8 %; HIV approx. 0.3 %). Primary HBV infection leads to chronic hepatitis in 2-5 % of immunocompetent adults, whereas HIV-infected patients experience chronification about five times more often. A possible reason for this is the HIV-associated T-cell defect. A polarization to a Th2-type response could result in the inhibition of specific cellular defense mechanisms (e.g. cytotoxicity, production of interferon- $\gamma$  and interleukin-2, and the T-cell proliferation rate). Genetic predisposition could also play an important role in the chronification of hepatitis B. Current data indicate that virus-specific factors, such as the extent of HBV viremia, genotype (A-H), or the emergence of escape mutants do not result in differences between HIV-infected and immunocompetent patients. It should be noted, that genotype A mainly affects homosexual men who tend to be positive for the hepatitis B antigen, whereas genotype D is predominantly seen among intravenous drug users in Southern Europe and seems to be associated more often with negative hepatitis B e antigen. Treatment response to interferon may be influenced by genotypes (with a possibly better response in patients with genotype A).

Hepatitis B and HIV have several common features, although hepatitis B is a double-stranded DNA virus. After entering the hepatocyte, viral DNA is integrated into the host genome. Viral RNA is translated by HBV reverse polymerase into new viral DNA and transcribed into viral proteins. Reverse transcription may be inhibited by nucleos(t)ides reverse transcriptase inhibitors. Integration of the virus into the host genome of hepatocytes and CD4+ T-cells prevents its eradication. Finally, the mechanisms for development of resistance are very similar for both viruses.

The diagnosis of HBV is established as in patients without HIV infection. Table 1 summarizes the interpretation of serological test results. Screening HIV-infected patients for HBV starts with HBsAg, anti-HBs, and anti-HBc. If a positive HBsAg is found, testing for HBeAg, anti-HBe, and HBV DNA should follow. There is debate about a so-called occult infection due to immune escape. This means patients lack HBsAg, but are positive for HBV DNA. Recent studies have not found evidence of such occult infection and the prevalence and impact in coinfection remains unclear.

Table 1: Interpretation of serological test results for HBV

Interpretation	HBsAg	anti-HBs	anti-HBc	HBeAg	anti-HBe	HBV-DNA
No prior contact with HBV	-	-	-	-	-	-
Acute infection	+	-	+ (IgM)	+	-	+
Past infection with immunity	-	+	+ (IgG)	-	+	-
Chronic hepatitis B	+	-	+ (IgG)	+	-	+
Occult infection <sup>1</sup>	-	-	+ (IgG)	-	-	+
Pre-core mutant	+	-	+ (IgG)	-	+	+
Inactive carrier state	+	-	+ (IgG)	-	+	-
Immunity after vaccination	-	+	-	-	-	-

<sup>1</sup> Controversial. See text above.

In general, patients with chronic hepatitis B should be screened for hepatocellular carcinoma (HCC) every 6 to 12 months. Serum alpha fetoprotein and an ultrasound of the liver should be performed. This recommendation is independent of apparent cirrhosis, as 10 to 30 % of patients who develop HCC do not have pre-existing cirrhosis.

## Course of hepatitis B with concurrent HIV infection

In HIV-infected patients, chronic hepatitis B has an unfavorable course compared with monoinfected patients, and the risk of liver-associated mortality is significantly increased.

Data from the Multicenter AIDS Cohort Study have demonstrated the unfavorable influence of HIV infection on hepatitis B (Thio 2002a). In approximately 5,000 patients observed over a period of 14 years, the risk of liver-associated mortality was 8 times higher than in HBs antigen negative HIV patients (14.2/1,000 person-years vs. 1.7/1,000) and 15 times higher than in HBs antigen negative patients without HIV infection (14.2/1,000 vs. 0.8/1,000). Liver-associated mortality due to hepatitis B has increased significantly since the introduction of HAART in this cohort. Results from the EuroSIDA cohort confirmed the unfavorable course of hepatitis B resulting in increased liver-related mortality (Konopnicki 2005).

In addition to increasing mortality, HIV coinfection accelerates the progression of hepatitis B and increases the risk of cirrhosis. Histological analysis of a series of 132 homosexual men with chronic hepatitis B, of which 65 were HIV-coinfected, showed a higher prevalence of liver cirrhosis in HBV/HIV-coinfected patients (Colin 1999). No difference was observed in the extent of inflammatory activity. Interestingly, several patients developed severe fibrosis and cirrhosis, in the presence of only minimal inflammatory activity. This phenomenon has also been described in other immunocompromised patient populations (e.g. organ transplant recipients). HIV-positive patients possibly experience more frequent reactivation episodes of chronic hepatitis B than HIV-negative patients.

Despite the worsening described, initially the clinical course is usually more benign in HIV-positive patients, although viral replication is increased. This seems contradictory at first, but can be explained by the impairment of cellular immunity, which

may lead to an increase in viral replication, but at the same time also reduces hepatocyte damage. Therefore, transaminases in HBV/HIV-coinfected patients are frequently only mildly increased. In contrast, HBV DNA, as a marker for viral replication, is higher than in immunocompetent patients. Accordingly, despite less inflammatory activity, liver fibrosis and cirrhosis are more common.

There is a direct correlation between the extent of immunosuppression and the control of viral replication of HBV: patients with AIDS more frequently show signs of active viral replication (HBs- and HBe antigen positive, HBV DNA detectable) than patients without AIDS. Even in cases with apparently resolved hepatitis B (anti-HBe positive, HBV DNA negative, even anti-HBs positive), increasing deterioration of the immune system may result in reactivation of the HBV infection. Notably, some cases of reactivation of hepatitis B have been described following immune reconstitution after initiation of HAART.

Most studies on the influence of hepatitis B infection on the course of HIV disease have not been able to determine a shorter survival time. HBV infection neither leads to a more rapid decline of CD4+ T-cells nor to an increased frequency of AIDS-defining events. However, the reduction in HIV-associated mortality has led to an increase in mortality resulting from liver-related complications. In addition, HAART-related hepatotoxicity develops about three times more frequently in patients with chronic hepatitis B. Whether or not the prognosis of HBV/HIV-infected patients is changed by HAART and HBV-effective therapies, remains to be seen.

## Prevention

All patients infected with HIV but with negative hepatitis B serology should be vaccinated! The vaccine may, however, be less effective due to immunosuppression. Approximately 30 % of HIV-infected patients have a primary non-response (only 2.5 % in immunocompetent individuals). This is particularly true for patients with CD4+ T-cell counts less than 500/ $\mu$ l whose response rate is only 33 %. Therefore, a conventional dose is administered to patients with CD4+ T-cell counts greater than 500/ $\mu$ l (20  $\mu$ g at months 0, 1, and 12), whereas an intensive schedule is recommended for patients with CD4+ T-cell counts less than 500/ $\mu$ l (20  $\mu$ g at months 0, 1, 2, and the last dose between month 6 and 12). In case of non-response (checked 12 weeks after each cycle), vaccination is repeated at double the dose in four steps (40  $\mu$ g at months 0, 1, 2, and 6-12). Patients with CD4+ T-cell counts less than 200/ $\mu$ l, who are not on HAART, should receive HAART first and HBV immunization thereafter.

Loss of protective immunity is seen in up to 30 % during each year following seroconversion. Therefore, anti-HBs should be monitored once a year and consideration should be given to booster doses if anti-HBs-antibody levels are less than 100 IU/l. HIV patients, who are not adequately immunized against HBV, should be screened yearly to look for newly acquired infection.

HIV/HBV-coinfected patients who are seronegative for hepatitis A should be vaccinated against hepatitis A (months 0, and 6), as there is an increased rate of severe or fulminant hepatitis in case of acute hepatitis A. Patients who are susceptible to both hepatitis A and B can be vaccinated with a bivalent vaccine (months 0, 1, and 6).

Following immunization, patients should be counseled about common measures to prevent further transmission and transmission of other viruses such as hepatitis C (safer-sex practices, avoidance of needle-sharing and others). They should be educated about strategies to prevent progression of liver disease such as avoidance of alcohol consumption, tobacco use (controversial), or herbal supplements, many of which are hepatotoxic. The application of hepatotoxic drugs (e.g. anti-tuberculous agents) should be carried out cautiously.

Newborns of mothers with chronic hepatitis B should receive hepatitis B-immunoglobulin and active immunization.

## Treatment

Treatment of chronic hepatitis B is problematic in coinfecting patients because of the impaired immune function. As HBV persists in infected cells even after successful treatment, eradication of HBV seems not possible with current treatment strategies. Similar, development of protective anti-HBs-antibodies with subsequent loss of HBsAg is difficult to achieve because the integrated HBV pool escapes the direct antiviral effect of most anti-HBV drugs. Current treatment goals are seroconversion from HBeAg to anti-HBe, a complete suppression of HBV DNA, normalization of transaminases, improvement of liver histology, and prevention of hepatocellular carcinoma. Other benefits of HBV therapy include the reduction in the risk of transmission and possibly in the risk of HAART-induced hepatotoxicity.

### Drugs with HBV activity

Studies with interferon from the pre-HAART era showed almost no response (response most often 0 %). Immune reconstitution with HAART and the introduction of pegylated interferons will change and newly define the role of interferons in treatment. In general, the efficacy of IFN- $\alpha$  therapy is higher in HBeAg-positive than in HBeAg-negative chronic hepatitis B. Patients with high ALT levels and low HBV DNA titers show the best responses. In HBV-monoinfected patients, positive for HBeAg, the rate of seroconversion is higher with interferon than with nucleos(t)ides. This raises the question whether treatment with interferon should be offered to the particular subset of coinfecting patients with several positive predictors of treatment response (HBeAg-positive, high CD4+ T-cell counts, elevated ALT levels) and no need for HAART. Results on PEG-interferon are currently being awaited. However, data are limited at the moment and the inclusion of patients in prospective clinical trials is highly recommended. Treatment with interferon is limited by its toxicity. In patients with decompensated liver disease, IFN- $\alpha$  is contraindicated. It should be used cautiously in patients with advanced liver disease. Detailed information on the use of interferons can be found in the sections on Hepatitis C and on Drugs.

In patients with low CD4+ T-cell counts, the response to IFN- $\alpha$  is much lower. Two drug classes are available for these patients: nucleoside and nucleotide analogs, both of which inhibit the HBV polymerase.

Lamivudine was the first nucleoside analog licensed for the treatment of chronic hepatitis B. It has excellent activity against HBV in addition to its antiretroviral efficacy. It can improve both markers of viral replication and histological activity. The rate of seroconversion in coinfecting patients is about 22 to 28 % (Benhamou

1996). The optimal duration of treatment is unclear. 6 to 12 months of treatment are recommended for HBV-positive patients without HIV infection. Longer periods of treatment are associated with better response rates. In HIV-infected patients, the treatment duration with lamivudine is usually determined by the underlying HIV infection. Long-term treatment with lamivudine is limited by the development of resistance. This is conferred by a mutation in the YMDD motif in the HBV DNA polymerase gene. Similar to a pre-core-mutant, HBeAg production may stop in case of mutations in this motif. The frequency of resistance development has been reported to be at least 20 % of patients per year. The effect of continuing lamivudine treatment on the course of hepatitis B in case of resistance is unknown. If lamivudine treatment is discontinued, the clinical picture of acute hepatitis may develop as a result of a reactivation.

Emtricitabine (FTC) has added new options for the treatment of hepatitis B. Seroconversion occurs in up to 30 % of patients after 2 years. FTC, like 3TC, is a cytosine analog licensed for the treatment of HIV infection. It should be considered interchangeable with 3TC, as both substances share cross-resistance and are very similar in terms of characteristics and tolerability. The effective dose is 200 mg once daily. FTC is well tolerated with no dose-limiting adverse events. Preliminary results suggest that resistance to FTC may occur less frequently than with 3TC.

The nucleotide analog adefovir is an alternative treatment. It has been licensed for the treatment of chronic hepatitis B since the end of 2002 in the USA and since 2003 in Europe. The *in vitro* efficacy of adefovir against HBV is excellent. Loss of HBeAg occurs in about 27 % of patients treated, seroconversion in 12 %. For a long time, no significant development of resistance to adefovir was observed. After 2 years of treatment, about 2.5 % of patients develop resistance, after 3 years about 6 % (Angus 2003, Xiong 2003, Hadziyannis 2005), although there seems to be no cross-resistance to lamivudine. Therefore, adefovir is still an option even after development of resistance to lamivudine. It is unclear whether it should be added to lamivudine therapy or given sequentially. Neither HIV resistance mutations nor an effect of adefovir on HIV have been observed to date. Nevertheless, more data are still needed to ensure adefovir does not select resistance mutations in HIV at low doses, which might compromise the future activity of tenofovir. A clinical picture of acute hepatitis may develop after discontinuation of adefovir, similar to stopping lamivudine.

The standard dose of adefovir is 10 mg once daily. Dose adjustment is necessary in cases of renal insufficiency. Several placebo-controlled studies have shown no increase in side effects when compared to placebo. In particular, the nephrotoxic effects that were observed at a dose of 120 mg have been reported with an incidence of less than 1 % after 96 weeks of observation on the lower dose.

Tenofovir is a further possibility. It is actually only licensed for treatment of HIV infection and not for treatment of hepatitis B. Several pilot studies have shown excellent effectiveness of tenofovir against hepatitis B in HIV-coinfected patients, with 70 % of patients showing undetectable HBV DNA levels after 2 years and 15 % of patients showing HBeAg seroconversion. Tenofovir is also effective in the presence of lamivudine resistance. Due to the potential (rare!) development of nephrotoxicity, creatinine and phosphate levels should be monitored regularly. Interestingly, tenofovir seems to be active if failure of adefovir therapy occurs.

Entecavir (Baraclude™) is the substance licensed most recently for HBV treatment. As it has no activity against HIV, it seems to be particularly suited for patients who do not need HAART. Activity against HBV appears to be excellent, even in patients pretreated with lamivudine. Patients naïve to 3TC are given 0.5 mg entecavir per day; 3TC-experienced patients receive 1 mg entecavir per day.

In the light of the lesson learned from HIV and the high resistance rate of HBV on lamivudine therapy, combination of at least two drugs seems prudent. However, studies on combination therapy found divergent results. Nevertheless, it is reasonable to assume that combination therapy enhances antiviral activity and delays the selection of HBV resistance. At present, combination therapy with one nucleoside and one nucleotide analog should be preferred to monotherapy if feasible.

Finally, liver transplantation may be an option for selected patients who have cirrhosis and/or develop hepatocellular carcinoma.

### Treatment guidelines

Several treatment guidelines have since been published (Murphy 2004, Alberti 2005, Soriano 2005, Brook 2005). In principle, due to accelerated progression and increased mortality in coinfection, treatment possibilities should be examined for every patient. Treatment is recommended if:

- ALT is consistently > 2-fold above the norm (high pre-treatment ALT values correlate with better treatment responses to interferon and lamivudine);
- HBeAg is positive;
- HBV DNA > 20,000 IU/mL, if HbeAg+; > 2,000 IU/mL, if HbeAg- (the optimal threshold is unknown; 20,000 IU correspond to approximately 10<sup>5</sup> copies/ml depending on the assay used)
- Significant inflammation or liver fibrosis has been detected bioptically.

The role of liver biopsy in coinfecting patients has been discussed controversially. Currently, the indication for HBV therapy is based on serological markers alone. Indeed, liver biopsy is seen as desirable, as knowledge of the severity of liver damage may influence the choice or length of treatment, and other causes of liver disease may be excluded. Liver biopsy is recommended particularly for patients with the inactive carrier state (positive for HBsAg, but no other marker of replication). Non-invasive assessment of liver fibrosis can also be considered (e.g. Fibroscan™, see above).

There are several histological classifications used. In Europe the METAVIR-Score is used most often. It distinguishes five stages of fibrosis (0 = no fibrosis, 1 = portal fibrosis without septa, 2 = few septa, 3 = numerous septa without cirrhosis, 4 = cirrhosis). Hepatitis activity is graded according to the intensity of necroinflammatory lesions (A0 = no activity, A1 = mild activity, A2 = moderate activity, A3 = severe activity). Treatment is recommended for grades F2-F4, it may be deferred for grades F0+F1.

The following non-binding treatment recommendations may be suggested, but need to be confirmed in further studies (figures 1 and 2). An effective treatment of HIV infection must not be put at risk. Accordingly, 3TC, FTC and tenofovir, which are effective against both HIV and HBV, have to be combined with other substances effective against HIV in order to ensure an adequate HAART. On the other hand,

adefovir is not effective for treatment of HIV and must not be considered as part of the HAART regimen.

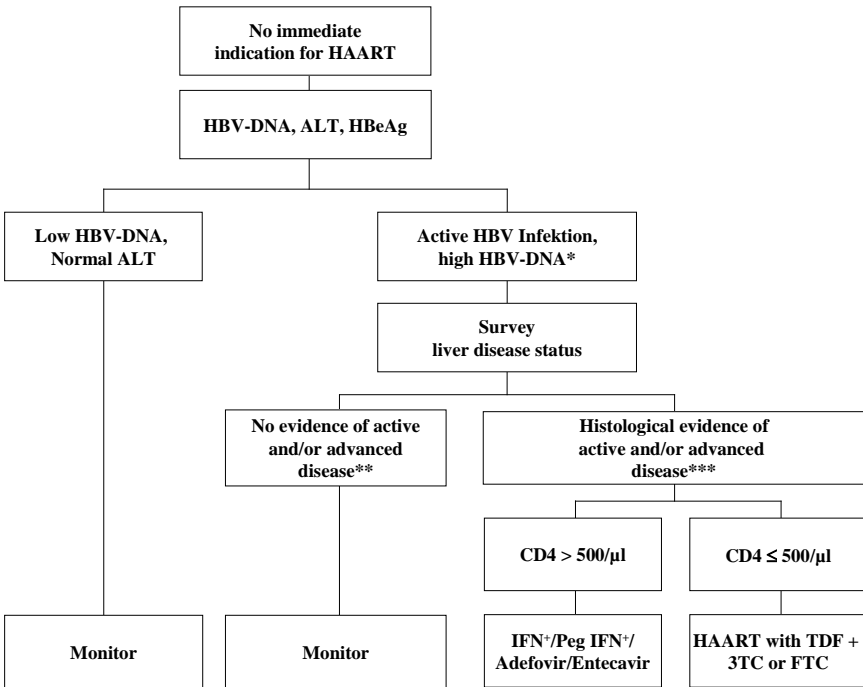


Figure 1: Treatment recommendations for HIV-HBV coinfection patients without indication for HAART (modified after Alberti 2005)

\* HBV-DNA > 20,000 IU/ml in HBeAg+ patients; > 2,000 IU/ml in HBeAg- patients

\*\* Metavir < A2 and/or < F2; \*\*\*Metavir ≥ A2 and/or F2 (for Metavir-Score refer to text)

Monitoring means: transaminases every 3 months, INR/HBV-DNA every 6 months

The main consideration is the need for HAART:

- If there is no need for HAART, the use of drugs without HIV activity seems the best choice (i.e. adefovir, entecavir or IFN-α; see figure 1). Lamivudine, emtricitabine, and tenofovir should be avoided.
- If the patient is under HAART or needs HAART due to low CD4+ T-cell counts, drugs with both HIV- and HBV-activity should be included in the HAART regimen (see figure 2). In treatment naïve patients who start therapy, the combination of FTC (or 3TC) and tenofovir is preferred as nuke backbone.

The drugs currently available and their dosages used are summarized in Table 2.



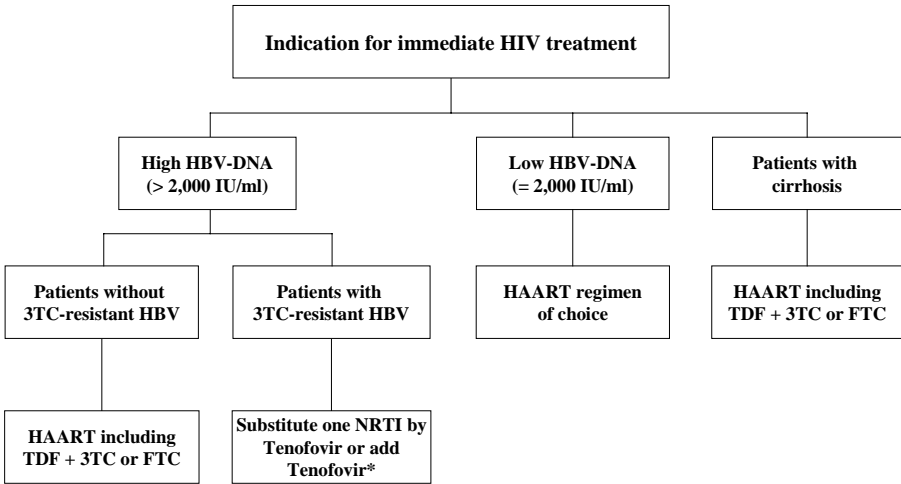


Figure 2: Treatment recommendations for HIV-HBV coinfecting patients with indication for HAART (modified after Alberti 2005)

\* If compatible with treatment of HIV infection. As an alternative, a substance without HIV-activity may be added (preferably entecavir).

Initial normalization of ALT and significant reduction of HBV DNA will be achieved in most cases by any anti-HBV agent. ALT levels do not correlate well with inflammatory activity and are influenced by many other factors such as hepatotoxicity of HAART or other drugs, alcohol consumption, and immune reconstitution. Therefore, their value for monitoring treatment is limited. HBeAg seroconversion will occur in as many as 25 % of patients. The most desirable endpoint of HBsAg loss is observed in only 5-10 % of patients within one year of the start of treatment with IFN- $\alpha$ , but occurs less frequently with nucleos(t)ide analogs.

Data on the durability of treatment responses are heterogeneous. HBeAg loss induced by IFN- $\alpha$  is durable in more than 80 % of the patients for more than 5 years. Durability after 3TC treatment is not as good, and relapses often occur when lamivudine is discontinued. Therefore, 3TC should be continued for at least 6 months after HBeAg seroconversion.

The optimal duration of treatment is not clear at the moment. Recommendations for HBV-monoinfected patients: after seroconversion (loss of HBe antigen) or loss of HBs antigen, treatment should continue for at least another 4 to 6 months. Seroconversion should be determined on two occasions 3 months apart. For HBe-negative mutants, the parameters for treatment success are transaminases and HBV DNA (< 2,000 IU/ml) or loss of HBs antigen. Otherwise treatment should be discontinued with loss of efficacy.

Table 2: Current therapeutic options for chronic hepatitis B in HIV/HBV coinfection.

Drug	Dose	Length of therapy
Interferon- $\alpha$	5 MU per day or 10 MU 3 days per week	4-6 months in HbeAg-positive patients 12 months in HbeAg-negative patients
PEG-Interferon	Pegasys™ 180 $\mu$ g once a week PEG-Intron™ 1.5 $\mu$ g/kg body weight once a week	Only Pegasys™ is licensed for hepatitis B in monoinfected patients. Here, length of therapy is 12 months.
Lamivudine	300 mg QD	Minimum of 12 months in HbeAg-positive patients and 6 months after HbeAg seroconversion Indefinite in HbeAg-negative patients
Emtricitabine	200 mg QD	Undefined
Adefovir	10 mg QD	Minimum of 12 months, possibly lifelong
Tenofovir	300 mg QD	Undefined
Entecavir	0.5 mg, if 3TC naive 1.0 mg, if 3TC experienced	Undefined

Treatment of HBV may have to be continued indefinitely after seroconversion due to the persistence of HBV. This may at least be the case in patients with ongoing immunosuppression.

A transient elevation of transaminases – which is usually moderate and soon resolves – may be observed after initiation of HBV therapy. It is caused by immunoreconstitution and subsequent increased inflammatory activity. In case of marked and/or ongoing elevation of transaminases, alternative explanations have to be considered (e.g. increasing HBV replication, resistance of HBV, lactic acidosis, hepatotoxicity of antiretroviral drugs, superinfection with hepatitis viruses other than hepatitis B).

As most cases of acute hepatitis B even in HIV-infected patients resolve spontaneously, only supportive treatment is recommended. In addition, data on this situation are sparse (e.g. danger of resistance in case of early therapy with no more options afterwards).

Two main issues will dominate the further development of HBV therapy in the near future. Firstly, combination therapies, including the combination with new compounds, are being investigated further and could significantly influence the development of resistance. Secondly, there are numerous new drugs with specific HBV activity that are still being developed and that will enable further progress (e.g. clobudine and telbivudine).

## References

1. Alberti A, Clumeck N, Collins S, et al. Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005; 42:615-624. <http://amedeo.com/lit.php?id=15916745>
2. Angus P, Vaughan R, Xiong S, et al. Resistance to adefovir dipivoxil therapy associated with the selection of a novel mutation in the HBV polymerase. *Gastroenterology* 2003;125:292-7. <http://amedeo.com/lit.php?id=12891527>

3. Benhamou Y, Bochet M, Thibault V, et al. Long-term incidence of hepatitis B virus resistance to lamivudine in HIV infected patients. *Hepatology* 1999, 30: 1302-1306. <http://amedeo.com/lit.php?id=10534354>
4. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients coinfecting with HIV-1 and lamivudine resistant hepatitis B virus: an open label pilot study. *Lancet* 2001, 358: 718-723. <http://amedeo.com/lit.php?id=11551579>
5. Benhamou Y, Katlama C, Lunel F, et al. Effects of lamivudine on replication of hepatitis B virus in HIV-infected men. *Ann Intern Med* 1996, 125:705-712. <http://amedeo.com/lit.php?id=8929003>
6. Brook MG, Gilson R, Wilkins EL. BHIVA Guidelines: coinfection with HIV and chronic hepatitis B virus. *HIV Medicine* 2003, 4:42-51
7. Colin JF, Cazals-Hatem B, Loriot MA, et al. Influence of HIV infection on chronic hepatitis B in homosexual men. *Hepatology* 1999, 29: 1306-1310. <http://amedeo.com/lit.php?id=10094979>
8. Cooper D, Cheng A, Coakley DF, et al. Anti-hepatitis B virus (HBV) activity of tenofovir disoproxil fumarate (TDF) in lamivudine (LAM) experienced HIV/HBV co-infected patients. [Abstract WePeB6015] 14th International AIDS Conference 2002, Barcelona.
9. Hadziyannis SJ, Tassopoulos NC, Heathcote EJ, et al. Long-term therapy with adefovir dipivoxil for HBeAg-negative chronic hepatitis B. *N Engl J Med*. 2005; 352:2673-81. <http://amedeo.com/lit.php?id=15987916>
10. Hofer M, Joller-Jemelka HI, Grob PJ, et al. Frequent chronic hepatitis B virus infection in HIV-infected patients positive for hepatitis B core antigen only. Swiss HIV Cohort Study. *Eur J Clin Microbiol Infect Dis* 1998, 17:6-13. <http://amedeo.com/lit.php?id=9512175>
11. Konopnicki D, Mocroft A, de Wit S, et al. Hepatitis B and HIV: prevalence, AIDS progression, response to highly active antiretroviral therapy and increased mortality in the EuroSIDA cohort. *AIDS* 2005; 19:593-601. <http://amedeo.com/lit.php?id=15802978>
12. Lai CL, Chien RN, Leung NW, et al: A one-year trial of lamivudine for chronic hepatitis B. *New Engl J Med* 1998, 339: 61-68. <http://amedeo.com/lit.php?id=9654535>
13. Mai AL, Yim C, O'Rourke K, Heathcote EJ. The interaction of HIV and hepatitis B infection in infected homosexual men. *J Clin Gastroenterol* 1996, 22: 299-304. <http://amedeo.com/lit.php?id=8771427>
14. Murphy MJ, Wilcox RD. Management of the coinfecting patient : human immunodeficiency virus/hepatitis B and human immunodeficiency virus/hepatitis C. *Am J Med Sci* 2004, 328 :26-36. <http://amedeo.com/lit.php?id=15254439>
15. Soriano V, Puoti M, Bonacini M, et al. Care of patients with chronic hepatitis B and HIV co-infection : recommendations from an HIV-HBV International Panel. *AIDS* 2005, 19 :221-240. <http://amedeo.com/lit.php?id=15718833>
16. Thio CL, Seaberg EC, Skolasky R Jr, et al.; Multicenter AIDS Cohort Study. HIV-1, hepatitis B virus, and risk of liver-related mortality in the Multicenter Cohort Study (MACS). *Lancet*. 2002a;360:1921-6. <http://amedeo.com/lit.php?id=12493258>
17. Thio CL, Seaberg EC, Skolasky R, et al. Liver disease mortality in HIV-HBV co-infected persons. Abstract 656, 9<sup>th</sup> CROI 2002b, Seattle.
18. Xiong S, Yabg H, Westland C, et al. Resistance surveillance of HBeAG-positive chronic hepatitis B patients treated for two years with adefovir dipivoxil. Abstract 779, 11<sup>th</sup> International Symposium on Viral Hepatitis and Liver Disease 2003, Sydney, Australia.



## 19. GBV-C Infection

Matthias Stoll

Almost one century ago, in 1917, the Austrian neurologist Julius Wagner von Jauregg was able to obtain improvement in patients with late stage symptomatic neurosyphilis, by infecting them with the malaria parasite. This approach might appear strange to physicians in the contemporary era of antimicrobial treatment. However, at that time it was by far the most effective option and it earned its discoverer the Nobel Prize for Medicine in 1927. Thus, even an infection with obligatory pathogens may result in harm reduction under certain conditions.

GB virus C is a flavivirus that is closely related to hepatitis C virus. The name GB virus stems from early experiments on the transmission of acute hepatitis from humans to marmoset monkeys. One of the first source patients had the initials "G.B." and was a 34-year old colleague of the author of the experiment (Deinhardt 1967). Later on, two hepatotropic viruses, GB virus A (GBV-A) and GB virus B (GBV-B), were isolated from these monkeys. Two independent research groups simultaneously discovered the related GB virus C (GBV-C) in humans with hepatitis in the middle of the 1990s. Subsequently, the GB virus C has promoted the discussion as to whether the natural course of HIV infection might be modulated in a favorable way by this particular coinfection. In addition, because GBV-C was first found in humans with hepatitis, and due to its close relationship to the hepatitic GBV-A and GBV-B viruses, GBV-C was also called "hepatitis G virus (HGV)" by one research group. This name should no longer be used, because it has since been shown that GBV-C neither causes hepatitis nor worsens preexisting hepatitis (Berenguer 1996, Tillmann 1998, Rambusch 1998, Stark 1999). In fact, GBV-C is not a hepatotropic but a lymphotropic virus. Despite intensive research, GBV-C has not been shown to cause any other known disease.

The virus is frequently found in humans: approximately 10 to 30 % of blood donors have specific antibodies against GBV-C and up to 5 % of them show GBV-C virus replication. Assuming that the virus is apathogenic, affected individuals are not excluded from the donation of blood and consequently, serological diagnostics on GBV-C are not routinely performed. Two serological markers for GBV-C infection exist: GBV-C viremia is determined using a PCR method; and antibodies to the envelope region E2 (anti-E2) are detected by ELISA. As they are mutually exclusive, either GBV-C viremia or the presence of anti-E2 is detectable in GBV-C infected individuals. In most cases, GBV-C viremia is transient and ends with seroconversion to anti-E2, resulting in immunity to new infections. However, this does not seem to be a lifelong immunity (Table 1). Transmission of GBV-C occurs parenterally and mucosally, thus similar to HIV, HBV and HCV infections.

### Is GBV-C a friendly virus?

The first report of decreased HIV disease progression and mortality in GBV-C coinfecting patients was from a German monocentric study, published in 1998. Initially, these results did not draw much attention, although they were confirmed by Australian and American working groups (Toyoda 1998, Heringlake 1998). In 2001, two

larger studies with a longer follow-up again showed a favorable prognosis for HIV-infected individuals with GBV-C viremia (Tillmann 2001, Xiang 2001). These results encountered considerable resonance in the international press – and articles in some newspapers reported in a vociferous manner a "miracle virus, which stops AIDS". As a consequence, some patients requested sources of supply for GB virus C from their physicians and wanted to infect themselves with it. In summary, the GBV-C story became involuntarily discredited by a couple of simplified and unscientific reports in the secondary literature. Concomitantly, a controversial discussion of the data started within the scientific community. In recent years, however, several studies have focused on the influence of GBV-C status on surrogate markers and clinical progression in HIV infection.

Table 1: Serological markers and stages of GBV-C infection

	<b>Marker: GBV-C-Viremia (RNA)</b> Method: PCR / b-DNA	<b>Anti-E2-Antibodies</b> ELISA
GBV-C negative	negative	negative
Replicative GBV-C Infection	positive	negative
Past GBV-C Infection	negative	positive

The heterogeneity of the HIV/GBV-C coinfecting cohorts is a major methodical problem in an attempt to compare the results from the different studies published recently. Some studies did not follow up the status of the GBV-C viremia longitudinally. The serological status of GBV-C, however, can change over time, and the distinction between the three possible stages of GBV-C serostatus is crucial for the interpretation of the studies (see table 1). Overall, it is agreed that there is no difference between the clinical course of HIV-infected individuals without contact to the GB virus C (GBV-C negative) and those with cleared GBV-C infection (anti-E2-positive). But GBV-C viremia (GBV-C RNA positive) is prolonged in HIV infection and persistent GBV-C RNA positive patients differ from the non-viremic subgroups in the majority of studies: in four studies from the pre-HAART era, GBV-C RNA positive patients revealed less rapid progression of clinical disease, lower death rates, smaller reduction in CD4 T cells, reduced increase in HIV plasma viremia, and improved quality of life – in comparison with HIV-infected individuals without GBV-C viremia (Toyoda 1998, Heringlake 1998, Yeo 2000, Xiang 2001). These observations were confirmed in several studies from the HAART era (Tillmann 2001, Nunnari 2003, Williams 2004, Tillmann 2004). The effects were more pronounced in studies with longer follow-up periods.

However, some studies – partially with considerable follow-up time – could not find an effect of GBV-C viremia on HIV infection (Sabin 1998, Birk 2002, Bjorkman 2004, Kaye 2005, Williams 2005). One of these studies summarized GBV-C viremic and anti-E2-positive patients as GBV-C positive group (Sabin 1998), but exclusively the GBV-C RNA positive HIV-coinfecting subgroup differed in clinical outcome in the other studies. Two studies (Kaye 2005, Williams 2005) were performed in women, so that a possible gender specific modulating effect of GBV-C on HIV could not be ruled out. In contrast to that hypothesis is one study investigating the GBV-C status in HIV-infected pregnant women (Handelsman 2006). The authors found a lower HIV viral load in GBV-C viremic women and less vertical

transmission of HIV from mother to child in the HAART era but not in the pre-HAART era.

Another conflicting result came from a recently published study (van der Bij 2005), which showed a more unfavorable course of HIV infection, using clinical and surrogate markers, for patients that were GBV-C viremic at the time of inclusion in the study. However, during follow up, this study also found a reduced mortality for those patients with a persisting GBV-C RNA (over years). Thus, this investigation again agrees with results from studies, which demonstrated a more favorable course for GBV-C RNA positive HIV-coinfected patients: in some of these studies the GBV-C seroconverters, who switched during the follow-up from GBV-C RNA positive status to anti-E2 positivity had a particularly worse prognosis (Williams 2004, Bjorkman 2004).

Several studies have described more pronounced antiretroviral and immunological effects of antiretroviral therapy in HAART-treated GBV-C RNA positive patients. However, other studies did not find these differences. But no study to date describes a negative influence of GBV-C viremia on the effect of HAART.

Therefore, to summarize the various cohort studies it could be cautiously concluded that a favorable clinical course of HIV infection in GBV-C RNA positive patients may be restricted to males and to those patients with ongoing GBV-C replication. However, it should be taken into account that, until now, most studies were retrospective and performed in only a few centers. Therefore, at present, it cannot be completely excluded that the association between GBV-C viremia and ameliorated HIV infection is at least in part biased by other factors.

The fundamental chicken-egg dilemma still remains unsolved: whether GBV-C viremia is an epiphenomenon or a cause for the different outcomes of HIV infection is not yet clear.

Some authors favor the explanation that GBV-C viremia is an epiphenomenon of higher CD4+ T-cell counts. GBV-C replicates predominantly in CD4 T-lymphocytes and therefore it could be expected that the level of GBV-C viremia decreases if the helper T-cell counts drop (van the Bij 2005). This hypothesis, however, does not explain why HIV-infected patients should not be able to induce the CD4+ T-cell dependent specific humoral immune response against the E2 envelope protein of GBV-C with high CD4+ T-cell levels and how they are later able to do so with an impaired immunity. Initial evidence for a causal role of GBV-C came from in vitro experiments on GBV-C and HIV coinfecting cell cultures (Xiang 2001). HIV replication in the cultured cells was decreased when the cells had been infected with GBV-C prior to HIV, but HIV replication remained on the same level when the cells were infected with GBV-C afterwards.

## **Does the knowledge about GBV-C have any practical use?**

The microbial zoo of pathogens of infectious diseases is crawling with lots of horrifying micro monsters, which can cause dreadful illnesses. In this frightening environment, the description of the little viral Tamagochi named GBV-C, which does not hurt its host and perhaps is able to protect him and to reduce harm caused by

another infection, would be a nice fable. But beyond the tales of a potentially healthy infection at least four questions are still open:

1. Does chronic GBV-C replication itself cause the reduced progression of HIV infection, or is the continuous GBV-C replication a secondary epiphenomenon, which is particularly frequent when HIV infection has a favorable clinical course for other reasons?
2. If GBV-C should play a causal role, on which pathophysiological mechanisms is this based?
3. If we were able to define the pathways of GBV-C-associated modulation of HIV disease, how could we translate them into new therapeutic approaches?

And last, but not least whilst this issue remains unsolved:

4. If persisting GBV-C viremia slows down the progression of an HIV coinfection, how can we maintain a durable replication of GBV-C in these patients?

We know that most humans develop anti-E2 antibodies soon after an infection with GBV-C and, at this time, GBV-C replication ends irreversibly. We also experienced that this E2 seroconversion, in the case of an HIV coinfection, is associated with a more rapid progression of HIV disease (Williams 2004, Bjorkman 2004). Until now, little has been known about the factors relevant for maintenance or termination of GBV-C replication. But, GBV-C replication can be durably terminated by interferon therapy, e.g. treatment of chronic hepatitis C. Although the question remains unsettled as to whether the clearance of GBV-C viremia induced by interferon therapy will have the same impact on the course of HIV infection as the observed cases of spontaneous clearance, this issue is of potential impact for counseling in HIV, HCV, and GBV-C coinfection. Therefore, there is at least a need for screening for GBV-C serostatus, individual counseling and a prospective follow-up during interferon therapy in controlled studies.

## Proposed pathomechanisms

A couple of immunomodulatory or antiviral mechanisms can be induced by GBV-C and may play an interacting role with HIV coinfection: in GBV-C-infected peripheral blood cells decreased expression of chemokine receptors (CCR5 and CXCR4) has been found on the surface of CD4<sup>+</sup> and CD8<sup>+</sup> T-cells. A potential pathomechanism for this down-regulation of chemokine receptors is the E2-protein-induced release of RANTES from T lymphocytes by its binding to the CD81 receptor (Tillmann 2002, Nattermann 2003, Xiang 2004). Chemokine receptors are targets for HIV. Therefore, a result of decreased chemokine receptor expression is a decrease in HIV replication. Surprisingly, anti-E2 antibodies were also able to inhibit HIV replication *in vitro* (Xiang 2006b), which is in contrast to the observation that anti-E2 seroconversion accelerates the clinical HIV progression. Another study showed that a peptide consisting of a 69-amino acid subunit from NS5A (which is a viral protein from GBV-C) was able to induce RANTES *in vitro* and therefore down-regulates HIV replication (Xiang 2006a). Complex disturbances of the cytokine profile have been described in HIV-infected individuals *in vivo*, but are less prevalent in individuals with GBV-C/HIV coinfection (Nunnari 2003). Focusing on the innate immunity, normalized levels of CD69 (Fas-ligand) could be demonstrated on NK cells and were less pronounced on lymphocytes in GBV-C viremic HIV-



infected individuals, resulting in down-regulation of apoptosis (Mönkemeyer 2006). In addition, further direct and indirect mechanisms of GBV-C or its components on HIV replication have been described. Contradictory extents of some effects of GBV-C on HIV in different cohorts could be due to different levels of lymphotropism of different GBV-C genotypes or to host-related factors.

The history of GBV-C, as well as that of HIV, is still young. The near future will bring further insight into possible mechanisms of HIV and GBV-C interaction and the roles that individual-specific host factors play. At present, GBV-C gives us the opportunity to obtain insight into clinically relevant regulation pathways of HIV. This could help us in the development of new therapeutic concepts prior to, or in addition to, HAART. Presumably, these concepts could be promising with respect to their clinical and therapeutic impact, because, in several studies, a benefit of GBV-C replication remained evident under HAART.

## References

- Berenguer M, Terrault NA, Piatak M, et al. Hepatitis G virus infection in patients with hepatitis C virus infection undergoing liver transplantation. *Gastroenterology* 1996, 111:1569-75. <http://amedeo.com/lit.php?id=8942736>
- Bjorkman P, Flamholz L, Naucler A, Molnégren V, Wallmark E, Widell A. GB virus C during the natural course of HIV-1 infection: viremia at diagnosis does not predict mortality. *AIDS* 2004, 18:877-86. <http://amedeo.com/lit.php?id=15060435>
- Deinhardt F, Holmes AW, Capps RB, Popper H. Studies on the transmission of human viral hepatitis to marmoset monkeys. Transmission of disease, serial passages, and description of liver lesions. *J Exp Med* 1967, 125: 673-88. <http://amedeo.com/lit.php?id=4960092>
- Handelsman E, Cheng I, Thompson B et al. The effect of maternal GBV-C infection on mother-to-child HIV transmission in the Women and Infant Transmission Study Cohort. Abstract 718, 13<sup>th</sup> CROI 2006, Denver. <http://www.retroconference.org/2006/Abstracts/27753.htm>
- Heringlake S, Ockenga J, Tillmann HL, et al. GB virus C/hepatitis G virus infection: a favorable prognostic factor in human immunodeficiency virus-infected patients? *J Infect Dis* 1998, 177:1723-6. <http://amedeo.com/lit.php?id=9607857>
- Kaufman T, McLinden J, Xiang J, et al. Interaction between GB Virus C Envelope Glycoprotein E2 and cell lines. Abstract 163, 12<sup>th</sup> CROI 2005, Boston. <http://www.retroconference.org/2005/cd/Abstracts/25169.htm>
- Kaye S, Howard M, Alabi A, Hansmann A, Whittle H, van der Loeff HS. No observed effect of GB virus C coinfection in disease progression in a cohort of African woman infected with IV-1 and HIV-2. *Clin Infect Dis* 2005, 40:876-8. <http://amedeo.com/lit.php?id=15736023>
- Lefrere JJ, Roudot-Thoraval F, Morand-Joubert L, et al. Carriage of GB virus C/hepatitis G virus RNA is associated with a slower immunologic, virologic, and clinical progression of HIV disease in coinfecting persons. *J Infect Dis* 1999, 179:783-9. <http://amedeo.com/lit.php?id=10068572>
- M Birk, Lindback S, Lidman C. No influence of GB virus C replication on the prognosis in a cohort of HIV-1-infected patients. *AIDS* 2002, 16: 2482-5. <http://amedeo.com/lit.php?id=12461426>
- Mönkemeyer M, Heiken H, Schmidt R: Decreased Fas Expression on Natural Killer Cells in GBV-C Co-infected HIV-1 Patients 13th Conference on Retroviruses and Opportunistic Infections, Denver February 2006 <http://www.retroconference.org/2006/PDFs/848.pdf>
- Nattermann J, Nischalke HD, Kupfer B, et al. Regulation of CC chemokine receptor 5 in hepatitis G virus infection. *AIDS* 2003, 17:1457-62. <http://amedeo.com/lit.php?id=12824783>
- Nunnari G, Nigro L, Palermo F, et al. Slower progression of HIV-1 infection in persons with GB virus C co-infection correlates with an intact T-helper 1 cytokine profile. *Ann Intern Med* 2003, 139:26-30. <http://amedeo.com/lit.php?id=12834315>
- Rambusch EG, Wedemeyer H, Tillmann HL, Heringlake S, Manns MP. Significance of coinfection with hepatitis G virus for chronic hepatitis C – a review of the literature. *Z Gastroenterol* 1998, 36: 41-53. <http://amedeo.com/lit.php?id=9531689>
- Sabin CA, Devereux H, Kinson Z, et al. Effect of coinfection with hepatitis G virus on HIV disease progression in hemophilic men. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998, 19: 546-48. <http://amedeo.com/lit.php?id=9859971>

## 570 GBV-C Infection

15. Stark K, Doering CD, Bienzle U, et al. Risk and clearance of GB virus C/hepatitis G virus infection in homosexual men: A longitudinal study. *J Med Virol* 1999, 59:303-6. <http://amedeo.com/lit.php?id=10502260>
16. Tillmann HL, Heiken H, Knapik-Botor A, et al. Infection with GB virus C and reduced mortality among HIV-infected patients. *N Engl J Med*, 2001;345:715-24. <http://amedeo.com/lit.php?id=11547740>
17. Tillmann HL, Heringlake S, Trautwein C, et al. Antibodies against the GB virus C envelope 2 protein before liver transplantation protect against GB virus C de novo infection. *Hepatology* 1998; 28: 379-84. <http://amedeo.com/lit.php?id=9696000>
18. Tillmann HL, Manns MP, Claes C, Heiken H, Schmidt RE, Stoll M. GB virus C infection and quality of life in HIV-positive patients. *AIDS Care* 2004, 16:736-43. <http://amedeo.com/lit.php?id=15370061>
19. Tillmann HL, Stoll M, Manns MP, Schmidt RE, Heiken H. Chemokine receptor polymorphisms and GB virus C status in HIV-positive patients. *AIDS* 2002, 16:808-9. <http://amedeo.com/lit.php?id=11964548>
20. Toyoda H, Fukuda Y, Hayakawa T, et al. Effect of GB virus C/hepatitis G virus coinfection on the course of HIV infection in hemophilia patients in Japan. *J Acquir Immune Defic Syndr Hum Retrovirol* 1998, 17:209-13. <http://amedeo.com/lit.php?id=9495219>
21. Van der Bij AK, Kloosterboer N, Prins M, et al. GB virus C coinfection and HIV-1 disease progression: The Amsterdam Cohort Study. *J Infect Dis* 2005, 191:678-85. <http://amedeo.com/lit.php?id=15688280>
22. Williams C, Allen J, Benning L, et al. Prevalence, acquisition, and clearance of GB virus type C in the Women's Interagency HIV study . Abstract 163, 12th CROI 2005, Boston. <http://www.retroconference.org/2005/cd/Abstracts/24123.htm>
23. Williams CF, Klinzman D, Yamashita TE, et al. Persistent GB virus C infection and survival in HIV-infected men. *N Engl J Med* 2004, 350:981-90. <http://amedeo.com/lit.php?id=14999110>
24. Xiang J, George SL, Wunschmann S, Chang Q, Klinzman D, Stapleton JT. Inhibition of HIV-1 replication by GB virus C infection through increases in RANTES, MIP-1alpha, MIP-1beta, and SDF-1. *Lancet* 2004, 363:2040-6. <http://amedeo.com/lit.php?id=15207954>
25. Xiang J, Mc Linden J, Chang Q et al. Monoclonal antibodies directed against the GB Virus C major envelope glycoprotein neutralize HIV infectivity differentially in PBMC than in TZB-bl Cells. 13<sup>th</sup> CROI 2006, Denver. <http://www.retroconference.org/2006/PDFs/417.pdf>
26. Xiang J, McLinden J, Chang Q et al. Deletion mapping of the GB Virus C nonstructural protein 5A identifies a 69 amino acid region required for inhibition of HIV replication in jurkat cells. Abstract 211, 13<sup>th</sup> CROI 2006, Denver. <http://www.retroconference.org/2006/PDFs/211.pdf>
27. Xiang J, McLinden J, Chang Q, Kaufman T, Stapleton J. GB virus C NS5A protein expression decreases HIV replication in jurkat cells. Abstract 163, 12th CROI 2005, Boston. <http://www.retroconference.org/2005/cd/Abstracts/25208.htm>
28. Xiang J, Wunschmann S, Diekema DJ et al. Effect of coinfection with GB virus C on survival among patients with HIV infection. *N Engl J Med* 2001, 345:707-14. <http://amedeo.com/lit.php?id=11547739>
29. Yeo AE, Matsumoto A, Hisada M, Shih JW, Alter HJ, Goedert JJ. Effect of hepatitis G virus infection on progression of HIV infection in patients with hemophilia. Multicenter Hemophilia Cohort Study. *Ann Intern Med* 2000, 132:959-63. <http://amedeo.com/lit.php?id=10858179>

## 20. HIV and Renal Function

By Ansgar Rieke

A quarter of the cardiac output is consigned to the perfusion of the kidneys – even though the kidneys amount to just 0.5 % of the total body weight. Approximately every 20 minutes, i.e. 70 times a day, the entire blood plasma is filtered by the kidneys. Therefore, kidney glomeruli are target organs for every hematogenous infection. Viral infection can cause primary glomerulonephritis, whereas an immune reaction can lead to secondary glomerulonephritis. HIV infection, hepatitis B and C as well as bacterial infections are all typical causes of renal disease. Nephrotoxic agents precipitate renal diseases that affect the interstitium and the tubular apparatus in particular, and these have to be differentiated from glomerulonephritis.

Both forms can cause renal impairment and can lead to end-stage renal disease. While HIV-associated nephropathy (HIV-AN) is predominantly found in Afro-Americans (80-85 %), in the HAART era the greater task will be to examine the renal safety of antiretroviral agents. However, only a small amount of literature is available on this subject to date.

### Clinical manifestation/diagnosis of nephropathy

The major symptoms of glomerulonephritis are proteinuria and “nephritic sediment”. HIV-AN is diagnosed in cases of nephrotic syndrome with edema, hypoalbuminemia, hyperlipidemia and proteinuria of more than 3.5 g/day. However, even a mild proteinuria is possible. The occurrence of proteinuria and erythrocyturia is pathognomonic for glomerulonephritis (GN) and, together with a nephritic sediment, usually confirms the diagnosis. Under a polarizing microscope, a trained eye can easily identify the renal (glomerular) origin of the erythrocytes, on the basis of glomerularly deformed acanthocytes. More than 5 acanthocytes per field of vision is a significant sign for GN. Extensive erythrocyturia (bleeding) below the renal pelvis (tumor of the urinary tract collection system?) can be excluded by sonography and, if necessary, by cystoscopy.

The clinical symptoms are determined by the extent of proteinuria with loss of protein and imbalance, as well as loss of renal function. The severity of edema, tiredness, reduced performance, susceptibility to infections, hyperlipidemia, anemia, metabolic acidosis, problems with the calcium-phosphate metabolism, as well as venous thrombi and newly diagnosed arterial hypertension is limited by the length and intensity of the renal insufficiency. Nephrotic syndrome, acute nephritic syndrome (acanthocytes), rapid-progressive glomerulonephritis, asymptomatic proteinuria or hematuria and chronic glomerulonephritis can be clinically differentiated, and are treated differently.

An increase in serum creatinine is not to be expected until the glomerular filtration rate (GFR) is below 50 %, and should be identified early by clearance measurements. Useful methods for estimating the GFR are the Cockcroft formula or the MDR Clearance, as a urine collection over two 24-hour periods is difficult to organize.

Interstitial nephropathy, especially when caused by indinavir, can present as a sterile leukocyturia or – on proof of bacteria – as a bacterial-interstitial nephritis, and can also lead to a loss of renal function.

Leukocyturia must be microbiologically clarified (culture of mid-stream urine) in order to initiate treatment with antibiotics according to the resistance situation. Tuberculosis of the urinary tract should be considered as a possible cause of abacterial leukocyturia.

The symptoms of drug-induced Fanconi's syndrome (tubulotoxic damage) are glucosuria + phosphaturia with a normal blood glucose (dropping the renal glucose limit) + hypophosphatemia. The patient feels tired and peaky, the symptoms are non-specific and an increase in serum creatinine is often delayed.

## **Routine tests for renal impairment**

The routine investigation of an HIV-infected person should include tests for sodium, potassium, calcium, phosphate (every three months) and creatinine (creatinine clearance). The urine should be tested for glucosuria, proteinuria, erythrocyturia and leukocyturia every 3 months.

If there is a significant rise in proteinuria or serum creatinine, a nephrologist should be asked for advice. There is no time to waste in the case of a rapid increase of creatinine (rapid-progressive glomerulonephritis?), an increase of LDH connected with hyperbilirubinemia and thrombocytopenia (hemolytic uremia syndrome, HUS), or severe electrolyte imbalance (especially hyperkalemia), or acidosis that can no be controlled, which can also occur on therapy as lactacidosis.

An asymptomatic, slight proteinuria with no rise in creatinine in untreated patients is normally a consequence of the infection of the glomerulus or tubular apparatus with HIV/hepatitis-viruses and should be monitored quarterly.

A decrease in renal function in patients with an HIV infection could be interpreted as a symptomatic HIV infection, and in untreated patients antiretroviral therapy might be considered. The use of a contrast medium (CM) for the urinary tract should be avoided, especially in cases of renal insufficiency, proteinuria and all forms of low intravasal volume (including cirrhosis of the liver), in order to avoid causing CM-induced renal failure. If the administration of CM is unavoidable, the patient should receive a non-ionic contrast medium and be given 0.9 % NaCl intravenously at 1ml/kg/h, 12 hours before and 12 hours after receiving the contrast medium. The addition of acetylcysteine 600 mg before and after receiving the contrast medium is well documented as an effective protection for the kidneys and probably works as a free radical scavenger on CM-exposure.

## **HIV-associated nephropathy (HIV-AN)**

HIV-AN is characterized by rapid loss of renal function, which is especially observed in Afro-Americans. The risk factors are genetic predisposition (97 % Afro-Americans), male gender and drug abuse.

Most patients have a poor immune status with < 100 CD4+ T-cells/ $\mu$ l (only 20 % have normal ranges). Individual cases of sudden renal insufficiency within an acute

HIV syndrome have been reported. But, there seems to be no correlation with HIV viral load and the duration of the HIV infection.

Nephrotic proteinuria usually presents clinically as more than 3.5 g/day, but a minor proteinuria is also possible. Progression is fast and can lead to end-stage renal disease (dialysis) in less than 10 months. The blood pressure is normal or slightly increased; the kidneys are within the normal size range when examined by ultrasound scan. Despite hemodialysis, the one-year-mortality rate is 50 %; on antiretroviral therapy it still reaches around 30 %.

The histological findings in biopsies mostly (70 %) correspond to a focal segmental sclerosing glomerulonephritis (FSGN), which is also frequently observed in “malignant hypertension” in Afro-Americans. However, other causes of a glomerulonephritis, such as an amyloid kidney are also possible with HIV (30 %). Single case descriptions with the histological course of disease have confirmed the direct infection of the glomerular basal membrane with HIV, and have documented an impressive positive effect of HAART on the histological changes.

Experience with other FSGN-forms has shown that only early intervention with HAART – before scarring of the glomeruli occurs due to the underlying disease – has a chance of success. The use of components of antiretroviral therapy should take into consideration the different means of renal elimination (adaptation of the dosing). ACE-inhibitors (captopril 6.25 to 25 mg bid, then change to a longer-term effective preparation such as enalapril 5 mg) should be added. The use of steroids is the subject of controversial discussion (1 mg/kg KG/day for 2 to 11 weeks).

## Post-infectious glomerulonephritis

Many infections are able to trigger or support an acute post-infectious glomerulonephritis or other forms of chronic GN. Viral infections such as CMV, EBV, VZV, influenza, adenovirus, and parvovirus B19 do this as well as HIV. After syphilis and infections with staphylococci, pneumococci, legionella, salmonelli and other infectious agents, an acute post-infectious glomerulonephritis can also occur. An acute HIV infection can cause renal insufficiency.

Membranous glomerulonephritis is a special form of secondary glomerulonephritis, which can appear in malignant tumors and hepatitis (B and C). Chronic hepatitis C can lead to a membrano-proliferative GN, or through cryoglobulinemia can also cause vasculitis with renal involvement.

Irrespective of the liver histology, hepatitis C-associated GN can also be a reason for therapy with interferon/ribavirin (observe adaptation of the dosing intervals). However, ribavirin shouldn't be used if the creatinine clearance is less than 50 ml/min/1.73 m<sup>2</sup> because of the danger of prolonged anemia.

## Principles of therapy of glomerulonephritis

The underlying cause of a post-infectious glomerulonephritis should be treated first, including hepatitis B, C and HIV infection.

Particular attention should be paid to the adjustment of blood pressure: target values are < 130/80 mm Hg or, in the presence of proteinuria < 120/80 mm Hg. ACE-

inhibitors as well as AT-II-receptor-antagonists are used to control blood pressure, usually in combination with diuretics.

Proteinuria should be treated with an ACE-inhibitor, also at high doses, if necessary, irrespective of the blood pressure, and should be combined additionally with AT-II-receptor-antagonists if the proteinuria is more than 0.5 to 1 g/day. The protein intake is reduced to 0.6-0.8 g/kg/day (low protein diets like the Mediterranean diet might be helpful).

Fluids should be restricted to 1.5 to 2 l/day and adapted according to the body weight and amount of edema. Forced drinking of large amounts, or rather the alleged “flushing” of the kidneys or the use of high-ceiling diuretics in combination with increased fluid flow rate, only has a limited effect on renal function. Not smoking is of vital importance because nicotine causes an increase in the risk of progression of glomerulonephritis.

Hyperlipidemia should be treated after dietary arrangements have been exhausted. HMG-CoA reductase inhibitors are ideal, provided that they can be combined with the antiretroviral therapy (see chapter on drug interactions). Fibrates or fibrates in combination with statins may only be used carefully when renal function is reduced (cumulation).

Analgesics should be waived as far as possible, which applies especially to the “small” analgesics, such as ASA and paracetamol. At the latest, when the creatinine clearance reaches a value of less than 50 ml/min/1.73 m<sup>2</sup>, treatment should be managed by a nephrologist.

## Treatment of hypertension

Please take note of the specific side effects of antihypertensive drugs. Note hyperkalemia with ACE-inhibitors; at a creatinine count of 1.4 mg/dl do not use potassium-saving diuretics; at creatinine > 1.8 mg/dl high-ceiling diuretics such as furosemid or torasemid should be used.

Table 1: Blood pressure adjustments

Category	Drug
ACE-inhibitors	Lisinopril, Benazepril-HCL, Fosinopril sodium, Enalapril, etc.
Beta-blockers	Metoprolol, Bisoprolol
AT II-receptor-antagonists	Valsartan, Candesatan, Telmisartan, etc.
Diuretics	Hydrochlorothiazide + Triamterene
Ca-antagonists	Amlodipine

## Renal safety of antiretroviral therapy

The spectrum of an allergic or autoimmune reaction in the kidney is no different from the skin. Reactions can be humoral or T-cell-mediated and can lead to renal insufficiency. The spectrum ranges from the type I immune reaction (acute interstitial nephritis after exposure to medication) to the type IV T-cell-mediated reaction

(special forms of a chronic interstitial nephritis). It is, therefore, important to know that even the one-off use of an analgesic (e.g. ibuprofen) can lead to renal failure. In principle, this is possible with antiretroviral drugs. Any change of treatment should be followed by a check of renal function.

The typical side effects of antiretroviral therapy are:

### **Indinavir-associated nephropathy**

As indinavir was established in 1996 and administered at the high dosage of 3 x 800 mg, the renal side effects ranged from asymptomatic crystalluria to renal failure. In different studies, the cumulative occurrence of the symptomatic nephrolithiasis in indinavir was indicated to be over 10 %.

Boosted indinavir (800 mg + 100 mg ritonavir) does not reduce the rate of nephrolithiasis, and brings about the interruption of therapy in to 6-9 % of cases. The classic symptoms of hematuria and flank pain, increasing to renal colic, indicates nephrolithiasis. Special risk factors are crystalluria, a high specific weight of the urine (higher than 1,025 mg/l, dehydration), an alkaline urine with a pH value > 6, little absorption of fluid (less than 2-3 l/day), obstructive uropathy, male gender, history of nephrolithiasis and a body mass index below 20.

The proof of typical indinavir crystals in the urine alone is no reason to discontinue indinavir therapy, as 80 % of these patients are clinically inconspicuous. Even so, these cases should be monitored. In our clinic, the patients with indinavir nephropathy are examined by ultrasound scan. If there is no obstruction, they receive fluid i.v. or orally. The combination of 1,000 ml fluid with spasmolytics and NSAR (Novaminsulfon) can control the situation.

If there is an obstruction and fever, urological intervention is necessary (double-J-catheter). The urine should be acidified to a pH value of 4-5. This works best with buttermilk, yoghurt, coke and avoidance of fruit juice. A brief interruption of indinavir, therapeutic drug monitoring and a conversion of the therapy to e.g. 600/100 mg should be considered.

When evaluating the triggering agent, it must be observed that other medicaments could have caused the crystalluria, and only resulted in nephrolithiasis on combination with indinavir (e.g. ampicillin, acyclovir, aspirine, ciprofloxacin, methotrexate, vitamin C, sulfonamide and also other drugs that lead to an increase in uric acid).

On abdominal x-ray, an indinavir stone is not usually apparent. However, in combination with calcium it can become radio-opaque, and could be confused with a calcium-oxalate-stone. Urate stones are transparent on x-rays.

Elevation of creatinine under long-term indinavir therapy was already observed at the end of the 90s. Typical signs of indinavir nephropathy include sterile leukocyturia and an echogenic transformation of the renal parenchyma in otherwise normal kidneys. Discontinuing indinavir leads to a normal function in most cases. One should pay heed to the possibility of tuberculosis in the urinary tract in sterile leukocyturia.

## **Tubulotoxic side effects of ART, Fanconi's syndrome**

Fanconi's syndrome is characterized by generalized disturbance of tubular function, while glomerular filtration is not primarily affected. The limited capacity of transportation and reabsorption of amino acids, glucose, phosphate, and bicarbonate leads to the loss of these components in the urine. The results are hypophosphatemia, hypocalcemia, osteoporosis and acidosis. The most prominent example is the glucose threshold of the kidneys (180 mg/dl).

The main symptoms of Fanconi's syndrome are the loss of phosphate, amino acids and glucose in the urine, a low phosphate value in the blood, or glucosuria at normal blood glucose levels. In the past, a drug-induced Fanconi's syndrome on didanosine, zalcitabine and zalcitabine has been observed. Because mitochondrial toxicity is discussed as a potential reason, this side effect is possible with any other NRTI.

In case reports, renal failure was above all described in patients with other reasons for renal insufficiency, mostly under boosted PI-regimes with tenofovir as well as secondary disorders and cirrhosis of the liver or hepatitis. Nephrologists advise caution in selecting antiretroviral therapy for patients with proteinuria, nephritic syndrome, cirrhosis of the liver, and/or dyslipoproteinemia. Nephrotoxic substances such as didanosine, zalcitabine and tenofovir should be avoided in these patients. According to the current data, there is no reason to categorize the one or the other substance as nephrotoxic ahead of time or to discourage patients from using them. A recently published overview concerning changes in the renal function under antiretroviral therapy saw no advantage of one particular therapy with regard to nephrotoxicity. Therefore, only careful monitoring of serum creatinine, proteinuria, erythrocyturia and serum phosphate is advised.

## **Tenofovir and the kidney**

In the past few years, a number of studies have investigated the kidney function on tenofovir. It must be emphasized in advance that, in comparison to other NRTIs, the licensing studies revealed no differences with regard to nephrotoxicity.

However, cohort analyses and case studies reported tubular damage suggestive of Fanconi's syndrome. This was almost always diagnosed in conjunction with hypophosphatemia, glucosuria (renal diabetes mellitus with normal blood sugar), and a mild proteinuria (not nephrotic). In the cohort studies, the serum creatinine increased on average to 2.7 mg/dl (0.9-7.8) and decreased again to a creatinine level that was slightly higher than the starting level, at 1.2 mg/dl (0.7-2.1), once tenofovir was discontinued.

According to the cases available at present, it can be assumed that tubular acidosis, hypokalemia, hypophosphatemia and glucosuria will all recede after tenofovir has been discontinued. Kidney biopsies performed on patients with Fanconi's syndrome who were taking tenofovir showed a proximal acute tubular necrosis without any glomerular, vascular or interstitial changes, corresponding to the clinical course of restitution ad integrum after discontinuation of tenofovir. Therefore, tenofovir should not be withdrawn immediately in the case of mild proteinuria or hypophosphatemia. In such cases, the kidney function can (and indeed should!) continue to be monitored.



The differential diagnosis of tenofovir-induced kidney damage and HIV-AN is very important. Low serum phosphate, glucosuria and a mild proteinuria all tend to point to side effects of tenofovir. In this differential diagnosis, asking for a simple urine disc electrophoresis can answer the question of selectivity of proteinuria, which can differentiate between the non-selective glomerular (HIV-AN), and the selective tubular (TDF) form of damage.

According to a number of cohort studies, the risk factors for tenofovir-associated impairment of kidney function are: advanced HIV infection (low CD4+ T-cells), limited kidney function at the beginning of treatment (increased serum creatinine), history of kidney disease, or arterial hypotonia – but, interestingly enough, not diabetes mellitus.

The measurement of serum creatinine alone identifies at least mild impairment of the kidney function on tenofovir in about 2 % of patients. When the more sensitive MDRD clearance is applied, the occurrence is 13 %. We therefore recommend a combination of serum creatinine and urine status/sediment to check progress in cases of tenofovir intake, as well as with other antiretroviral therapies. To be particularly thorough, this can be supplemented by a calculated MDRD clearance. We consider urine collection to be less useful, for there is nothing more unreliable than a 24-hour urine collection at home by a patient who has not been given precise instructions beforehand.

In the case of tubulotoxic damage, an overlapping toxicity of tenofovir with boosted PIs due to a blockade of the MRP2-efflux-transport-protein of the tubule cell by ritonavir is possible. The increased AUC levels of tenofovir combined with atazanavir/r or ddI could also have a cytotoxic effect on tubule cells, but this is still hypothetical. At present, the clinical data do not justify to categorically abandon such combinations. However, for combinations of ddI, tenofovir and boosted PIs (especially atazanavir), the kidney function should be monitored carefully, as an increase in the tenofovir level can be expected.

Acute kidney failure or acute tubular necrosis is also possible when taking acyclovir, ganciclovir, adefovir, aminoglycosides or pentamidine. Tubular dysfunctions can also occur when taking ddI, d4T, or 3TC. An acute allergic interstitial nephritis can arise in the context of the hypersensitivity reaction with Abacavir. Membrano-proliferative glomerulonephritides have been described in connection with atazanavir and enfurvirtide (T-20).

Thus, all that remains is the reminder to always perform routine checks on kidney function where HAART is involved. On the other hand, from a nephrological viewpoint, there is no reason at present to issue a general warning about one substance or another.

## Nephroprotection

In view of the prolonged use of antiretroviral medication, long-term renal side effects are to be expected. This applies especially to the discussion about hyperlipidemia and lipodystrophy. Similar to experiences with diabetes mellitus and diabetic nephropathy, the principles of therapy should be particularly emphasized: adjustment of blood pressure values to < 130/80 mm Hg and no smoking. However, they have not yet been scientifically investigated in relation to HIV infection. The con-

sequent adjustment of diabetes mellitus or change of therapy to avoid a metabolic syndrome are in principle advantageous and will probably have a long-lasting positive side effect on renal function.

On the basis of current data, the viral changes of the glomeruli and the renal tubules due to HIV infection should be reason enough to start/maintain an antiretroviral therapy in a symptomatic patient, rather than to worry too much about potential nephrotoxic side effects.

## Estimating the GFR

According to Cockcroft and Gault:  $((140 - \text{age}) \times \text{kg body-weight})$  divided by  $(\text{serum creatinine, mg/dl} \times 72)$ . For women, the result is multiplied by 0.85.

The MDRD-formula (<http://nephron.com/cgi-bin/MDRDSI.cgi>) is more exact. It just needs laboratory data (creatinine, urea, albumin), age and sex but no urine collection (the adjustment for dark-skinned persons can be disregarded). The formula is:

$$\text{Creatinine-clearance [MDRD]} = 170 \times \text{Crea [mg/dl]}^{-0.999} \times \text{age}^{-0.176} \times (\text{urea [mg/dl]} \times 0.46)^{-0.170} \times \text{albumin [g/dl]}^{0.318} \text{ (for women: } \times 0.762)$$

The original formula displays SUrea (= Urea-nitrogen), which is the reason for the conversion “x 0.46”.

## Dosage of antiretrovirals in renal insufficiency

In each case, the technical information of the individual substances must be taken into consideration. Because NNRTIs and PIs are almost exclusively hepatically eliminated, a dose rate adjustment is normally only necessary for the NRTI, unless a coexistent insufficiency of the liver is present.

Within the scope of hepatitis C therapy, ribavirin should be omitted in patients with renal insufficiency (note: prolonged anemia) if the creatinine clearance is under 50 ml/min/1.73 m<sup>2</sup>. T-20 (Fuzeon™) can be used up to an endogenous creatinine clearance of 30 ml/min/1.73 m<sup>2</sup> without dose reduction; no data is available for more severe renal insufficiency.

Table 2: Dosage of antiretroviral medicaments in renal insufficiency (in each case diurnal dosages, if not otherwise stated) HD=Hemodialysis

Category	Standard dose	CrCl (ml/ min)	Dose in renal insufficiency
AZT (Retrovir <sup>®</sup> )	2 x 250 mg	> 10	2 x 250 mg
		< 10	300 – 400 mg
3TC (Epivir <sup>®</sup> )	1 x 300 mg or 2 x 150 mg	> 50	Standard dose
		30 – 49	1 x 150 mg
		15 – 29	150 mg on day 1; 100 mg/day thereafter
		5 – 14	150 mg on day 1; 50 mg/day thereafter
AZT+3TC (Combivir <sup>®</sup> )	2 x 1 Tabl.	> 50	Standard dose
		< 50	Not recommended
ABC (Ziagen <sup>®</sup> )	2 x 300 mg	> 50	Standard dose
		< 50	contraindicated
AZT/+3TC+ABC (Trizivir <sup>®</sup> )	2 x 1 Tabl.	> 50	Standard dose
		< 50	Not recommended
d4T (Zerit <sup>®</sup> )	2 x 40 mg (> 60 kg) 2 x 30 mg (< 60 kg)	> 50	Standard dose
		30 - 49	half standard dose
		< 30	quarter standard dose
ddl (Videx <sup>®</sup> )	1 x 400 mg (> 60 kg) 1 x 250 mg (< 60 kg) (combined with TDF never exceed 1 x 250 mg)	> 60	Standard dose
		30 - 59	half standard dose
		10 - 29	1 x 150 or 100 mg
		< 10	1 x 100 or 75 mg
TDF (Viread <sup>®</sup> )	1 x 245 mg	>50	Standard dose
		30 - 49	245 mg every 2 days
		10 - 29	245 mg every 72-96 h
		HD patients	245 mg every 7 days past HD
FTC (Emtriva <sup>®</sup> )	1 x 200 mg	> 50	Standard dose
		30 - 49	200 mg every 2 days
		15 - 29	200 mg every 72 h
		< 15 (incl. HD)	200 mg every 96 h

## Ols and renal insufficiency

### Pneumocystis pneumonia

As cotrimoxazole is nephrotoxic as a high-dose therapy, its use must be carefully considered. Systemic administration of pentamidine should also be avoided in patients with renal insufficiency.

Table 3: PCP treatment in renal insufficiency

	GFR normal	GFR >50 ml/min	GFR 10-50 ml/min	GFR <10 ml/min	Dose adaptation for HD/CAPD/cont. NET
Cotrimoxazole	960 mg 3 x 3/die  (total of 120 mg/ kg daily)	960 mg 2 x 3/die  (100 % every 12 h)	960 mg 1-2 x 3/die  (100 % every 12-24 h)	480 mg 1 x 3/die  (50 % every 24 h)	HD: + half dose after dialysis CAPD: no adaptation CAVH: GFR 10-50 CVVHD: GFR < 10
Dapsone	100 mg every 24 h	50-100 %	50 %	avoid	avoid
Atovaquone	750 mg every 12 h	100 %**	100 %**	100 %**	HD: no adaptation CAPD: no adaptation* CAVH: (GFR < 10)**
Pentamidine	4 mg/kg every 24 h	100 %	100 % every 24-36 h	100 % every 48 h see text !!!	HD: (GFR < 10)*** CAPD: (GFR < 10)** CAVH: (GFR < 10)**

\* no studies available, normal dosage recommended,

\*\* no studies available, dosage as for GFR < 10ml/min recommended.

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

## Toxoplasmosis encephalitis

Table 4: Treatment of cerebral toxoplasmosis with renal insufficiency

	GFR normal	GFR > 50 ml/min	GFR 10-50 ml/min	GFR < 10 ml/min	Dose adaptation for HD/CAPD/cont. NET
Pyrimethamine	50-75 mg every 24 h	100 %	100 %	100 %	HD: no adaptation CAPD: no adaptation CAVH: no adaptation
Clindamycin	150- 300 mg every 6 h	100 %	100 %	100 %	HD: no adaptation CAPD: (GFR < 10)* CAVH: (GFR < 10)* CVVHD: GFR normal
Sulfadiazine	2 g every 6 h	Avoid	Avoid	Avoid	Avoid

\*= no studies available, dosage as for GFR < 10 ml/min recommended.

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

## CMV, HSV, VZV infection

Table 5: Treatment of CMV, HSV, VZV in renal insufficiency

Drug	GFR normal	GFR > 50 ml/min	GFR 10-50 ml/min	GFR < 10 ml/min	Dose adaptation for HD/CAPD/cont. NET
Acyclovir	5-10 mg/kg every 8 h	5 mg/kg every 8-12 h	5 mg/kg every 12-24 h	2.5 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR < 10 CAVH: 3.5 mg/kg every 24 h CVVHD: 6.5-15 mg/kg every 24 h
Ganciclovir	5 mg/kg every 12 h	3 mg/kg every 12 h if GFR 25-50 ml	3 mg/kg every 24 h if GFR 10-25 ml	15 mg/kg every 24 h	HD: Dose after dialysis CAPD: GFR < 10 CAVH: 3.5 mg/kg every 24 h CVVHD: 2.5 mg/kg every 24 h
Valganciclovir	900 mg every 12 h	GFR 40-59 ml/min 450 mg every 12 h GFR 25-39 ml/min 450 mg every 24 h GFR 10-24 ml/min 450 mg every 48 h for induction		unknown	unknown
Foscavir	90 mg/kg every 12 h	50-100 %	10-50 %	avoid	HD: Dose after dialysis CAPD: 60 mg/kg every 48-72 h CAVH: GFR 10-50
Cidofovir	5 mg/kg every 7 days	100 %	0.5-2 mg/kg every 7 days	avoid	HD: GFR 10-50 CAPD: GFR 10-50 CAVH: avoid
Famciclovir	250 mg every 8 h p.o.	Every 12 h	Every 48 h	50 % every 48 h	HD: Dose after dialysis CAPD: ? CAVH: GFR 10-50

(cont. NET = continuous dialysis, HD = intermittent hemodialysis, CAPD = continuous ambulant peritoneal dialysis; CAVH = continuous arterio-venous hemofiltration, CVVHD = continuous veno-veno hemodiafiltration).

## References

1. Appen VK, Beuers U, et al. Chronische HIV- und HBV – Infektion mit Erythrocyturie und Proteinurie. DMW 1998, 123: 185-188.
2. Arribas J, et al. Superior outcome for tenofovir, FTC & efavirenz compared to fixed dose AZT/3TC (Combivir) & efavirenz in antiretroviral naive patients. 18th International Conference on Antiviral Research 2005, Barcelona.
3. Becker S, Balu R, Fusco J. Beyond serum creatinine: identification of renal insufficiency using glomerular filtration: implications for clinical research and care. Abstract 819, 12th CROI 2005, Boston.

## 582 HIV and Renal Function

4. Benhamou Y, Bochet M, Thibault V, et al. Safety and efficacy of adefovir dipivoxil in patients co-infected with HIV-1 and lamivudine-resistant hepatitis B virus: an open-label pilot study. *Lancet* 2001, 358:718-723.
5. Benitez Bermijo, et al. Decreased glomerular filtration in HIV patients treated with tenofovir. Abstract TuPe2.3C21, 3th IAS 2005, Rio.
6. Blick G, Greiger-Zanlungo P, Garton T, Hatton E, Lopez RJ. Tenofovir may cause severe hypophosphatemia in HIV/AIDS patients with prior adefovir-induced renal tubular acidosis. Abstract 718, 10th CROI 2003, Boston.
7. Breton et al. Tubulopathy consecutive to Tenofovir-containing antiretroviral therapy in two patients infected with Human Immunodeficiency Virus-1. *Scand J Infect Dis* 2004, 36: 527-528. 454.
8. Gallant et al. (TDF) Compared to Nucleoside Reverse Transcriptase Inhibitors (NRTIs); IAS 2005: Abstract TuPe2.3C18.
9. Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. *JAMA* 2004;292:191-201.
10. Gallant J, Parish M, Keruly J, Moore R. Decline in renal function associated with tenofovir DF compared with nucleoside reverse transcriptase inhibitor treatment. Abstract 820, 12th CROI, 2005, Boston.
11. Gallais H, Lazzarin A, Adam A, et al. The Viread Expanded Access Program in Europe/Australia: summary of the safety and efficacy of tenofovir disoproxil fumarate in antiretroviral treatment experience patients. Abstract TuPeB4552, 15th IAC, 2004, Bangkok.
12. Callens St et al. Fanconi-like syndrome and rhabdomyolysis in a person with HIV infection on highly active antiretroviral treatment including TNF. *J Infection* 2003, 47: 262-263.
13. Cheng A, Wulfsohn M, Cheng SS, Toole JJ. 2 year long term safety profile of tenofovir DF (TDF) in treatment-experienced patients from randomized, double-blind, placebo-controlled clinical trials. Abstract 156, 9th EACS 2003, Warsaw.
14. Chin-Beckford N, Kaul S, Jayaweera DT. Comorbidities drive nephrotoxicity associated with tenofovir fumarate: a case series from Florida. Abstract WePeB5970, 15th IAC 2004, Bangkok,
15. Coca St et al. Acute renal failure associated with TNF: Evidence of drug induced nephrotoxicity. *Am J Med Sci* 2002, 324: 342-344.
16. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976, 16: 31-41.
17. Conaldi PG, Bottelli A et al. HIV-persistent infection and cytokine induction in mesangial cells: a potential mechanism for HIV-associated glomerulosclerosis. *AIDS* 2000, 14: 2045-2053.
18. Créput C, Gonzales-Canali G, et al. Renal lesions in HIV-1-positive patient treated with tenofovir. *AIDS*. 2003, 17:935-937.
19. Estrada V, Ena J, Domingo P, et al. Renal safety of tenofovir DF in HIV treatment-experienced patients with adverse events related to NRTI use: a recover study. Abstract H-169, 44th ICAAC, 2004, Washington.
20. Fellay J, Boubaker K et al. Prevalence of adverse events associated with potent antiretroviral treatment: a Swiss HIV cohort study, *Lancet* 2001 ,358: 1322-27
21. Franceschini et al. Incidence and etiology of acute renal failure among ambulatory HIV-infected patients. *Kidney International* 2005, 67:393-403.
22. Gaspar G et al. Fanconi syndrome and acute renal failure in a patient treated with tenofovir: a call for caution. *Aids* 2004, 18: 351-352.
23. Grases F, Casta- Banza A, et al. Indinavir crystallization and urolithiasis. *Int J Urology Nephrology* 1999 ,31: 23 – 29.
24. Horberg MA, Klein DB, Yu J, Sinn K, Yu J. Effect of tenofovir on renal function in a "real world" clinic setting. Abstract WePpB2066, 15th IAC, 2004, Bangkok.
25. Inui KI, Masuda S, et al. Cellular and molecular aspects of drug transport in the kidney, *Kidney Int.* 2000 ,58: 904- 958.
26. Izzedine H, Hulot JS, Vittecoq D, et al. Long-term renal safety of tenofovir disoproxil fumarate in antiretroviral-naïve HIV-1-infected patients data from a double-blind randomized active-controlled multicentre study. *Nephrol Dial Transplant* 2005, 20:743-6.
27. Jaegel-Guedes E, Wolf E, Ruemmelein N, et al. Incidence of tenofovir-related nephrotoxicity in a large outpatient cohort. Abstract WePeB5937, 15th IAC 2004, Bangkok.
28. Johnson M, Grinsztejn B, Rodriguez C, et al. Atazanavir plus ritonavir or saquinavir, and lopinavir/ritonavir in patients experiencing multiple virological failures. *AIDS* 2005,19:685-694.
29. Jones R, Stebbing J, Nelson M, et al. Renal dysfunction with tenofovir disoproxil fumarate-containing HAART regimens is not observed more frequently: a cohort and case-control study. *J Acquir Immune Defic Syndr* 2004; 37:1489-1495.

30. Kopp JB, Miller KD, et al. Crystalluria and urinary tract abnormalities associated with indinavir. *Annals Int Med* 1997, 127: 119-125.
31. Karras A et al. Tenofovir related nephrotoxicity in human immunodeficiency virus- infected patients: three cases of renal failure, fanconi syndrome, and nephrogenic diabetes insipidus. *CID* 2003, 36: 1070-1073.
32. Kearney BP, Liaw S, Yale K, et al. Pharmacokinetics following single dose administration of tenofovir DF in subjects with renal impairment. Abstract P4, 6th Int Con Drug Ther HIV Inf 2002, Glasgow.
33. Kinai E, Hanabusa H et al. Renal tubular toxicity associated with tenofovir assessed using urine-beta 2 microglobulin, percentage of tubular reabsorption of phosphate and alkaline phosphatase levels. *AIDS* 2005, 19:2031-2041.
34. Klotman PE. HIV-associated nephropathy. *Kidney Int* 1999,56: 1161-1176.
35. Leen et al. Pharmacokinetics of enfurvitide in a patient with impaired renal function. *CID* 2004, 39:e119-e121.
36. Lewis S, Gathe J, Ebrahimi R, Flaherty J, Wallace RJ. Comparative evaluation of renal function in HIV-infected, treatment-naïve patients of African American descent receiving HAART regimens containing either tenofovir DF or zidovudine. Abstract TuPeB4599, 15th IAC 2004, Bangkok.
37. Louie S, Ballard C, Bi L, Beringer P. Factors increasing the risk of renal dysfunction with tenofovir difumarate (TDF). Abstract TuPe3.5B01, IAS 2005, Rio de Janeiro.
38. Malik et al. Acute renal failure and fanconi syndrome in an AIDS patient on tenofovir treatment-case report and review of literature. *J Infect* 2005, 51: E61-65.
39. Marras D, Bruggeman L A et al. Replication and compartmentalization of HIV-1 in kidney epithelium of patients of HIV-associated nephropathy. *Nature medicine* 2002, 8: 522-526.
40. Mauss S, Berger F, Schmutz G. Antiretroviral therapy with tenofovir is associated with mild renal dysfunction. *AIDS* 2005, 19:93-95.
41. Molina JM, Gathe J, Lim PL, et al. Comprehensive resistance testing in antiretroviral naïve patients treated with once-daily lopinavir/ritonavir plus tenofovir and emtricitabine: 48-week results from study 418. Abstract WePeB5701, 15th IAC 2004, Bangkok.
42. Murphy MD et al. Fatal lactic acidosis and acute renal failure after assition of tenofovir to an antiretroviral regimen containing didanosine. *CID* 2003, 36: 1082-1085.
43. Nickeleit V, Klimkait T, Binet IF et al. Testing for polyomavirus type BK DNA in plasma to identify renal-allograft recipients with viral nephropathy. *NEJ*; 2000, 342: 1309-1315.
44. Padilla et al. Low frequency of renal function impairment during one-year of therapy with tenofovir-containing regimens in the real-world: A Case Control Study. *AIDS Pat Care STDs* 2005, 19:421-424.
45. Peyriere H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. *J Acquir Immune Defic Syndr*. 2004,35:269-273.
46. Reislser R, Jacobson L, Gupta S, et al. Chronic kidney disease and the use of HAART. Abstract 818, 12th CROI 2005, Boston.
47. Roca B, Gisbert C, Cabestany B, Perez AP, Ventura JM. Metabolic and renal profile before and after tenofovir DF. Abstract B10708, 15th IAC, 2004, Bangkok.
48. Rollot F et al. Tenofovir-related fanconi syndrome with nephrogenic diabetes insipidus in a patient with acquired immunodeficiency syndrome: The role of lopinavir-ritonavir-didanosine. *CID* 2003: 37.
49. Rodriguez-Gomez et al. Tenofovir-related fanconi syndrome in HIV positive patients: The role of interaction with other antiretroviral drugs. Abstract TuPe2.4C06, IAS 2005, Rio.
50. Schooley RT, Ruane P, Myers RA, et al. Tenofovir DF in antiretroviral-experienced patients: results from a 48-week, randomized, double-blind study. *AIDS* 2002, 16:1257-1263.
51. Scott JD, Wolfe PR, Quiros J, Behrooznia E, Buyer B, Bolan RK. Rare occurrence of renal toxicity when retrospectively evaluating the use of tenofovir DF in 2 clinical practices. Abstract TuPeB4532, 15th IAC, 2004, Bangkok.
52. Squires K, Pozniak AL, Pierone G, et al. Tenofovir DF in antiretroviral-experienced, nucleoside-resistant HIV-1 infected patients with incomplete viral suppression. *Ann Int Med* 2003, 139:313-320.
53. Stephens EB, Tian C, et al. Simian-immunodeficiency virus-associated nephropathy in macaques: *AIDS Research Vol. 16*, 13: 1295- 1306.
54. Stephens E B, Tian C et al. Rhesus macaques infected with macrophage-tropic simian immunodeficiency virus exhibit extensive focal segmental and global glomerulosclerosis. *J Virology* 1998, 72: 8820-8832.
55. Szczech LA. Renal diseases associated with human immunodeficiency virus infection: epidemiology, clinical course and management, *CID* 2001, 33:115-119.
56. Wali RK, Drachenberg CI et al. HIV-1-associated nephropathy and response to highly-active antiretroviral therapy. *Lancet* 1998, 352:783-784.

## 584 HIV and Renal Function

57. Winston JA, Bruggeman LA et al. Nephropathy and establishment of a renal reservoir of HIV type 1 during primary infection. *NEJM* 2001 , 344: 1979-1984.
58. Winston et al. Minor changes in calculated creatinine clearance and anion-gap are associated with tenofovir DF containing highly active antiretroviral therapy. Abstract TuPe2.3C23, IAS 2005, Rio.



## 21. HIV-associated Skin and Mucocutaneous Diseases

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### Introduction

Since 1981, when the first reports about AIDS were published in medical literature, skin and mucocutaneous diseases played an important role in the clinical diagnosis of acquired immunodeficiency. Kaposi's sarcoma in young homosexual men was the first symptom that made AIDS a visible disease (Friedman-Kien 1981, 1990). Additionally, opportunistic infections of the skin and oral cavity such as herpes simplex and candidiasis were published as being clinical markers of acquired immunodeficiency (Gottlieb 1981, Siegal 1981). In the early years of HIV infection, a broad spectrum of common cutaneous infections was noted in patients due to viruses, bacteria, fungi, protozoa, and parasites as well as many unusual manifestations of common dermatoses (Friedman-Kien 1989, Farthing 1989, Schöfer 1990, Schöfer 1991, Berger 1997).

The alterations of the cell-mediated immune system enable organisms considered to be non-pathogens to penetrate into the tissue and cause infections. Such opportunistic infections, as well as any other infections in the immunodeficient host, sometimes behave aggressively leading to a life-threatening clinical course.

The most frequent skin diseases documented in a prospective long-term study in HIV-infected patients at the Department of Dermatology and Venereology, University Hospital, Frankfurt/M, Germany, between 1983 and 2004, are summarized in Table 1.

Differences in the prevalence and incidence of mucocutaneous disease between countries may be attributable to climate, endemic diseases, hygienic standards and the availability of specialized medical facilities and drugs, as well as social, economic and cultural factors. The risk groups observed – homosexual men, IVDA, heterosexuals, and children – play an important role in the incidence and prevalence of HIV-associated mucocutaneous diseases (Tzung 2004, Geoghagen 2004, Shimizu 2000, Munoz-Perez 1998, Sivayathorn 1995, Smith 1994, Pallangyo 1992).

Among sexually transmitted diseases, chancroid is an important indicator of the spread of the HIV epidemic in tropical and subtropical regions; whereas in Europe, herpes simplex infections and a resurgence of syphilis in homosexual men are more important indicators. Recently, there has been increased reportage of lymphogranuloma venereum, an STD caused by *Chlamydia trachomatis* (L1-3), in homosexual men in several big cities throughout Europe. It is suspected that this is due to the changing sexual behavior of homosexual men during the past 5 to 7 years. Fear of acquiring HIV infection by unsafe sexual practices has lessened as patients live longer, healthier lives on HAART therapy. There may be a sense among patients that HIV infection no longer confers a death sentence because HAART decreases viral loads resulting in fewer diseases. In addition, many men are not aware of the risk of infection through orogenital contact with other STDs such as syphilis.

Table 1: Frequency of skin diseases	No. patients	% of all HIV patients
Oral candidiasis	636	30%
Seborrheic dermatitis	619	28%
Xeroderma	600	28%
Tinea	502	23%
Folliculitis	492	23%
Syphilis (active/seropositive)	485	23%
Kaposi's sarcoma	460	21%
Pruritus	436	20%
Genital warts	368	17%
Candida infections, others	355	16%
Drug eruptions	349	16%
Herpes simplex genitoanalisis	349	16%
Herpes zoster	345	16%
Gonorrhea (active/history)	340	16%
Bacterial infections	315	15%
Mollusca contagiosa	301	14%
Warts (HPV)	278	13%
Herpes simplex labialis	214	10%
Oral hairy leukoplakia	188	9%
Hair loss	135	6%
Psoriasis	117	5%
Basal cell carcinoma (BCC)	25	1.2%
Squamous cell carcinoma (SCC)	23	1.1%
Malignant melanoma	9	0.4%
Total number of patients 1982 - 2000	2149	100%

Notice: The frequency of skin diseases listed here mirrors the clinical symptoms of 2149 HIV-infected patients, who visited the Frankfurt University Hospital between 1982 and 2000 because of skin problems. Most of these patients were referred with a known HIV infection. Others were detected to be HIV-positive by their dermatological symptoms, which were interpreted as clinical markers of severe acquired immunodeficiency and led to HIV antibody testing. The majority of these patients (75 %) was seen in the pre-HAART era (between 1982-1996). Since 1996, more than 80 % of the patients living with HIV/AIDS in Frankfurt/M. are on HAART. This led to a significant reduction in opportunistic skin diseases (by 90 %) and Kaposi's sarcoma (by 90 %). The high frequency of skin disease summarized in this table is still seen in patients who are not on HAART or not yet diagnosed to be HIV-infected.

In urban areas, syphilis is now seen 4 to 10 times more frequently in homosexual men in comparison to 2000. Until today, there has been no observable increase in the incidence and prevalence of syphilis in European women, but it is very likely that the epidemic in homosexual men will be followed by a heterosexual epidemic within a few years. According to the epidemiological data, provided by the Robert Koch Institute in Berlin, the registration of new syphilis cases exceeded the number of newly registered HIV infections in 2003 by more than 1000 cases (RKI 2003).

It has become evident that a functional cell-mediated immune system plays an important role in the protection against epithelial tumors. The likelihood of developing squamous cell carcinomas, basal cell carcinomas, lymphomas, or even malignant melanoma is correlated with the length of time HIV-infected immunocompromised patients survive. Nowadays, HIV-infected patients survive longer than patients from the pre-HAART era. For this reason, these patients need to be monitored for primary cutaneous malignancies such as basal cell carcinoma, squamous cell carcinoma, melanoma, and cutaneous lymphomas.

Analogous to the long-term immunosuppressed organ transplant recipient, the HIV-infected patient has to be examined periodically for melanoma as well as non-melanoma skin cancers including actinic keratoses (Schöfer 1998). Factors such as UV-light, smoking and oncogenic viruses (especially mucocutaneous infections with HPV 16 and HPV 18) must be considered as cofactors in carcinogenesis. Skin cancer precursors such as actinic keratoses, bowenoid papulosis, Bowen's disease, and intraepithelial neoplasias of the genital or anal region must be treated early and aggressively. The incidence of anal carcinoma, an epithelial tumor typically found in old men, is now increasing in young HIV-infected homosexual men. It seems that the total duration, rather than the severity of immunodeficiency is important for the manifestation of these tumors. As in non-immunocompromised patients, risk factors such as pigmentation characteristics, sun sensitivity, sun exposure behavior patterns, and geographic location must be considered in the evaluation.

## **Dermatological examination and therapy in HIV-infected patients**

HIV-infected patients with advanced disease often suffer from common skin diseases (Table 1), but they also present with rare dermatoses, unique to HIV infection. Careful dermatologic evaluation may lead to the diagnosis of serious systemic infections in this population such as cryptococcosis, bacillary angiomatosis, oral hairy leukoplakia, and *Penicillium marneffei* infections of the skin. Common dermatoses often present with atypical findings and may pose diagnostic dilemmas. For example, herpes simplex labialis may present as large superficial erosions or deeply ulcerating lesions rather than the classical small vesicles on an erythematous base. Eruptions of secondary syphilis may ulcerate and form rupial lesions accompanied by high fever and constitutional symptoms (malignant syphilis). It is therefore important to pursue diagnosis of all cutaneous eruptions through appropriate tests such as tissue cultures, biopsy, and swabs of lesions prior to the initiation of therapy.

Because HIV-infected patients are at high risk of contracting other STDs due to the common modes of transmission, they should be screened for them. During the past three years, 39 % of all syphilis patients who attended our Department, had HIV coinfection. Dermatologic evaluation should include complete cutaneous inspection, oral cavity examination, inspection of the anogenital region and palpation of the lymph nodes. Standard treatment regimens for skin and mucocutaneous diseases may be inadequate in HIV-infected patients due to unusual strains of organisms leading to drug resistance. In these cases, high dose regimens or second and third line therapies may have to be considered (Osborne 2003). Diagnostic and therapeutic

tic regimens of the most frequent HIV-associated skin diseases are compiled in alphabetical order in Appendix 1 of this chapter.

Table 2: Clinical Diagnostic Tools

Indication	Performance	Interpretation
	<b>Dark-field microscopy</b>	
Presumptive diagnosis of ulcers (mainly of syphilitic ulcers)	Secretion (mechanical pressure, if necessary use ether in local anesthesia) of serous exudate is applied to a glass slide, covered with a coverslip. Examination by dark-field microscopy (1000x).	Negative test does not exclude syphilis; false negative testing may be due to: prior treatment with antibiotics/antiseptics
Exudative lesions (condylomata lata, possibly secondary syphilis lesions).	Lesions in the mouth: examination not possible due to saprophytic bacteria	A positive test confirms the diagnosis
	<b>Biopsy</b>	
Differential diagnosis of tumors, skin lesions without definite clinical diagnosis, or to confirm a clinical diagnosis	Under local anesthesia: 4-mm punch-biopsy; if necessary: excisional biopsy. Fixation of the material in 10 % formalin; for special investigations (immunohistology, electron-microscopy, HPV-typing) use only saline.	Dermatopathologist
	<b>Skin-scraping for KOH examination</b>	
Presumptive diagnosis of dermatophytosis	Clean the skin with 70 % alcohol, let it dry. Use a scalpel or glass slide to scrape scales at the active edge onto a glass slide. A drop 10 - 20 % KOH is put on top of the specimen and covered with a cover slip. After ~ 20 minutes or immediately after gentle heating the specimen can be examined microscopically (10-40x magnification) for fungal elements. The specimen may be cultured as well.	Fungal elements (spores and hyphae) are not digested by KOH and can be visualized with light microscopy.
	<b>Herpes-virus detection</b>	
Presumptive diagnosis of herpes infections (grouped vesicles or ulcers)	A smear of cells from the base of the skin lesion is taken (for culture: special swabs: Culturette™; use pressure to obtain cells). Sample can be put onto a glass slide for immediate direct fluorescent antibody testing (DFA) which will distinguish between HSV and VZV infections.	Tzanck-preparation: multinucleated giant cells (Giemsa- or Wright-stain; 400x magnification) Viral lab, positive culture proves diagnosis; demonstration of DNA or antigen does not differentiate between living and dead viruses
	<b>Allergy testing</b>	
Drug eruptions, presumptive allergic contact dermatitis	Serology: (RAST, lymph. transformation test); skin tests Type I reactions: Prick- and intracutaneous-tests. Type IV reactions: "Scratch"- and patch testing. A specialist in allergy should perform tests and interpretation.	Allergist

## HAART: Influence on (muco-) cutaneous diseases

The introduction of HAART in 1996 revolutionized the dermatological management of HIV-infected patients. Opportunistic infections and the clinical manifestations of Kaposi's sarcoma abated to a level of 10 % compared to the pre-HAART era (Reinmöller 1997, Schöfer 1998, Sepkowitz 1998, Calista 2002). An Italian hospital reported that HAART had reduced the total number of HIV patients with skin problems by 40 %. The percentage of patients with cutaneous infections dropped from 66 to 53 %; the percentage of non-infectious, inflammatory diseases from 25 to 21 %; however, the percentage of patients with drug reactions increased from 8 to 23 % (Calista 2002). Appendix 2 is a compilation of antiretroviral drugs, and their cutaneous side effects. Atypical clinical courses of skin diseases and resistance to therapy, which were very common in patients with severe immunodeficiency in the pre-HAART era, are rare conditions now. They still occur, however, in patients not taking antiretroviral therapy (Mirmirani 2001). Cutaneous infections and inflammatory skin diseases have been replaced by drug eruptions caused by almost 20 currently available antiretroviral drugs. In some patients, immune system reconstitution, following 1 to 2 months after the introduction of HAART, causes clinical disease summarized as immune reconstitution inflammatory syndrome (IRIS).

Drug eruptions have many clinical patterns including macular or maculopapular exanthemas, follicular eruptions, urticaria, and toxic epidermal necrolysis (TEN), to name a few. Severe, sometimes life-threatening reactions such as Stevens-Johnson-syndrome or TEN were mainly reported in patients on combination therapy with zidovudine, didanosin, nevirapine, indinavir or amprenavir. In 86 % of these patients, the drug eruptions occurred within the first 4 weeks of treatment (Rotunda 2003). Instead of discontinuing therapy, less severe drug eruptions without mucosal involvement, blistering, or constitutional symptoms (apart from pruritis), may be treated with antihistamines and corticosteroids. This is especially important for patients, whose choice of antiretroviral combination drugs is already limited by drug resistance or severe side effects such as hematotoxicity or polyneuritis. Patients who are "treated through" drug eruptions must be monitored frequently. Corticosteroid treatment should not exceed the equivalent of 1 mg/kg/d bodyweight of prednisone.

Blister formation, involvement of the mucous membranes and constitutional symptoms (hypersensitivity syndrome) are absolute indications to stop antiretroviral therapy. TEN (e.g. induced by efavirenz, nevirapine) and hypersensitivity syndrome (e.g. induced by abacavir) may be fatal.

Drug interactions between HAART and agents used to treat cutaneous diseases are frequent and need to be carefully evaluated before being prescribed (see Chapter "Drug interactions", McNicoll 2004). Azole derivatives, retinoids and drugs metabolized via the p450 pathway frequently interact with antiretrovirals.

Immunosuppressive therapies, such as ultraviolet light and cyclosporin, should be limited to a few conditions such as severe autoimmune diseases, and used only with careful clinical and laboratory monitoring. Photo(chemo)therapy is able to provoke viral infections such as herpes zoster and herpes simplex, epithelial tumors, and to increase the HIV viral load. Despite this, we have seen the benefit of UVB 311nm phototherapy in HIV-infected patients with extreme pruritus associated with papu-

lar dermatoses or eosinophilic folliculitis, resistant to all other therapies. As long as these patients were under the protection of HAART, UV therapy caused no observable worsening of the immune status.

Eliciting the cause of a drug eruption can be challenging, especially if the patient is taking complementary medication not prescribed by a physician. It is necessary to ask explicitly whether any herbal medicines, vitamins, minerals, or food complements are being taken to improve the general health. Substances with a potential risk of sensitization or toxicity can be the cause of drug reactions (Witkowski 2003). Urticaria, angioedema, and exanthemas due to food complements are reported in the literature (Gised 1996).

The treatment of KS varies with the clinical manifestation of the tumor, the immune status of the patient and his additional symptoms associated with the HIV infection (details see Chapter “Kaposi’s sarcoma”).

## Conclusions

The dermatologist’s role in the care of HIV-infected patients is to be familiar with HIV-associated skin and mucocutaneous diseases, their diagnoses, and management. It is also a part of the extensive interdisciplinary knowledge necessary for any physician who takes care of HIV-infected patients.

Considering the lifelong duration of antiretroviral therapy with complications such as drug intolerance, development of epithelial tumors induced by UV-light exposure or oncogenic viruses, it is recommended that patients have a dermatologic consultation before the start of antiretroviral therapy. Complete skin examination with attention to the presence of STDs should be performed. Education should include prevention of photodamage, safe sex practices, and skin care to avoid infections, especially when HIV-associated xerosis is already evident.

Despite the fact that HIV-associated opportunistic infections are less frequent in the HAART era, knowledge about these diseases and adequate treatment is still of high clinical relevance. The full spectrum of these skin diseases is still found in untreated patients around the world.

Dermatological markers of disease of severe acquired immunodeficiency (see Appendix 1) play an important role in this situation (Schöfer 1991), especially if several diseases are diagnosed in the same patient. In the absence of other immunodeficiency, HIV antibody testing must be offered to the patient as a diagnostic tool to elicit the cause of the clinical presentation.

At present, syphilis and HIV co-morbidity is of special interest. The incidence of syphilis in Western Europe has increased 4 to 10 times over the past 4 years. As HIV and *Treponema pallidum* share the same route of transmission, any patient with syphilis must be checked for HIV infection. The delayed seroconversion for HIV antibodies should be taken into account and, if initially negative, HIV testing should be repeated after 3 months.

## Appendix 1:

**Most frequent HIV-associated skin diseases**

**Acute HIV exanthema:** In 40-90 % of all patients infected with HIV-1, an acute, febrile, mononucleosis-like disease with constitutional symptoms and an exanthema occurs (details see Chapter “Acute HIV-1 Infection”). This nonspecific eruption starts 1 to 3 weeks after HIV transmission, and several weeks before HIV seroconversion. The macular exanthema favors the upper trunk and is characterized as fairly non-pruritic with erythematous macules from 0.5 to 1 cm in diameter. Morbilliform or rubella-like eruptions and palmoplantar hyperkeratotic eczema occur less frequently. Histopathology reveals a nonspecific perivascular and interstitial infiltrate in the upper and mid dermis (Barnadas 1997). Oral aphthous ulcers, frequently in combination with shallow genital ulcers (bipolar aphthosis) are another important clinical sign (Hulsebosch 1990, Porras-Luque 1998). Differential diagnosis includes other viral infections (EBV, CMV), Mediterranean spotted fever (Segura 2002), secondary syphilis, drug eruptions (Hecht 2002, Daar 2001) and Behcet’s disease.

**Aphthous ulcers:** At least three different kinds of aphthous ulcers occur in the oral cavity of HIV-infected patients. The most frequent diagnosis is recurrent aphthous stomatitis (canker sores) (1) with single or few painful lesions usually localized in the vestibule of the mouth. The ulcers occur at sites of mechanical injuries, are 3 to 10 mm in diameter and heal spontaneously after a few days. Single or multiple large aphthae (2) which are >1cm in diameter and usually persist for several weeks are less common. Both variants are of unknown origin (Rogers 1997). In a few cases, especially when multiple small lesions occur, herpes simplex viruses can be involved. Large ulcers in combination with severe immunodeficiency can be caused by cytomegaloviruses, which are usually part of a generalized CMV infection. Bipolar aphthosis (3), involving the oral and genital mucosal membranes, is an important clinical symptom of acute HIV infection or Behcet’s disease. In addition to these clinical variants of aphthous ulcers, several authors have discussed the direct role of HIV retroviruses in aphthous stomatitis (Kerr 2003). The treatment of recurrent aphthosis is based upon topical anesthetics, and corticosteroids. Large persistent aphthae can require intralesional corticosteroids or systemic prednisone. Immunomodulators, such as thalidomide, are suggested for use as prophylaxis in patients with frequent and painful recurrences.

**Folliculitis:** pustular, papular or edematous-papular follicular lesions, involving the proximal limbs and the upper trunk. Possible causes include *Staphylococcus*, *Malassezia furfur*, *Demodex folliculorum*, and drugs such as indinavir. Treatment depends on the etiologic agent detected by bacterial swabs and histopathology if needed. Antimicrobials against staphylococcus, and malassezia, or changing the antiretroviral drug regimen may be required. DADPS, a 10 % crotamiton or polidocanol ointment, or low-dose UV-311nm radiation are effective against severe pruritus in these patients (Holmes 2001, Simpson-Dent 1999). Today, it is well established that

HAART naive patients with pruritic eosinophilic folliculitis significantly improve after the initiation of antiretroviral therapy.

**Genital warts (condylomata acuminata):** Genital warts are hyperkeratotic and verrucous papules of the anogenital region, caused by human papilloma viruses (HPV 6, 11, 16, 18, etc.) which are sexually transmitted. HIV-infected patients have a high prevalence of these lesions (17 %), which depends on the number of sexual partners. Genital warts, located in the perianal or intra-anal region are characteristic of receptive anal intercourse. Patients who have anogenital warts, should be offered HIV testing, especially if they have other HIV risk factors.

In general, the clinical manifestations of common genital warts in immunodeficient patients do not differ from those in immunocompetent patients. They are diagnosed by their typical clinical features as condyloma acuminata, condyloma plana, bowenoid papulosis, Bowen's disease and giant condyloma (Buschke-Loewenstein tumor). In contrast to the findings in the immunocompetent population, HPV 16-associated lesions, such as bowenoid papulosis and Bowen's disease, which are now classified as anal intraepithelial neoplasias (AIN I-III including the erythroplasia of Queyrat), are more prevalent in immunodeficient patients. These premalignant conditions have a low rate of spontaneous remission and are very resistant to therapy (frequent relapses). It is now accepted, that genitoanal lesions due to oncogenic HPV types, especially HPV 16 and 18, are substantial risk factors for malignant cervical, penile, and anal carcinomas (Palefsky 1998). HPV 16 and 18 are able to immortalize human keratinocytes by downregulating the tumor suppressor genes p53 and pRB. The transformation rate to malignant carcinomas is low in bowenoid papulosis, but almost 30 % in Bowen's disease, which is rated as a carcinoma in situ. In contrast to the beneficial effects of HAART on the incidence and the clinical course of Kaposi's sarcoma and NHL, there is no clear impact on cervical and anal carcinoma. The incidence of these tumors is still increasing. Analogous to cervical intraepithelial neoplasia (CIN) and cervical cancer in women, regular screening (every 2 to 3 years) for AIN and anal carcinoma is advised for all HIV-infected patients on HAART (Papathanasiou 2003). Screening should include clinical inspection, aceto-white-stain, colposcopy, proctoscopy, cytology (Pap smear) and, if necessary, histopathology (Horster 2003). Clear margins should be the goal of treatment.

The typical treatment for anogenital warts is destruction by cryosurgery, electrocautery, carbon dioxide, Nd-YAG laser, trichloroacetic acid, or podophyllotoxin. CIN, PIN, and AIN are treated surgically with histological control of the excision edges to ensure complete removal of the lesion.

All of the destructive treatments have disadvantages. Since virus-harboring keratinocytes can remain in the clinically normal surrounding tissue, relapses are as frequent as 50 % in immunocompetent patients and up to 70 % in immunodeficient patients within 4 months. Alternative therapies with immunomodulatory activity, such as systemic and topical interferons, have shown some efficacy, but the outcome of the studies was closely related to the different treatment regimens and the cost of therapy was extremely high. Topical interferon (IFN-gel with 0,15 Mio IU/g) was only effective in very small warts and as an adjuvant after surgery. The relapse rate could be reduced by almost 50 %.



The immune response modifier imiquimod has been approved for the treatment of genital warts since 1998. As demonstrated in several controlled studies (Edwards 1998, Gollnik 2001, Cusini 2004), imiquimod treatment is safe and effective and has the lowest relapse rate of all treatments (6-13 % in immunocompetent patients). Imiquimod is not approved for the treatment of anogenital warts in immunodeficient patients and intraepithelial neoplasias, but results of several successful treatments of genital warts (Cusini 2004), bowenoid papulosis and Bowen's disease in HIV-infected patients have been published (Kreuter 2004, Klencke 2003, Cooley 2003). The only antiviral agent active against HPV is cidofovir, but there is little experience in HIV-infected patients (Snoeck 2001).

**Tinea** (dermatophytosis, ringworm infections): Infections of the skin, hair or nails with dermatophytes (in Western Europe predominantly *Trichophyton*, *Microsporum* and *Epidermophyton species*). Tinea has a high prevalence in the general population. There is no significant difference between HIV-negative and HIV-infected adults. The prevalence is dependent upon climate, profession, clothing, and participation in team sports. In homosexual men, the prevalence is 29 to 37 % (Torssander 1988, Schöfer see Table 1).

Typical clinical findings are superficial, scaling, round or oval erythematous plaques, that expand centrifugally with an inflammatory edge and central clearance. Deep infections, with tissue destruction and abscess formation, are rare in Europe and North America, but common in tropical regions. According to Torssander (1988), onychomycosis due to dermatophytes is frequent in HAART-naive patients and difficult to treat. Nails are discolored (white, yellow, green, black), thickened, and show growth disturbances (onychodystrophy). Subungual hyperkeratosis and onycholysis are common.

Psoriasis, yeast infections and trauma can imitate onychomycosis, so it is necessary to identify the causative organisms on KOH and fungal culture. Direct microscopic examination with addition of 10-15 % KOH solution shows translucent, septated hyphae (mycelium) and arthrospores. Culture on Sabouraud's or Kimmig's medium identifies different fungi by their growth characteristics.

Treatment of superficial fungal infections of the skin is best achieved with topical broad spectrum antifungals such as ciclopirox or azoles, applied twice daily. In severe inflammatory disease, it is helpful to start with combination therapy including topical corticosteroids for 3 or 4 days, to achieve quick relief of discomfort. Deep infections and infections involving terminal hairs (tinea capitis, tinea barbae) require systemic treatment with griseofulvin (500-1000 mg/day), terbinafine (250 mg/day), fluconazole (50 mg/day), or itraconazole (100-400 mg/day) (Elewski 2001, Millikan 2001). There are different regimens to treat onychomycosis. Itraconazole and terbinafine are typically used for two months for fingernails and three months for toenails. Griseofulvin may be used for up to 9 months or longer, until the infection clears (Aly 1996, Myskowski 1997, Torssander 1988). If only the distal part of the nail plate is infected, topical treatment with nail varnish containing antifungals, which are able to penetrate the nail plate, are advised to avoid drug interactions between systemic antifungals and antiretroviral medications (see Chapter "Drug Profiles"). If systemic therapy is necessary, fluconazole has less drug interactions in HIV-infected patients than the other antifungals mentioned.

**Herpes simplex virus infections:** Herpetic infections of the skin and mucous membranes are frequent opportunistic infections in HIV-infected patients. The clinical symptoms differ substantially according to the patient's immune status. As long as the cell-mediated immune functions are normal, typical localized infections with itching, erythema and grouped vesicles will appear and heal spontaneously within a few days. In contrast, very painful, deep and large ulcerations of the anogenital region, but also of the face and other parts of the body (e.g. herpetic whitlow) will appear in patients with advanced HIV infection and severe immunodeficiency (CD4+ T-cell count < 100/ $\mu$ l). Clinical diagnosis can be difficult in these patients because grouped vesicles might be absent and only erosions or ulcers might be visible. Along with other STDs, genital herpes plays an important role in the dynamic of the worldwide HIV pandemic. As a genital ulcer disease, herpes lesions ease HIV transmission between sexual partners by breaking the epithelial barriers (1), stimulating HIV reproduction via pro-inflammatory cytokines (2) and enhancing (3) expression of cellular HIV receptors (CD4, etc.) on the surfaces of immunocompetent cells (Jonsson 2004, Celum 2004, Steen 2004, Solomon 2003) (see Chapter "Opportunistic Infections").

**(Herpes) Zoster:** Shingles is an early marker disease during the natural course of HIV infection. Frequently, this secondary endogenous *Varicella zoster virus* infection is diagnosed several years prior to any other opportunistic infection. HIV infection or any other kind of acquired immunodeficiency must be suspected in any zoster patient who is (1) younger than 50 years and has no other known cause of immunodeficiency, or (2) shows atypical clinical features such as multisegmental or generalized distribution of normal, hemorrhagic, or necrotic lesions. Latent VZV infections can be activated in the frame of immune reconstitution syndrome a few weeks after the initiation of effective HAART (Tangsinmankong 2004, Maurer 2004) (See also Chapter "Opportunistic Infections").

**Immune reconstitution inflammatory syndrome (IRIS) related skin reactions:** HAART recovers the TH-1 immune response and the tuberculin test reactivity (Girardi 2002). In association with this immune reconstitution, clinical manifestations of herpes zoster, mucocutaneous herpes simplex infections, mycobacterial infections, eosinophilic folliculitis, foreign-body granulomas and cutaneous sarcoidosis were reported recently (Handa 2001, Hirsch 2004). These infectious, as well as some non-infectious inflammatory skin diseases, occur within a few days to 3 months after the initiation of HAART. The therapy depends on the severity of clinical manifestations and consists of specific antibiotics, steroidal and non-steroidal anti-inflammatory drugs (For details, see Chapter "IRIS").

**Kaposi's sarcoma:** the most frequent malignant tumor of the skin and mucosal membranes associated with HIV infection (see Chapter "Kaposi's sarcoma").

**Lipodystrophy and metabolic syndrome:** See chapter "Lipodystrophy syndrome".

**Malignant cutaneous lymphomas:** Malignant B and T-cell lymphomas are rare in HIV-infected patients (Beylot-Barry 1999, Biggar 2001). Cutaneous B-cell lym-

phomas usually grow as red to violaceous nodules, that are easily mistaken for Kaposi's sarcoma. They can also look like persistent hematoma or nonspecific asymptomatic papules. A biopsy should be performed on any clinically unclear tumor of the skin.

Cutaneous T-cell lymphomas are rare malignancies in HIV-infected patients. The prevalence among 2149 HIV patients in Frankfurt/M. was 0.06 %. The clinical course starts with nonspecific eczematous patches (stage I), which are usually not diagnosed as cutaneous lymphoma, even after several biopsies because of the paucity of findings such as cellular atypia. These lesions are usually diagnosed as eczematous dermatitis. A linear pattern of patchy or slightly infiltrated lesions in the relaxed skin tension lines can be an early clinical indication of cutaneous T-cell lymphoma known as parapsoriasis (Munoz-Peres 1999). Histopathology becomes more evident during the plaque stage (stage II), and is striking when in stage III multiple tumors of the mycosis fungoides present. Biggar et al (2001) calculated a relative risk for cutaneous T-cell lymphomas in HIV-infected patients of 15.0 in comparison to the general population. In both HIV-infected and HIV-negative patients, the leukemic phase (Sézary syndrome) is characterized by erythroderma involving the palms and soles. In patients with erythroderma who have darker skin types and lack the histopathological signs of cutaneous T-cell lymphoma, the so-called "pseudo-Sézary syndrome" has to be considered in the differential diagnosis (Picard-Dahan 1996). Therapy with potent topical steroids (e.g. clobetasol) is effective in the patch and plaque stages. Solitary tumors can be controlled by radiotherapy (20-24 Gy) or photodynamic therapy (Paech 2002). Widespread, multiple tumors, and Sézary syndrome are treated with a combination of retinoids and interferons or chemotherapy. Recently, remission of a CD8+ pseudolymphoma treated solely with HAART was reported (Schartz 2003).

**Molluscum contagiosum:** This is a benign viral infection of the skin, usually seen in children, and often in association with atopic dermatitis. The pox virus causes multiple papular skin-colored lesions with a typical central umbilication. The diagnosis is usually made on clinical grounds. After several weeks or months, an inflammatory reaction indicates the onset of spontaneous healing. In adults, mollusca are detected in the anogenital area and regarded as a sexually transmitted disease (Agromajor 2002). In HIV-infected patients, the clinical manifestations can differ significantly from those seen in the normal host. Spontaneous healing is rare; most patients have high numbers of lesions, typically occurring in the face and neck region, which is otherwise a rare location. The presence of multiple mollusca on the face, is a typical disease marker, indicating advanced cell-mediated immunodeficiency with CD4+ T-cell counts <100/ $\mu$ l (Schöfer 1991, Schwartz 1992). The growth of mollusca in the immunocompromised host is not always exophytic, sometimes endophytic lesions occur. Multiple mollusca have to be differentiated from hematogenous dissemination of cryptococcosis, histoplasmosis, and coccidioidomycosis, which are usually associated with fever, headache, and sometimes pulmonary infiltrates. In such cases, skin biopsies (and tissue culture) and chest x-rays are indicated. Single molluscum can exceed 1 cm in diameter and grow exophytically, which can cause confusion with keratoacanthoma, squamous cell carcinoma, basal cell carcinoma, or common warts.

Mollusca are treated surgically with a special type of forceps, electrocautery, curettage, or with liquid nitrogen. Recently, photodynamic therapy with 5-aminolevulinic acid (Moiin 2003) and imiquimod 5 % cream were effective as well (Hengge 2000, Calista 1999, Calista 2000, Liota 2000, Smith 2002). Imiquimod is applied by the patient 3x/week (off label use). An inflammatory reaction (erythema), occurring after 3 to 4 weeks of topical treatment, indicates the beginning of the immune reaction, which leads to complete resolution of the mollusca after 6-8 weeks.

**Oral hairy leukoplakia (OHL):** is a clinical manifestation of Epstein-Barr virus infection, which is almost exclusively found in patients with untreated advanced HIV disease. Non-cytolytic viral replication in the glossal epithelium, especially in the lateral parts of the tongue, leads to asymptomatic white verrucous plaques that do not rub off. OHL is diagnosed on clinical findings; initially parallel white or grayish hyperkeratotic rows arranged vertically on the lateral aspects of the tongue are characteristic. Unilateral lesions are possible, but bilateral occurrence of several plaques is more typical. Important differential diagnoses include other leukoplakias, lichen planus mucosae and oral candidiasis (Patton 2002, Cherry-Peppers 2003). If the diagnosis is in doubt, a biopsy or cytology can confirm the diagnosis. As the lesions will respond to antiviral drugs such as aciclovir, ganciclovir, or foscarnet (Walling 2003), but not antifungals, treatment can be used as a diagnostic tool to distinguish OHL from candidiasis. Both diseases however, respond well on HAART, which has led to a significant decrease of these oral diseases since HAART was introduced (Triantos 1997, Ramirez-Amador 2003).

**Pruritus:** Chronic, often unremitting pruritus is one of the most frequent clinical symptoms of HIV infection. One in three patients is affected. Etiology remains unclear in most patients, and therefore only symptomatic treatment can be offered which may be unsatisfying (Moses 2003, Singh 2003). Pruritus in HIV-infected patients can be a complication of infectious diseases. Viral, bacterial, and fungal infections (e.g. *Malassezia furfur* folliculitis) and scabies can cause severe itching. Also, dry eczematous skin (xerosis), papulosquamous skin diseases, systemic lymphomas, renal insufficiency and hepatic disease are causative conditions. Finally, many antiretroviral and other drugs given to the HIV-infected patient can cause pruritus (with or without rash).

To diagnose idiopathic pruritus, it is necessary to exclude all skin and systemic diseases mentioned above. In patients on HAART, it can be useful to change the treatment regimen. Systemic antihistamines and topical corticosteroids are symptomatic treatment standards. If they are ineffective, or a prolonged systemic treatment is necessary, phototherapy (UVA-1, UVB-311nm) or photochemotherapy (PUVA) is an alternative or adjuvant therapy. (Smith 1997, Gelfand 2001, Zirwas 2001, Singh 2003) Concerning the immunosuppressive effects of ultraviolet light, it seems that patients on HAART at less risk.

**Papular dermatoses:** Patients can present either with monomorphic skin colored to red papules (size 2 – 5 mm) or with combined eruptions consisting of papules and pustules (sterile eosinophilic pustulosis Ofuji). There is no special predilection for any site. The etiology of papular eruptions is heterogeneous. According to the clini-

cal presentation and to laboratory findings (elevation of IgE, eosinophilia in peripheral blood and affected skin) they resemble the prurigo of atopic dermatitis found in adults. Autoimmune reactions against follicular antigens have also been discussed (eosinophilic folliculitis; Fearfield 1999). These papules can be due to a *hypersensitivity reaction* to drugs, microbiological agents (viruses, bacteria, fungi), parasites, or saprophytes (*Sarcoptes scabiei*, *Demodex folliculorum*, *Pityrosporum ovale* and others). A thorough history of drugs, microbiological and histological examinations (including special stains such as PAS) are required for a correct diagnosis.

If possible, specific infectious agents are treated. In case of sterile eosinophilic pustulosis (Ojufi), or papular dermatosis of unknown origin, therapy is symptomatic. Depending on the clinical situation, antihistamines, itraconazole (200 mg/d for 2 weeks), isotretinoin, dapsone, mild PUVA or UVB (311= narrowband UVB; most effective therapy!) or 5 % permethrin-cream can be tried (Ellis 2004). Topical tacrolimus (0.1 %) also was shown to be effective (Kawaguchi 2004).

**Paronychia and ingrown nails:** Ingrown toenails and inflammatory reactions of the proximal nailfold are a well known complication in diabetics, but also in patients on beta-blockers, or retinoid therapy. A few cases might be due to local pressure (wrong shoes) or occur spontaneously. Patients on HAART are the latest group of patients to regularly develop ingrown nails. These are ascribed to retinoid-like side effects of several antiretrovirals, especially indinavir, but also lamivudine. Usually, the great toenails are involved, but all other toenails and fingernails can be affected. The therapy of choice in these patients, is to replace indinavir or lamivudine as a part of the HAART regimen by other antiretrovirals. This led to complete remission in several of our patients. Surgical measures, such as Emmetplasty or its modification after Hanneke, should only be performed on patients in whom the exchange of HAART medications did not lead to a remission after 3 to 6 months (Tosti 1999, Alam 1999, Garcia-Silva 2002).

**Psoriasis vulgaris:** Today, psoriasis is regarded as an autoimmune disease and affects approximately 1 % of the general population. It has multifactorial inheritance with variable penetrance. Physical stimuli such as friction and UV-light, or endogenous factors such as infections, drugs, and “stress” may trigger psoriatic flares. When HIV-infected persons are exposed to such factors, psoriasis may appear for the first time or can be aggravated. The incidence of psoriasis has been reported to be between 2.5 % (Braun-Falco 1988) and 4.9 % (Schöfer 1990). The use of antiretrovirals improves psoriasis.

Typical psoriatic plaques can be eruptive, guttate, or chronic and stationary.) Atypical findings include inverse localization on the palms or soles and in the genital region and axillae, exudative, pustular, or erythrodermic manifestations. In general, the severity of psoriasis parallels the impairment of the immune system. Besides infection, drugs have to be considered as possible triggers. In the final stages of HIV infection, psoriasis can be generalized and extremely resistant to therapy. Alternatively, the disease may disappear completely.

The typical psoriatic plaque is a sharply demarcated, erythematous plaque covered with silvery scales. Clinically and histologically, it may be difficult to differentiate it from seborrheic dermatitis.

Triggering factors should be eliminated, if possible. Treatment is more difficult if the immune system is impaired. An antiretroviral therapy should be initiated or optimized. Localized lesions can be treated topically with corticosteroids, anthralins, calcium-agonists (calcipotriol or tacalcitol) or the topical retinoid, tazarotene. The scalp and nails can be treated topically with corticosteroids. Generalized or exudative eruptions are usually treated systemically: acitretin (25 – 75 mg/d) is not immunosuppressive. Methotrexate or cyclosporin are immunosuppressive and should be avoided. In some cases, however, it is necessary to use them. Recently, the successful use of hydroxyurea was reported (Kumar 2001). AZT has a beneficial effect on psoriasis, probably by improving the immune status. To treat refractory psoriasis, experimental therapies such as cimetidine (400 mg, 4x/d) have been tried successfully.

The clinical relevance of immunosuppression by UV-radiation is unknown. At present, it is believed that phototherapy or photochemotherapy have no real detrimental effect for HIV patients and that they are justifiable (Akarapathanth 1999, Schoppelrey 1999). These treatments are as effective as in patients without HIV-infection. UVB311 (=narrowband UVB) is well tolerated and effective. Broadband UVB is an alternative. In case of treatment failure, photochemotherapy can be instituted (local = bath or cream PUVA, or systemic PUVA). Interactions of the mentioned antipsoriatics with antiretroviral substances are unknown. Recently, several “biologics” were introduced for the therapy of psoriasis. These compounds specifically interact with certain elements of the inflammatory cascade in psoriasis, such as TNF alpha. Up until now, only case reports can be found in the literature regarding treatment in HIV-infected patients (Bartke 2004).

**Reiter’s syndrome:** Reiter’s syndrome is regarded as a variant of psoriasis in patients who carry HLA B27. This rare chronic-relapsing disease mainly affects young men, the incidence being higher in HIV-infected men than in the general population (0.6 to 6 %; Kaye 1989).

The classical triad consists of: urethritis (sterile yellow urethral discharge), conjunctivitis (serous or purulent) and arthritis (mainly knee-, foot- or sacroiliac joints; causing pain and leading to immobility). The triad is found in about 30 % of patients. Furthermore, constitutional symptoms (attacks of fever, malaise, leukocytosis, elevated ESR) and skin lesions can be found. The skin lesions are characterized by erythema with sterile pustules on the palms and soles, and later, hyperkeratotic, scaling, exudative lesions known as keratoderma blenorrhagicum. Psoriatic plaques can be seen as well as the typical circinate balanitis presenting as crusting, desiccated plaques in circumcised men and shallow, moist, serpiginous, painless ulcers with slightly raised borders in uncircumcised men.

The diagnosis depends on the typical pattern of arthritis plus one or more of the mentioned clinical symptoms. Gonorrhoea or Chlamydia urethritis have to be excluded by microbiological methods. Psoriatic arthritis should have other clinical signs of psoriasis (nail changes) and lacks fever.

Initially, symptomatic therapy with non-steroidal anti-inflammatory agents, or possibly corticosteroids (short-term, high-dose pulse-therapy) should be given. Acitretin (25 - 75mg/d) in combination with topical fluorinated corticosteroids also proved to be effective. Alternatively, sulfasalazine has been used successfully. Ar-

thrititis is also treated with oral gold. There is one report on the successful use of infliximab in a patient with Reiter's syndrome without negative effects on the HIV viral load (Gaylis 2003).

**Scabies:** Scabies can be found worldwide; the prevalence varies from < 1 % to 30 % depending on the socio-economic circumstances. Scabies is characterized by extreme pruritus, especially at night. In general, the clinical presentation does not differ from that seen in HIV-negative persons. In the interdigital areas, volar sides of the joints of the hands, breasts, axillae, periumbilical region, or penile shaft, fine red burrows (S-shaped or straight lines) may be found. There may be a small papule or vesicle at one end. Excoriations and/or secondary infections make the identification of burrows difficult. Generalized eczematous eruption may be seen. Typically, in the groin or on the genitals, red-brown pruritic nodules are found. These scabies granulomas can persist for months, even after successful therapy.

In the case of severe cellular immunodeficiency, crusted scabies or Norwegian scabies can occur. Besides HIV-patients, persons with general physical or mental debilitation are affected. Over weeks to months, eczematous lesions covered with asbestos-like crusts extend over large areas and the plaques can be mistaken for psoriasis. Crusted scabies is extremely infectious and carries many more mites than regular scabies – up to 10,000 mites/g scales. The history of unremitting and intractable itching is suggestive of scabies. The diagnosis is made by the clinical picture and proven by the demonstration of the mites, their ova, or fecal droppings in the scales. On histology, the female mite can be visualized in the stratum corneum.

A single application of permethrin 5 % cream is performed (whole body application from chin to toes, usually excluding the face; leave on skin for 8 hrs, then shower off). In cases of crusted scabies, the scales have to be removed over several days (salicylic ointments) and therapy has to be repeated over 3 – 4 days. Alternative therapies are: hexachlorocyclohexane (lindane), benzoylbenzoate, pyrethrum-extracts or allethrin/piperonylbutoxid, which all have to be applied for 3 days. It is important to treat all contact persons at the same time as well!

Linen and bed-clothes have to be changed daily. Depending on the clinical presentation, another treatment one week later is sometimes recommended (“safety-day”). In cases of severe immunodeficiency, the scalp has to be treated too.

If more than 50 % of the skin is affected, or several recurrences have occurred, a combination of keratolytic/topical therapy against scabies and systemic treatment with ivermectin is recommended. Hygienic measures to prevent contact infections are extremely critical. The single therapy with 2 tablets (6 mg each; some 200µg/kg) is generally sufficient. Ivermectin is not licensed for this indication. There are no reports on complications after this therapy in HIV-infected patients (Dourmishev 1998).

**Seborrheic dermatitis:** The incidence in the general population is estimated to be 3–5 % of all young men. The lipophilic yeast *Malassezia furfur* (formerly named *pityrosporum ovale*) is believed to be of pathogenetic relevance. Here the specific subtype appears to be more important than the density of colonization. In HIV-infection 20–60 % are affected depending on the immune status. Seborrheic dermatitis appearing de novo or exacerbation of mild seborrheic dermatitis in a known

HIV-positive patient could indicate seroconversion from a latency state to a symptomatic state (Ippolito 2000).

Areas rich in sebaceous glands, such as the scalp, forehead, eyebrows, nasolabial folds, over the sternum, between the shoulder blades, external ear canal, and retroauricular area, develop yellowish, oily scales and crusts on mildly erythematous to very red plaques. The lesions may be pruritic.

The clinical picture is typical in most cases. Differentiation from psoriasis may be difficult both clinically and histologically. Initially, other forms of eczema such as allergic contact dermatitis and atopic dermatitis may have similar presentations.

Due to the pathogenic role of *Pityrosporum ovale*, topical antifungals such as ketoconazole cream, other topical imidazoles or triazoles, or alternatively selendisulfide, metronidazole, and low-dose dithranol or lithiumsuccinate- and zinc-sulfate-creams are used. For the scalp, antimycotic shampoos, zinc pyrithione or tar-containing products are used. In severe cases, systemic antimycotics are given: ketoconazole (1 x 200 mg/d), itraconazole (1 x 100 mg/d) or terbinafine (250 mg/d).

**Syphilis:** In general, syphilis in HIV-infected patients is clinically no different from syphilis in the immunocompetent host. In some patients however, atypical findings complicate the clinical and serological diagnosis as well as the treatment. In primary syphilis, painful anal or oral chancres occur. Persistent chancres can still be found when the exanthemas of secondary syphilis and symptoms such as generalized lymphadenopathy appear. In secondary syphilis, syphilids can ulcerate and develop thick crusts (*rupia syphilitica*), which are accompanied by high fever and severe illness. This unusual and otherwise rare course of syphilis, which is termed “malignant” syphilis, is found in 7 % of all syphilis associated with HIV infection. In addition, early neurosyphilis and a very short latent period before the onset of tertiary symptoms of syphilis are described. Neurosyphilis is partly due to a reduced blood-brain barrier and a failure of benzathine penicillin to prevent neurosyphilis in these patients. The interpretation of syphilis serologies, especially in patients with repeated infections and severe immunodeficiency, can be complicated by false negative results and persistent antibodies. Therefore, it is advisable to verify *T. pallidum* infection in any clinical manifestation suspected to be syphilis by direct proof (dark-field microscopy, direct fluorescent antibody testing of exudates, or biopsy specimens).

The recommended treatment of syphilis, which is penicillin for all stages of the disease, has not changed over the past 60 years. *T. pallidum* has developed some resistance against macrolides (erythromycin, azithromycin), but not against penicillin. Syphilis therapy, as recommended by the CDC, WHO, and the German STD Society (DSTDG) is identical for HIV-infected and non-HIV-infected patients. It is advised however, not to use benzathine penicillin G in patients, in whom early neurosyphilis cannot be excluded. If neurosyphilis is suspected, and the patient refuses CSF puncture, high-dose penicillin G (6x5 Mega or 3x10 Mega IV should be given for 2 (early syphilis) or 3 weeks (late syphilis). Ceftriaxone, 1g/day IM for 10 days is a widely used, but not approved alternative.

Standard regimens for early syphilis (primary and early secondary syphilis until one year after infection) are procaine penicillin G, 1.2 million units IM/day for 14 days,



or benzathine penicillin G, 2.4 million units IM in a single dose, injected into different sites.

Late syphilis (any stage of disease at more than one year after infection and any syphilis of unknown duration, excluding neurosyphilis) is treated like early syphilis, but for three weeks instead of two weeks. (For more details about HIV and *T. pallidum* coinfection, see Chapter “HIV and Sexually Transmitted Diseases”). HIV-infected patients should be evaluated clinically and serologically for failure of treatment at 3, 6, 9, 12, and 24 months after therapy.

**Xerosis/Dry skin:** Dry skin is a very frequent complication of any kind of immunodeficiency. In the pre-HAART-era, we diagnosed dry skin in one in three HIV-infected patients (see Table 1). The patients complain of dry, itchy skin, which is exacerbated by any stimulus. Overall, these skin problems are very much like atopic dermatitis (Rudikoff 2002) and can culminate in acquired ichthyosis. The prevalence of dry skin in HIV-infected patients decreased after the introduction of HAART, but is sometimes seen in patients on indinavir (Garcia-Silva 2000). Some years ago, we showed that the lipid film of the skin surface has a different composition in HIV-infected patients, but is not diminished in quantity (C. Semrau: unpublished data, doctoral thesis).

Dry itchy skin is treated with the application of emollients that contain 5 to 10 % urea, or 3 to 4 % lactic acid, and dexpanthenol. If the patients take too many showers, the frequency should be reduced to one shower every (other) day, and 1 to 2 oil baths per week should be recommended. In cases with severe inflammation and fissures (eczema craquele) topical class 3 or 4 corticosteroids are very helpful in reducing the patients symptoms. They should not be used for longer than 3 to 5 days.

## Appendix 2:

# Skin and mucocutaneous disease related to antiretroviral drugs

## 1. Nucleoside analog reverse transcriptase inhibitors (NRTIs)

**AZT, zidovudine, Retrovir™:** Drug eruptions (6 %) mostly macular, rarely severe reactions such as erythema multiforme and Stevens-Johnson syndrome, melanonychia striata medicamentosa, pigmentation and lichenoid eruptions of mucosal membranes, vasculitis, urticaria, pruritus, hyperhidrosis (5-19 %), tongue ulcers.

**ddI, didanosine, Videx™:** Drug eruptions and itching (4 %), erythema multiforme, oral dryness (30 %), papuloerythrodermia Ofuji.

**d4T, stavudine, Zerit™:** Drug eruptions with fever.

**3TC, lamivudine, Epivir™:** Exanthemas, vasculitis, light sensitivity, linear nail hyperpigmentation, hair loss, paronychia, ingrown toenails.

**FTC, emtricitabine, Emtriva™:** Exanthemas, especially in combination with ddI and efavirenz (10 %), cause unidentified.

**ABC, abacavir, Ziagen™:** Maculopapular exanthemas, hypersensitivity syndrome (5 %) after 9 (3-42) days, frequently associated with respiratory problems, nausea, and vomiting, increase in liver transaminases. Any suspicion of hypersensitivity syndrome forces immediate cessation of treatment (Clay 2002). Abacavir re-exposure is contraindicated (severe, sometimes lethal reactions). For details of the management of abacavir hypersensitivity syndrome, see alphabetical drug register.

**Tenofovir, Viread™:** rare exanthemas.

## 2. Non-nucleoside analog reverse transcriptase inhibitors (NNRTIs)

**Nevirapine, Viramune™:** frequent drug eruptions (33 %), severe reactions 6 % (mostly within the first 6 weeks of treatment), Stevens-Johnson syndrome 0.5 %, and few cases of toxic epidermal necrolysis. Less frequent drug reactions (22 %), when therapy is initiated with low doses. Cetirizine, as a prophylactic, is not effective (Launay 2004). Treatment must be stopped in 3-5 %. Reasons are severe skin reactions, exanthemas with fever, conjunctivitis, pain of the limbs, meningitis, eosinophilia (DRESS syndrome = Drug rash with eosinophilia and systemic symptoms; Bourezane 1998, Lanzafame 2001), occasionally diffuse loss of hair. Exanthemas are 7x more frequent, and therapy has to be stopped 3.5 x more often in women compared to men (Bersoff-Matcha 2001). According to the producer's report (Boehringer Ingelheim, February 2004), complications have to be expected mainly during the first 6 weeks of treatment (up to 18 months). During this period, hepatotoxic reactions with high transaminases and exanthemas are frequent. Patients, especially women older than forty, with residual cell mediated immune functions (CD4 cells > 250/μl), are particularly at risk.

**Delavirdine, Rescriptor™:** Maculopapular or erythematous rashes, with or without pruritus in up to 50 %, starting 2-3 weeks after initiation of treatment and involving especially the trunk and upper arms. Mild exanthemas without other complications can regress spontaneously without a need to discontinue treatment.

**Efavirenz, Sustiva™:** Frequent macular or urticarial exanthemas (11 %). Light exanthemas can regress spontaneously without discontinuation of treatment. In case of complications, it is necessary to stop treatment.

## 3. Protease inhibitors (PI)

**Saquinavir, Invirase™:** Aphthous oral lesions (6 %), cheilitis, exanthemas (4 %), rarely Stevens-Johnson syndrome, bullous eruptions, papular pruritic folliculitis.

**Ritonavir, Norvir™:** exanthemas (0.9-2.6 %), papular pruritic folliculitis (8 %), perioral paresthesia (25 %).

**Indinavir, Crixivan™:** In many patients a sicca syndrome with very dry skin, dry mouth and eyes is observed. In addition, exanthemas are frequently papular and intensely itching, involving the lateral parts of the upper arms, the upper trunk and the lateral neck in particular, can occur. Differential diagnosis: papular pruritic eruption (folliculitis). Paronychia (pyogenic granuloma-like) and ingrown toenails, light diffuse loss of hair (12 %), severe and generalized loss of terminal and vellus hair in 1-2 %. Hematoma and hemarthrosis in hemophiliacs. Lipodystrophy ("Crixiv-

belly”, buffalo hump, facial lipotrophy, etc.), metabolic syndrome and asymptomatic hyperbilirubinemia.

**Nelfinavir, Viracept™**: Exanthemas (infrequent).

**Amprenavir, Agenerase™**: Exanthemas (3 %, mostly starting during the 2nd week of treatment, Pedneault 2000), perioral paresthesia.

**Atazanavir, Reyataz™**: Exanthemas (Goldsmith 2003), hyperbilirubinemia, in some cases with jaundice and scleral icterus (Orrick 2004).

**Lopinavir/r, Kaletra™**: Exanthemas (infrequent). Lipodystrophy.

#### 4. Entry-Inhibitors

**T-20, Enfuvirtide, Fuzeon™**: Erythemas and indurations at the injection sites (96%, almost obligatory), exanthemas <1% (Ball 2003).

## References

1. Agan BK, Dolan MJ. Laboratory diagnosis of Bartonella infections. *Clin Lab Med* 2002; 22: 937-62. <http://amedeo.com/lit.php?id=12489289>
2. Agromayor M, Ortiz P, Lopez-Esteban JL et al. Molecular epidemiology of molluscum contagiosum virus and analysis of the host-serum antibody response in Spanish HIV-negative patients. *J Med Virol* 2002; 66:151-8. <http://amedeo.com/lit.php?id=15282318>
3. Akaraphanth R, Lim HW. HIV, UV and immunosuppression. *Photodermatol Photoimmunol Photomed* 1999; 15:28-31. <http://amedeo.com/lit.php?id=9990666>
4. Alam M, Scher RK. Indinavir-related recurrent paronychia and ingrown toenails. *Cutis* 1999; 64:277-8.
5. Alberici F, Pagani L, Ratti G, Viale P. Ivermectin alone or in combination with benzyl benzoate in the treatment of human immunodeficiency virus-associated scabies. *Br J Dermatol* 2000; 142:969-72. <http://amedeo.com/lit.php?id=10809857>
6. Aly R, Berger T. Common superficial fungal infections in patients with AIDS. *Clin Infect Dis* 1996; Suppl 2: S128-32 <http://amedeo.com/lit.php?id=8722840>
7. Aweeka F, Trapnell C, Chernoff M, et al. Pharmacokinetics and pharmacodynamics of thalidomide in HIV patients treated for oral aphthous ulcers: ACTG protocol 251. AIDS Clinical Trials Group. *J Clin Pharmacol* 2001; 41:1091-7. <http://amedeo.com/lit.php?id=11583477>
8. Ball RA, Kinchelov T; ISR Substudy Group. Injection site reactions with the HIV-1 fusion inhibitor enfuvirtide. *J Am Acad Dermatol* 2003; 49:826-1. <http://amedeo.com/lit.php?id=14576660>
9. Barkwell R, Shields S. Deaths associated with ivermectin treatment of scabies. *Lancet* 1997; 349:1144-5.
10. Barnadas MA, Alegre M, Baselga E et al. Histopathological changes of primary HIV infection. Description of three cases and review of the literature. *J Cutan Pathol* 1997; 24:507-10 <http://amedeo.com/lit.php?id=9331897>
11. Bartke U, Venten I, Kreuter A et al. Human immunodeficiency virus-associated psoriasis and psoriatic arthritis treated with infliximab. *Br J Dermatol*. 2004; 150:784-6. <http://amedeo.com/lit.php?id=15099388>
12. Basarab T, Jones RR. HIV-associated eosinophilic folliculitis: case report and review of the literature. *Br J Dermatol* 1996; 134:499-503. <http://amedeo.com/lit.php?id=8731676>
13. Berger TG. Dermatological care in the AIDS patient. In: Sande MA, Volberding PA (Hrsg.) *The Medical Management of AIDS*. 5. Auflage 1997, Saunders, S. 159-68.
14. Bersoff-Matcha SJ, Miller WC, Aberg JA et al. Sex differences in nevirapine rash. *Clin Infect Dis* 2001; 32:124-9. <http://amedeo.com/lit.php?id=11118391>
15. Beylot-Barry M, Vergier B, Masquelier B, et al. The Spectrum of cutaneous lymphomas in HIV infection: a study of 21 cases. *Am J Surg Pathol* 1999;23:1208-16. <http://amedeo.com/lit.php?id=10524521>
16. Bigby M. Rates of cutaneous reactions to drugs. *Arch Dermatol* 2001; 137:765-70. <http://amedeo.com/lit.php?id=11405768>

## 604 HIV-associated Skin and Mucocutaneous Diseases

17. Biggar RJ, Engels EA, Frisch M, Goedert JJ; AIDS Cancer Match Registry Study Group. Risk of T-cell lymphomas in persons with AIDS. *J AIDS* 2001; 26:371-6. <http://amedeo.com/lit.php?id=11317081>
18. Blanche P. Acitretin and AIDS-related Reiter's disease. *Clin Exp Rheumatol* 1999; 17:105-6.
19. Bourezane Y, Salard D, Hoen B et al. DRESS (drug rash with eosinophilia and systemic symptoms) syndrome associated with nevirapine therapy. *Clin Infect Dis* 1998; 27:1321-2. <http://amedeo.com/lit.php?id=9827291>
20. Braun-Falco O, Fröschl M, Gürtler L, et al. Dermato-venerologische Erkrankungen als Indikatoren für Diagnose und Prognose der HIV-Infektion. *Münch Med Wschr* 1988; 130:331-6.
21. Buccheri L et al. Acitretin therapy is effective for psoriasis associated with human immunodeficiency virus infection. *Arch Dermatol* 1997; 133:711-5. <http://amedeo.com/lit.php?id=9197824>
22. Buffet M, Dupin, N. Current treatments for scabies. *Fundam Clin Pharmacol* 2003; 17:217-25. <http://amedeo.com/lit.php?id=12667233>
23. Calista D, Boschini A, Landi G. Resolution of disseminated molluscum contagiosum with Highly Active Anti-Retroviral Therapy (HAART) in patients with AIDS. *Eur J Dermatol* 1999; 9:211-3. <http://amedeo.com/lit.php?id=10210787>
24. Calista D, Morri M, Stagno A, Boschini A. Changing morbidity of cutaneous diseases in patients with HIV after the introduction of highly active antiretroviral therapy including a protease inhibitor. *Am J Clin Dermatol* 2002; 3:59-62. <http://amedeo.com/lit.php?id=11817969>
25. Calista D. Topical cidofovir for severe cutaneous human papillomavirus and molluscum contagiosum infections in patients with HIV/AIDS. A pilot study. *J Eur Acad Dermatol Venereol* 2000; 14:484-8. <http://amedeo.com/lit.php?id=11444271>
26. Celum CL. The interaction between herpes simplex virus and human immunodeficiency virus. *Herpes* 2004; Suppl 1:36A-45A. <http://amedeo.com/lit.php?id=15115628>
27. Chang E, Absar N, Beall G. Prevention of recurrent herpes simplex virus (HSV) infections in HIV-infected persons. *AIDS Patient Care* 1995; 9:252-5. <http://amedeo.com/lit.php?id=11361407>
28. Cherry-Peppers G, Daniels CO, Meeks V et al. Oral manifestations in the era of HAART. *J Natl Med Assoc* 2003; 95(2 Suppl 2):21S-32S. <http://amedeo.com/lit.php?id=12656429>
29. Clay PG, Rathbun RC, Slater LN. Management protocol for abacavir-related hypersensitivity reaction. *Ann Pharmacother* 2000; 34:247-9. <http://amedeo.com/lit.php?id=10676833>
30. Clay PG. The abacavir hypersensitivity reaction: a review. *Clin Ther* 2002; 24:1502-14. <http://amedeo.com/lit.php?id=12462283>
31. Cockerell CJ. Bacillary angiomatosis and related diseases caused by *Rochalimaea*. *J Am Acad Dermatol* 1995; 32:783-90.
32. Cooley TP. Non-AIDS-defining cancer in HIV-infected people. *Hematol Oncol Clin North Am* 2003; 17:889-99. <http://amedeo.com/lit.php?id=12852661>
33. Corbett EL et al. Crusted ("Norwegian") scabies in a specialist HIV unit: successful use of ivermectin and failure to prevent nosocomial transmission. *Genitourin Med* 1996; 72: 115-7. <http://amedeo.com/lit.php?id=8698358>
34. Costner M, Cockerell CJ. The changing spectrum of the cutaneous manifestations of HIV disease. *Arch Dermatol* 1998; 134:1290-92.
35. Cusini M, Salmaso F, Zerboni R et al. 5% Imiquimod cream for external anogenital warts in HIV-infected patients under HAART therapy. *Int J STD AIDS* 2004; 15:17-20. <http://amedeo.com/lit.php?id=14769165>
36. Daar ES, Little S, Pitt J, et al. Primary HIV Infection Recruitment Network. Diagnosis of primary HIV-1 infection. *Ann Intern Med* 2001; 134:25-9. <http://amedeo.com/lit.php?id=11187417>
37. Danby FW, Maddin WS, Margesson LJ, Rosenthal D. A randomized, double-blind, placebo-controlled trial of ketoconazole 2% shampoo versus selenium sulfide 2.5% shampoo in the treatment of moderate to severe dandruff. *J Am Acad Dermatol* 1993; 29:1008-12. <http://amedeo.com/lit.php?id=8245236>
38. Disla E et al. Improvement in CD 4 lymphocyte count in HIV-Reiter's syndrome after treatment with sulfasalazine. *J Rheumatol* 1994; 21:662-4. <http://amedeo.com/lit.php?id=7913502>
39. Diz Dios P, Scully C. Adverse effects of antiretroviral therapy: focus on orofacial effects. *Expert Opin Drug Saf* 2002; 1:307-17. <http://amedeo.com/lit.php?id=12904130>
40. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with HIV type-1 infection. *Am J Med* 2001; 110:605-6. <http://amedeo.com/lit.php?id=11382367>
41. Dourmishev A, Serafimova A, Dourmishev L. Efficacy and tolerance of oral ivermectin in scabies. *J Eur Acad Dermatol Venereol* 1998; 11:247-51. <http://amedeo.com/lit.php?id=9883437>

42. Edwards L et al. Self administered topical 5% imiquimod cream for external anogenital warts. *Arch Dermatol* 1998; 134:25-30
43. Elewski B, Smith S. The safety and efficacy of terbinafine in patients with diabetes and patients who are HIV positive. *Cutis* 2001; 68 (1 Suppl):23-9.
44. Ellis E, Scheinfeld N. Eosinophilic pustular folliculitis: a comprehensive review of treatment options. *Am J Clin Dermatol* 2004; 5:189-97. <http://amedeo.com/lit.php?id=15186198>
45. Farthing CF, Brown SE, Staughton RC. A colour atlas of AIDS and HIV Disease (2nd edition). Editions Roche, Basel 1989.
46. Fearfield LA, Rowe A, Francis N, Bunker CB, Staughton RC. Itchy folliculitis and HIV infection: clinicopathological and immunological features, pathogenesis and treatment. *Br J Dermatol* 1999; 141:3-11. <http://amedeo.com/lit.php?id=10417509>
47. Fontes V, Machel L, Huttenberger B, Lorette G, Vaillant L. Recurrent aphthous stomatitis: treatment with colchicine. An open trial of 54 cases. *Ann Dermatol Venereol* 2002; 129:1365-9. <http://amedeo.com/lit.php?id=12536172>
48. Frean J, Arndt S, Spencer D. High rate of Bartonella henselae infection in HIV-positive outpatients in Johannesburg, South Africa. *Trans R Soc Trop Med Hyg* 2002; 96:549-50. <http://amedeo.com/lit.php?id=12474487>
49. Friedman-Kien AE, Saltzman BR. Clinical manifestations of classical, epidemic African, and epidemic AIDS-associated Kaposi's sarcoma. *J Am Acad Dermatol* 1990; 22:1237-50. <http://amedeo.com/lit.php?id=2193952>
50. Friedman-Kien AE. *Color Atlas of AIDS*, 1989 (W.B. Saunders Co.)
51. Friedman-Kien AE. Disseminated Kaposi's sarcoma syndrome in young homosexual men. *J Am Acad Dermatol* 1981; 5:468-71.
52. Funnye AS, Akhtar AJ. Syphilis and HIV co-infection. *J Natl Med Assoc* 2003; 95:363-82. <http://amedeo.com/lit.php?id=12793793>
53. Garbe C, Husak R., Orfanos CE. HIV-assozierte Dermatosen und ihre Prävalenz bei 456 HIV-Infizierten. *Hautarzt* 1994; 45:623-9. <http://amedeo.com/lit.php?id=7960770>
54. Garcia-Silva J, Almagro M, Juega J, et al. Protease inhibitor-related paronychia, ingrown toenails, desquamative cheilitis and cutaneous xerosis. *AIDS* 2000; 14:1289-1291.
55. Garcia-Silva J, Almagro M, Pena-Penabad C, Fonseca E. Indinavir-induced retinoid-like effects: incidence, clinical features and management. *Drug Saf* 2002; 25:993-1003. <http://amedeo.com/lit.php?id=12408731>
56. Gaylis N. Infliximab in the treatment of an HIV positive patient with Reiter's syndrome. *J Rheumatol* 2003; 30:407-11. <http://amedeo.com/lit.php?id=12563704>
57. Gaylis N. Infliximab in the treatment of an HIV positive patient with Reiter's syndrome. *J Rheumatol* 2003; 30:407-11. <http://amedeo.com/lit.php?id=12563704>
58. Gelfand JM, Rudikoff D. Evaluation and treatment of itching in HIV-infected patients. *Mt Sinai J Med* 2001; 68:298-308. <http://amedeo.com/lit.php?id=11514917>
59. Geoghagen M, Pierre R, Evans-Gilbert T, Rodriguez B, Christie CD Tuberculosis, chickenpox and scabies outbreaks in an orphanage for children with HIV/AIDS in Jamaica. *West Indian Med J* 2004; 53:346-351.
60. Girardi E, Palmieri F, Zaccarelli M et al. High incidence of tuberculin skin test conversion among HIV-infected individuals who have a favourable immunological response to highly active antiretroviral therapy. *IDS* 2002; 16:1976-9. <http://amedeo.com/lit.php?id=12351964>
61. GISED. Cutaneous reactions to alimentary tract medications: results of a seven-year surveillance program and review of the literature. Gruppo Italiano Studi Epidemiologici in Dermatologia (GISED). *Dermatology* 1996; 193:11-6. <http://amedeo.com/lit.php?id=8864611>
62. Goldsmith DR, Perry CM. Atazanavir. *Drugs* 2003; 63:1679-3. <http://amedeo.com/lit.php?id=12904086>
63. Goldstein SM. Advances in the treatment of superficial candida infections. *Semin Dermatol*. 1993, 12:315-30
64. Gollnik H et al. Safety and efficacy of imiquimod 5% cream in the treatment of penile genital warts in uncircumcised men when applied three times weekly or once per day. *Int J STD AIDS* 2001; 12: 22-8
65. Gottlieb MS, Schroff R, Schanker HM, Fan PT, Saxon A, Weisman DO. Pneumocystis carinii pneumonia and mucosal candidiasis in previously healthy homosexual men. *N Engl J Med* 1981; 305:1425-1431. <http://amedeo.com/lit.php?id=6272109>
66. Greenspan D, Shirlaw PJ. Management of the oral mucosal lesions seen in association with HIV infection. *Oral Dis* 1997; 3 Suppl 1:S229-34. <http://amedeo.com/lit.php?id=9456695>
67. Gupta AK, Nicol KA. Seborrheic dermatitis of the scalp: etiology and treatment. *J Drugs Dermatol* 2004; 3:155-8. <http://amedeo.com/lit.php?id=15098970>

## 606 HIV-associated Skin and Mucocutaneous Diseases

68. Hagedorn H-J, MIQ. Qualitätsstandards in der mikrobiologisch-infektiologischen Diagnostik. Heft 16: Syphilis. Urban & Fischer, München, Jena, 2001.
69. Handa S, Bingham JS. Dermatological immune restoration syndrome: does it exist? *J Eur Acad Dermatol Venereol* 2001; 15:430-2. <http://amedeo.com/lit.php?id=11763384>
70. Hartmann M, Petzoldt D. Lipodystrophie-Syndrom bei HIV-Infektion. *Hautarzt* 2000; 51:159-63. <http://amedeo.com/lit.php?id=10789076>
71. Hecht FM, Busch MP, Rawal B, Webb M, et al. Use of laboratory tests and clinical symptoms for identification of primary HIV infection. *AIDS* 2002; 16:1119-29. <http://amedeo.com/lit.php?id=12004270>
72. Hengge UR, Esser S, Schultewolter T, Behrendt C, Meyer T, Stockfleth E, Goos M. Self-administered topical 5% imiquimod for the treatment of common warts and molluscum contagiosum. *Br J Dermatol* 2000, 143:1026-31.
73. Herranz P, Arribas JR, Navarro A, et al. Successful treatment of aphthous ulcerations in AIDS patients using topical granulocyte-macrophage colony-stimulating factor. *Br J Dermatol* 2000; 142:171-6. <http://amedeo.com/lit.php?id=10651717>
74. Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV-infected patients. *Clin Infect Dis* 2004; 38:1159-66. <http://amedeo.com/lit.php?id=15095223>
75. Holmes RB, Martins C, Horn T. The histopathology of folliculitis in HIV-infected patients. *J Cutan Pathol* 2001; 29:93-5. <http://amedeo.com/lit.php?id=12150139>
76. Horster S, Thoma-Greber E, Siebeck M, Bogner JR. Is anal carcinoma a HAART-related problem? *Eur J Med Res* 2003; 8:142-6. <http://amedeo.com/lit.php?id=12765859>
77. Hulsebosch HJ, Claessen FA, van Ginkel CJ et al. Human immunodeficiency virus exanthem. *J Am Acad Dermatol* 1990; 23:483-6. <http://amedeo.com/lit.php?id=2120292>
78. Ippolito F, Passi S, Di Carlo A. Is seborrhoeic dermatitis a clinical marker of HIV-disease? *Minerva Ginecol* 2000; 52:54-8. <http://amedeo.com/lit.php?id=11526689>
79. Jonsson MK, Wahren B. Sexually transmitted herpes simplex viruses. *Scand J Infect Dis* 2004; 36:93-101. <http://amedeo.com/lit.php?id=15061661>
80. Kawaguchi M, Mitsuhashi Y, Kondo S. Successful treatment of eosinophilic pustular folliculitis with topical tacrolimus. *Int J Dermatol* 2004; 43: 608-10. <http://amedeo.com/lit.php?id=1530419>
81. Kaye BR. Rheumatologic manifestations of infection with human immunodeficiency virus (HIV). *Ann Intern Med* 1989; 111:158-67. <http://amedeo.com/lit.php?id=2662849>
82. Kerr AR, Ship JA. Management strategies for HIV-associated aphthous stomatitis. *Am J Clin Dermatol*. 2003; 4:669-80 <http://amedeo.com/lit.php?id=14507229>
83. Klencke BJ, Palefsky JM. Anal cancer: an HIV-associated cancer. *Hematol Oncol Clin North Am* 2003; 17:859-72. <http://amedeo.com/lit.php?id=12852659>
84. Koehler JE, Sanchez MA, Tye S et al. Prevalence of Bartonella infection among human immunodeficiency virus-infected patients with fever. *Clin Infect Dis*. 2003; 37:559-66. <http://amedeo.com/lit.php?id=12905141>
85. Kreuter A, Hochdörfer B, Stucker M et al. Treatment of anal intraepithelial neoplasia in patients with acquired HIV with imiquimod 5% cream. *J Am Acad Dermatol*. 2004; 50:980-1. <http://amedeo.com/lit.php?id=15153912>
86. Kreuter A, Schugt I, Hartmann M et al.. Dermatological diseases and signs of HIV infection. *Eur J Med Res* 2002;7:57-62. <http://amedeo.com/lit.php?id=11891145>
87. Kumar B, Saraswat A, Kaur I. Rediscovering hydroxyurea: its role in recalcitrant psoriasis. *Int J Dermatol* 2001; 40: 530-4. <http://amedeo.com/lit.php?id=11703528>
88. Lanzafame M, Rovere P, De Checchi G et al. Hypersensitivity syndrome (DRESS) and meningoencephalitis associated with nevirapine therapy. *Scand J Infect Dis* 2001, 33:475-6. <http://amedeo.com/lit.php?id=11450872>
89. Launay O, Roudiere L, Boukli N, et al.; Viramune-Zyrtec Study Group. Assessment of cetirizine, an antihistamine, to prevent cutaneous reactions to nevirapine therapy: results of the viramune-zyrtec double-blind, placebo-controlled trial. *Clin Infect Dis* 2004; 38:66-72.
90. Lim et al. UVB phototherapy is an effective treatment for pruritus in patients infected with HIV. *J Am Acad Dermatol* 1997; 37:414-7. <http://amedeo.com/lit.php?id=9308556>
91. Liota E, Smith KJ, Buckley R, Menon P, Skelton H. Imiquimod therapy for molluscum contagiosum. *J Cutan Med Surg* 2000; 4:76-82. <http://amedeo.com/lit.php?id=11179929>
92. Lowhagen GB, Bergbrant IM, Bergstrom T, Ryd W, Voog E. PCR detection of Epstein-Barr virus, herpes simplex virus and human papillomavirus from the anal mucosa in HIV-seropositive and HIV-seronegative homosexual men. *Int J STD AIDS*. 1999, 10:615-8.
93. Maguina C, Gotuzzo E. Bartonellosis. New and old. *Infect Dis Clin North Am* 2000; 14:1-22. <http://amedeo.com/lit.php?id=10738670>

94. Manzione CR, Nadal SR, Calore EE. Postoperative follow-up of anal condylomata acuminata in HIV-positive patients. *Dis Colon Rectum*. 2003; 46:1358-65. <http://amedeo.com/lit.php?id=14530675>
95. Maurer T, Rodrigues LK, Ameli N et al.. The effect of highly active antiretroviral therapy on dermatologic disease in a longitudinal study of HIV type 1-infected women. *Clin Infect Dis*. 2004; 38:579-84. <http://amedeo.com/lit.php?id=14765353>
96. McNicholl IR. Drug Interactions Among the Antiretrovirals. *Curr Infect Dis Rep*. 2004; 6:159-162. <http://amedeo.com/lit.php?id=15023279>
97. Millikan LE (2001). Role of oral antifungal agents for the treatment of superficial fungal infections in immunocompromised patients. *Cutis* 68 (1 Suppl):6-14 Mimirani P, Hessol NA, Maurer TA, et al. Prevalence and predictors of skin disease in the Women's Interagency HIV Study (WIHS). *J Am Acad Dermatol* 2001; 44:785-8. <http://amedeo.com/lit.php?id=11312425>
98. Moini A. Photodynamic therapy for molluscum contagiosum infection in HIV-coinfected patients: review of 6 patients. *J Drugs Dermatol*. 2003; 2:637-9. <http://amedeo.com/lit.php?id=14711142>
99. Moore PS, Chang Y. Kaposi's sarcoma (KS), KS-associated herpesvirus, and the criteria for causality in the age of molecular biology. *Am J Epidemiol* 1998; 147:217-21. <http://amedeo.com/lit.php?id=9482495>
100. Morfeldt-Manson L, Julander I, Nilsson B. Dermatitis of the face, yellow toe nail changes, hairy leukoplakia and oral candidiasis are clinical indicators of progression to AIDS/ opportunistic infection in patients with HIV-infection. *Scand J Infect Dis* 1989; 21:497-505. <http://amedeo.com/lit.php?id=2587953>
101. Moses S. Pruritus. *Am Fam Physician*. 2003; 68:1135-42. <http://amedeo.com/lit.php?id=14524401>
102. Munoz-Perez MA, Rios-Martin JJ, Rodriguez-Pichardo A, Camacho F. Cutaneous T-cell lymphoma and HIV infection: 2 cases and a review of the literature. *Acta Derm Venereol* 1999; 79:153-155. <http://amedeo.com/lit.php?id=10228639>
103. Munoz-Perez MA, Rodriguez-Pichardo A, Camacho F, Colmenero MA. Dermatological findings correlated with CD4 lymphocyte counts in a prospective 3 year study of 1161 patients with human immunodeficiency virus disease predominantly acquired through intravenous drug abuse. *Br J Dermatol* 1998; 139:33-39.
104. Myskowski PL, White MH, Ahkami R. Fungal disease in the immunocompromised host. *Dermatol Clin*. 1997; 15:295-305. <http://amedeo.com/lit.php?id=9098638>
105. Namazi MR. Paradoxical exacerbation of psoriasis in AIDS: proposed explanations including the potential roles of substance P and gram-negative bacteria. *Autoimmunity*. 2004; 37:67-71. <http://amedeo.com/lit.php?id=15115314>
106. Neumann S, Kretz F, Schubert S et al.. Reiter's syndrome as a manifestation of an immune reconstitution syndrome in an HIV-infected patient: successful treatment with doxycycline. *Clin Infect Dis*. 2003; 36:1628-9. <http://amedeo.com/lit.php?id=12802773>
107. Orrick JJ, Steinhart CR. Atazanavir. *Ann Pharmacother*. 2004; 38:1664-74.
108. Osborne GE, Taylor C, Fuller LC. The management of HIV-related skin disease. Part I: infections. *Int J STD AIDS*. 2003; 14:78-86. <http://amedeo.com/lit.php?id=12716492>
109. Paasch U, Haustein UF. Behandlung der endemischen Skabies mit Allethrin, Permethrin und Ivermectin Evaluation eines Behandlungskonzeptes. *Hautarzt* 2001; 52:31-7. <http://amedeo.com/lit.php?id=11220236>
110. Paech V, Lorenzen T, Stoehr A et al., Plettenberg A. Remission of a cutaneous Mycosis fungoides after topical 5-ALA sensitisation and photodynamic therapy in a patient with advanced HIV-infection. *Eur J Med Res* 2002; 7:477-9. <http://amedeo.com/lit.php?id=12568975>
111. Palefsky JM, Holly EA, Ralston ML, Jay N. Prevalence and risk factors for human papillomavirus infection of the anal canal in human immunodeficiency virus (HIV)-positive and HIV- negative homosexual men. *J Infect Dis* 1998; 177:361-7.
112. Pallangyo KJ. Cutaneous findings associated with HIV disease including AIDS: experience from Sub Saharan Africa. *Trop Doct* 1992; 22 (Suppl 1): 35-41
113. Panse I, Vasseur E, Raffin-Sanson ML, Staroz F, Rouveix E, Saiag P. Lipodystrophy associated with protease inhibitors. *Br J Dermatol* 2000; 142:496-500. <http://amedeo.com/lit.php?id=10735957>
114. Papatheanasiou K, Giannoulis C, Vaitisi V, Kalahanis J. Cervical human papillomavirus infection; epithelial abnormalities in human immunodeficiency virus infected women. *Clin Exp Obstet Gynecol*. 2003; 30:107-8. <http://amedeo.com/lit.php?id=12854854>
115. Parsad D, Pandhi R, Negi KS, Kumar B. Topical metronidazole in seborrhoeic dermatitis – a double blind study. *Dermatology* 2001; 202:35-37. <http://amedeo.com/lit.php?id=11244226>
116. Patton LL, Bonito AJ, Shugars DA. A systematic review of the effectiveness of antifungal drugs for the prevention and treatment of oropharyngeal candidiasis in HIV-positive patients. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; 92:170-9. <http://amedeo.com/lit.php?id=11505264>

117. Patton LL, Phelan JA, Ramos-Gomez FJ et al. Prevalence and classification of HIV-associated oral lesions. *Oral Dis* 2002;8 Suppl 2:98-109. <http://amedeo.com/lit.php?id=12164670>
118. Pechere M, Krischer J, Remondat C, Bertrand C, Trellu L, Saurat JH. Malassezia spp carriage in patients with seborrheic dermatitis. *J Dermatol* 1999; 26:558-61. <http://amedeo.com/lit.php?id=10535248>
119. Pedneault L, Brothers C, Pagano G, et al. Safety profile and tolerability of amprenavir in the treatment of adult and pediatric patients with HIV infection. *Clin Ther* 2000; 22:1378-4. <http://amedeo.com/lit.php?id=11192131>
120. Penneys NS. *Skin manifestations of AIDS*. 2nd Edition. Martin Dunitz, London 1995.
121. Picard-Dahan C, Le Guyadec T, Grossin M, et al. Pigmented erythroderma in AIDS. 5 cases. *Ann Dermatol Venereol* 1996; 123:307-3. <http://amedeo.com/lit.php?id=8761082>
122. Plettenberg A, Lorenzen T, Burtsche BT et al. Bacillary angiomatosis in HIV-infected patients--an epidemiological and clinical study. *Dermatology* 2000;201(4):326-31. <http://amedeo.com/lit.php?id=11146343>
123. Plettenberg A, Lorenzen T, Burtsche BT, et al. Bacillary angiomatosis in HIV-infected patients--an epidemiological and clinical study. *Dermatology* 2000; 201:326-31. <http://amedeo.com/lit.php?id=11146343>
124. Porras-Luque JI, Valks R, Casal EC, Fernandez-Herrera JM. Generalized exanthem with palmo-plantar involvement and genital ulcerations. Acute primary HIV infection. *Arch Dermatol*. 1998,134:1279 <http://amedeo.com/lit.php?id=9801685>
125. Portu JJ, Santamaria JM, Zuberu Z, et al. Atypical scabies in HIV-positive patients. *J Am Acad Dermatol* 1996; 34:915 -7. <http://amedeo.com/lit.php?id=8621828>
126. Ramirez-Amador V, Esquivel-Pedraza L, Sierra-Madero J, et al. The changing clinical spectrum of HIV-related oral lesions in 1,000 consecutive patients: A 12-Year study in a referral center in Mexico. *Medicine (Baltimore)* 2003; 82:39-50. <http://amedeo.com/lit.php?id=12544709>
127. Reichart PA. Oral ulcerations in HIV infection. *Oral Dis* 1997; Suppl 1:S180-2. <http://amedeo.com/lit.php?id=9456685>
128. Reinmüller S. Dissertation Frankfurt/M 1999 und Abstrakt: HIV-assoziierte Dermatosen: Manifestationszeitpunkte im Verlauf der HIV-Infektion. 39. Tagung der Deutschen Dermatologischen Gesellschaft (DDG) 1997, Karlsruhe. *Hautarzt* 1997; 48 (Suppl.1): S121.
129. Resto-Ruiz S, Burgess A, Anderson BE. The role of the host immune response in pathogenesis of *Bartonella henselae*. *DNA Cell Biol*. 2003; 22:431-40. <http://amedeo.com/lit.php?id=12906736>
130. Rico MJ et al. Guidelines of care for dermatologic conditions in patients infected with HIV. *J Amer Acad Dermatol* 1997; 37:450-72.
131. Robert Koch Institut (2003) Syphilis in Deutschland 2002. *Epid Bull* 36/2003 S285-289.
132. Röcken M, Breit R. Dermatologie bei HIV-Infektion und AIDS. Grundlagen, Klinik, Therapie. In H. Jäger (Hrsg.): *AIDS und HIV-Infektion in Klinik und Praxis* (Band 1). Ecomed-Verlag, Landsberg 1990.
133. Rodriguez-Rosado R, Soriano V, Dona C, Gonzalez-Lahoz J. Opportunistic infections shortly after beginning highly active antiretroviral therapy. *Antivir Ther* 1998; 3:229-31. <http://amedeo.com/lit.php?id=10682143>
134. Rogers RS 3rd. Recurrent aphthous stomatitis: clinical characteristics and associated systemic disorders. *Semin Cutan Med Surg* 1997, 16:278-83.
135. Rotunda A, Hirsch RJ, Scheinfeld N, Weinberg JM. Severe cutaneous reactions associated with the use of human immunodeficiency virus medications. *Acta Derm Venereol* 2003; 83:1-9. <http://amedeo.com/lit.php?id=12636014>
136. Rudikoff D. The relationship between HIV infection and atopic dermatitis. *Curr Allergy Asthma Rep* 2002; 2:275-81. <http://amedeo.com/lit.php?id=12044260>
137. Sanders A, Penno S. Semiquantitative species-specific detection of *Bartonella henselae* and *Bartonella quintana* by PCR-enzyme immunoassay. *J Clin Microbiol* 1999; 37:3097-101. <http://amedeo.com/lit.php?id=10488160>
138. Sanders A, Kaliebe T, Bredt W. *Bartonella (Rochalimaea) Infektionen: Katzenkratzkrankheit und bazilläre Angiomatose*. *Deutsch Med Wschr* 1996; 121:65-9
139. Scaparro E., Quadri G, Virno G, et al. Evaluation of the efficacy and tolerability of oral terbinafine (Daskil) in patients with seborrheic dermatitis. A multicentre, randomized, investigator-blinded, placebo-controlled trial. *Br J Dermatol* 2001; 144:854-7. <http://amedeo.com/lit.php?id=11298548>
140. Schartz NE, De La Blanchardiere A, Alaoui S et al. Regression of CD8+ pseudolymphoma after HIV antiviral triple therapy. *J Am Acad Dermatol*. 2003; 49:139-41. <http://amedeo.com/lit.php?id=12833028>



141. Schöfer H, Baur S. Dermatologische Manifestationen. In: AIDS und die Vorstadien. Ein Leitfaden für Klinik und Praxis. Hrsg: L'age-Stehr J, Helm EB, Kap. III.5, S 1-48. Springer, Berlin, Heidelberg, New York, London, Paris, Tokyo 1999.
142. Schöfer H, Imhof M, Thoma-Greber E, et al. Active syphilis in HIV infection: a multicentre retrospective survey. The German AIDS Study Group (GASG). *Genitourin Med* 1996; 72:176-81. <http://amedeo.com/lit.php?id=8707318>
143. Schöfer H, Reinmüller S, Milbradt R. Manifestation of HIV-associated dermatoses during the time course of HIV disease – a changing pattern? Abstracts 32264, 12th Int AIDS Conference 1998, Geneva.
144. Schöfer H. Cutaneous tumors in immunodeficient patients: pathogenetic aspects and treatment strategies. *Onkologie* 1998; 21:299-304 .
145. Schöfer H. Frühsymptome der HIV-Erkrankung an Haut und Schleimhäuten. *AIDS-Forschung (AIFO)* 1991; 6: 633-8.
146. Schöfer H. *Hauterkrankungen bei HIV-Infektion und AIDS*. Schwer Verlag, Stuttgart. (1990)
147. Schöfer H. Kaposi-Sarkom. In: Körtng HC, Callies R, Reusch M, Schlaeger M, Sterry W (Hrsg.) *Dermatologische Qualitätssicherung. Leitlinien und Empfehlungen*. D5 S. 180-189, 3. Aufl. 2002. bzw. [www.awmf-online.de](http://www.awmf-online.de) (AWMF Leitlinienregister 032/025)
148. Schwartz, JJ, Myskowski PL. Molluscum contagiosum in patients with human immunodeficiency virus infection. *J Am Acad Dermatol* 1992;27: 583-588.
149. Schoppelrey HP, Breit R. UV-Therapie bei HIV- Patienten. *Hautarzt* 1999; 50: 643-8
150. Scully C, Gorsky M, Lozada-Nur F. The diagnosis and management of recurrent aphthous stomatitis: a consensus approach. *J Am Dent Assoc*. 2003; 134:200-7. <http://amedeo.com/lit.php?id=12636124>
151. Segura F, Anton E, Font B et al. , Primary HIV type-1 infection misdiagnosed as Mediterranean spotted fever. *Eur J Clin Microbiol Infect Dis* 2002,21:478-9. <http://amedeo.com/lit.php?id=12111608>
152. Sepkowitz KA. Effect of HAART on natural history of AIDS-related opportunistic disorders. *Lancet* 1998; 351:228-30.
153. Shapiro DL, Masci DR. Treatment of HIV associated psoriatic arthritis with oral gold. *J Rheumatol* 1996; 23:1818-20. <http://amedeo.com/lit.php?id=8895167>
154. Shimizu S, Chen KR, Tagami H, Hanabusa H. Mucocutaneous manifestations in Japanese HIV-positive hemophiliacs. *Dermatology* 2000; 201:321-325.
155. Sivayathorn A, Srihra B, Leesanguankul W. Prevalence of skin disease in patients infected with human immunodeficiency virus in Bangkok, Thailand. *Ann Acad Med Singapore* 1995; 24:528-533.
156. Siegal FP, Lopez C, Hammer GS, et al. Severe acquired immunodeficiency in homosexual males, manifested by chronic perianal ulcerative herpes simplex lesions. *N Engl J Med* 1981; 305:1439-44. <http://amedeo.com/lit.php?id=6272110>
157. Simpson-Dent S, Fearfield LA, Staughton RC. HIV associated eosinophilic folliculitis--differential diagnosis and management. *Sex Transm Infect* 1999; 75:291-3. <http://amedeo.com/lit.php?id=10616350>
158. Singh F, Rudikoff D. HIV-associated pruritus: etiology and management. *Am J Clin Dermatol* 2003; 4:177-88. <http://amedeo.com/lit.php?id=12627993>
159. Smith KJ, Skelton H. Molluscum contagiosum: recent advances in pathogenic mechanisms, and new therapies. *Am J Clin Dermatol*. 20 2002; 3:535-45. <http://amedeo.com/lit.php?id=12358555>
160. Smith KJ, Skelton HG, Yeager J, Lee RB, Wagner KF. Pruritus in HIV-1 disease: therapy with drugs which may modulate the pattern of immune dysregulation. *Dermatology* 1997; 195:353-8. <http://amedeo.com/lit.php?id=9529556>
161. Smith KJ, Skelton HG, Yeager J, Ledsky R, McCarthy W, Baxter D, Turiansky GW, Wagner KF, Turianski G. Cutaneous findings in HIV-1-positive patients: a 42-month prospective study. Military Medical Consortium for the Advancement of Retroviral Research (MMCARR). *J Am Acad Dermatol* 1994; 31:746-754.
162. Snoeck R, Bossens M, Parent D, Delaere B, Degreef H, Van Ranst M, Noel JC, Wulfsohn MS, Rooney JF, Jaffe HS, De Clercq E. Phase II double-blind, placebo-controlled study of the safety and efficacy of cidofovir topical gel for the treatment of patients with human papillomavirus infection. *Clin Infect Dis*. 2001; 33:597-602.
163. Solomon L, Cannon MJ, Reyes M et al. Task Force on Herpes Simplex Virus Resistance. Epidemiology of recurrent genital herpes simplex virus types 1 and 2. *Sex Transm Infect*. 2003; 79:456-9. <http://amedeo.com/lit.php?id=12111608>
164. Spira R, Mignard M, Doutre MS, Morlat P, Dabis F. Prevalence of cutaneous disorders in a population of HIV-infected patients. *Arch Dermatol* 1998; 134:1208-12. <http://amedeo.com/lit.php?id=9801675>

## 610 HIV-associated Skin and Mucocutaneous Diseases

165. Steen R, Dallabetta G. Genital ulcer disease control and HIV prevention. *J Clin Virol.* 2004; 29:143-51. <http://amedeo.com/lit.php?id=15002487>
166. Steigleder GK, Rasokat H. Haut- und Schleimhautveränderungen bei HIV-Infektion und AIDS. Thieme, Stuttgart, New York 1990.
167. Stern RS, Mills DK, Krell K, et al. HIV-positive patients differ from HIV-negative patients in indications for and type of UV therapy used. *J Am Acad Dermatol* 1998; 39:48-55. <http://amedeo.com/lit.php?id=9674397>
168. Stern RS, Steinberg LA. Epidemiology of adverse cutaneous reactions to drugs. *Dermatol Clin.* 1995; 13:681-8. <http://amedeo.com/lit.php?id=7554515>
169. Taiwo BO. Use of thalidomide in HIV infection. *AIDS Read* 2001, 11:511-513, 518-9, 523-4. <http://amedeo.com/lit.php?id=11708084>
170. Tangsinmankong N, Kamchaisatian W, Lujan-Zilbermann J et al. Varicella zoster as a manifestation of immune restoration disease in HIV-infected children. *J Allergy Clin Immunol.* 2004; 113:742-6. <http://amedeo.com/lit.php?id=7554515>
171. Torssander J, Karlsson A, Morfeldt-Manson L et al. Dermatophytosis and HIV infection. A study in homosexual men. *Acta Derm Venereol.* 1988, 68:53-6. <http://amedeo.com/lit.php?id=2449012>
172. Tosti A, Piraccini BM, D'Antuono A, Marzaduri S, Bettoli V. Paronychia associated with antiretroviral therapy. *Br J Dermatol* 1999; 140:1165-8. <http://amedeo.com/lit.php?id=10354091>
173. Tourne L et al. Alleviation of HIV-associated psoriasis and psoriatic arthritis with cyclosporine. *J Amer Acad Dermatol* 1997; 37:501-2.
174. Triantos D, Porter SR, Scully C, Teo CG. Oral hairy leukoplakia: clinicopathologic features, pathogenesis, diagnosis, and clinical significance. *Clin Infect Dis* 1997; 25:1392-96. <http://amedeo.com/lit.php?id=9431384>
175. Tzung TY, Yang CY, Chao SC, Lee JY. Cutaneous manifestations of human immunodeficiency virus infection in Taiwan. *Kaohsiung J Med Sci* 2004; 20:216-224.
176. Vafai A, Berger M. Zoster in patients infected with HIV: a review. *Am J Med Sci* 2001; 321:372-80. <http://amedeo.com/lit.php?id=11417752>
177. Vukasin P. Anal condyloma and HIV-associated anal disease. *Surg Clin North Am* 2002, 82:1199-211. <http://amedeo.com/lit.php?id=12516848>
178. Walling DM, Flaitz CM, Nichols CM. Epstein-Barr virus replication in oral hairy leukoplakia: response, persistence, and resistance to treatment with valacyclovir. *J Infect Dis.* 2003; 188:883-90. <http://amedeo.com/lit.php?id=12964120>
179. Ward HA, Russo GG, Shrum J. Cutaneous manifestations of antiretroviral therapy. *J Am Acad Dermatol* 2002; 46:284-93. <http://amedeo.com/lit.php?id=11807442>
180. Weitzul S, Duvic M. HIV-related psoriasis and Reiter's syndrome. *Semin Cutan Med Surg.* 1997, 16:213-8 <http://amedeo.com/lit.php?id=9300632>
181. Witkowski JA, Parish LC. Dermatologic manifestations of complementary therapy. *Skinmed.* 2003; 2:175-80. <http://amedeo.com/lit.php?id=14673295>
182. Zafar AB, Beidas SO, Sylvester LK. Control of transmission of Norwegian scabies. *Infect Control Hosp Epidemiol* 2002; 23:278-9. <http://amedeo.com/lit.php?id=12026155>
183. Zirwas MJ, Seraly MP. Pruritus of unknown origin: a retrospective study. *J Am Acad Dermatol* 2001, 45:892-6. <http://amedeo.com/lit.php?id=11712035>

## 22. HIV and Sexually Transmitted Diseases

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### Syphilis

Syphilis, also called Lues, is caused by *Treponema pallidum*. The risk of transmission is greatest in the early stages of the disease, especially if skin or mucosal ulcers are present. For a single unprotected sexual contact, the risk of transmission is about 30 to 60 %. Like other STDs, syphilis favors the transmission of HIV due to lesions in the genital mucosa. In some European and North-American areas, the incidence of syphilis, which was relatively constant during the 1980s and early 1990s, increased to levels last seen in the mid twentieth century. In some large cities, the number of newly diagnosed infections doubled or tripled. Germany had the highest incidence of syphilis in Western Europe in 2003.

### Symptoms

Classic syphilis progresses in four stages, listed in Table 1:

Table 1: Course of classic syphilis

Stage	Typical clinical appearances	Time since infection
Lues I	Ulcus durum / chancre	approx. 3 weeks
Lues II	Disseminated exanthemas	approx. 6-8 weeks
Lues III	Tuberous syphilis, gumma	several years
Lues IV	Tabes dorsalis, progressive paralysis	decades

In patients coinfectd with HIV, the latency period between stage II and the late stages III and IV may be significantly shorter than usual. In some cases, symptoms of the different stadiums may be present at the same time.

Furthermore, unusual manifestations with dramatic skin ulcers or necrosis, high fever and fatigue are described. Occurrence of these clinical symptoms is called *Lues maligna*.

Another unusual aspect in HIV-infected patients is a possible endogenous reactivation after prior *Treponema pallidum* infection.

### Diagnosis

Routine screening for syphilis with TPHA, TPPA or VDRL may not be reliable in HIV-infected patients. False-negative results can be explained by inadequate production of antibodies or by suppression of IgM production due to exorbitant IgG levels. In case of doubt, specific tests such as FTA-ABS (IgG and IgM) or cardiolipin tests should be carried out.

In erosive skin or mucosal lesions, dark field microscopy should be performed to demonstrate *Treponema pallidum* directly.

In cases where infection has been proven serologically, a neurological examination should be performed, especially on HIV-infected patients because of the merging of clinical stages. Patients with neurological symptoms should undergo cerebrospinal fluid examination, which is particularly important for making decisions regarding the type of therapy (intramuscular or intravenous).

### Therapy

Therapy of syphilis should be adapted to the stage of disease.

Recommendations for the early stages of syphilis include three intramuscular injections of benzathine penicillin 2.4 MU administered in weekly intervals (Anglo-American recommendations: only twice). In some countries, clemizol-penicillin is still available. It should be administered intramuscularly at a dose of 1 MU daily for 2 weeks.

In cases of penicillin intolerance, doxycycline (2 x 100 mg), tetracycline (4 x 500 mg) or erythromycin (4 x 500 mg) can be administered orally for 4 weeks, but these drugs are considered to be less effective than penicillin. Consequently, patients should be treated with the same scheme used in neurosyphilis.

Neurosyphilis is usually treated with 5 MU benzylpenicillin given intravenously every 4 hours for 21 days. Other recommendations prefer administration of benzylpenicillin for 14 days, followed by three intramuscular doses of 2.4 MU benzathine penicillin given at weekly intervals.

In cases of penicillin intolerance, neurosyphilis can also be treated with 2 g intravenous ceftriaxone once daily for 14 days. Some guidelines prefer an initial dose of 4 g ceftriaxone. Observational studies in small groups suggest ceftriaxone to be as effective as penicillin in the treatment of syphilis. However, cross-sensitivity may occur.

Alternative treatment options are doxycycline 2 x 100-200 mg per day or erythromycin 4 x 500 mg per day for at least 3 weeks. When treating with macrolides, the possible development of resistance should be considered.

On initiation of syphilis therapy, one should be aware of a possible Jarisch-Herxheimer reaction. This reaction is caused by a massive release of bacterial toxin due to the first dose of antibiotic given. By triggering inflammation mediators, patients may experience shivering, fever, arthritis or myalgia. The symptoms of the Jarisch-Herxheimer reaction may be avoided, or at least reduced, by administering 25-50 mg of prednisolone prior to the first dose of antibiotic.

Serological controls should be performed at 3, 6 and 12 months after syphilis therapy. Because of a possible endogenous reactivation or reinfection in some patients, annual controls should be considered.

### References

1. Arbeitsgruppe für STD und dermatologische Mikrobiologie der ÖGDV: Richtlinien zur Therapie der klassischen Geschlechtskrankheiten und Sexually Transmitted Diseases. <http://www.univie.ac.at/Immundermatologie/download/std.pdf>
2. Blocker ME, Levine WC, St Louis ME. HIV prevalence in patients with syphilis, United States. *Sex Transm Dis* 2000; 27:53-9. <http://amedeo.com/lit.php?id=10654870>
3. Brown TJ, Yen-Moore A, Tying SK. An overview of sexually transmitted diseases. Part I. *J Am Acad Dermatol* 1999; 41: 511-529. <http://amedeo.com/lit.php?id=10495370>

4. Czelusta A, Yen-Moore A, Van der Staten M, Carrasco D, Tyring SK. An overview of sexually transmitted diseases. Part III. Sexually transmitted diseases in HIV-infected patients. *J Am Acad Dermatol* 2000; 43:409-432. <http://amedeo.com/lit.php?id=10954653>
5. Deutsche Gesellschaft für Neurologie: Leitlinien für Diagnostik und Therapie in der Neurologie: Neurosyphilis; 2. überarbeitete und erweiterte Auflage 2003, ISBN 3131324120. <http://www.uni-duesseldorf.de/WWW/AWMF/II/neur-101.htm>
6. Deutsche STD-Gesellschaft.: Diagnostik und Therapie der Syphilis. Elektronische Publikation in AWMF online, 2005. <http://www.uni-duesseldorf.de/AWMF/II/059-002.htm>
7. Gregory N, Sanchez M, Buchness MR. The spectrum of syphilis in patients with HIV infection. *J Amer Acad Derm* 1990; 6: 1061-1067. <http://amedeo.com/lit.php?id=2370332>
8. Lorenzen T, Adam A, Weitner L, et al. Increase of syphilis cases in HIV-positive patients in the metropolitan region of Hamburg, Germany. 8th ECCAT 2001, Lissabon, Portugal.
9. Lukehart SA, Godornes C, Molini BJ et al. Macrolide resistance in *Treponema pallidum* in the United States and Ireland. *N Engl J Med* 2004; 351:154-8. <http://amedeo.com/lit.php?id=15247355>
10. Marra CM, Boutin P, McArthur JC et al. A pilot study evaluating ceftriaxone and penicillin G as treatment agents for neurosyphilis in human immunodeficiency virus-infected individuals. *Clin Infect Dis* 2000; 30:540-4. <http://amedeo.com/lit.php?id=10722441>
11. Medical Society for the Study of Venereal Diseases (MSSVD). Clinical standards for the screening and management of acquired syphilis in HIV-positive adults. London, 2002. [http://www.guideline.gov/summary/summary.aspx?doc\\_id=3440](http://www.guideline.gov/summary/summary.aspx?doc_id=3440)
12. Plettenberg A, Bahlmann W, Stoehr A, Meigel W. Klinische und serologische Befunde der Lues bei HIV-infizierten Patienten. *Dtsch Med Wschr* 1991; 116: 968-972. <http://amedeo.com/lit.php?id=2049984>
13. Plettenberg A, Meyer T, von Krosigk A, Stoehr A: Sexuell übertragbare Krankheiten auf dem Vormarsch. *Hamburger Ärzteblatt* 2004; 6: 372 [http://www.ifi-medizin.de/BaseCMP/documents/5000/Hamburger\\_Aerzteblatt\\_\\_6\\_04.pdf](http://www.ifi-medizin.de/BaseCMP/documents/5000/Hamburger_Aerzteblatt__6_04.pdf)
14. Robert Koch-Institut. Ausbrüche von Syphilis unter homosexuellen Männern in mehreren Ländern. *Epidem Bull* 2001; 10:73-74 [http://www.rki.de/INFEKT/EPIBULL/2001/10\\_01.PDF](http://www.rki.de/INFEKT/EPIBULL/2001/10_01.PDF). In addition: <http://www.rki.de/INFEKT/STD/EPIDEM/SE.HTM>
15. Sellati TJ, Wilkinson DA, Sheffield JS, et al. Virulent *Treponema pallidum*, lipoprotein, and synthetic lipopeptides induce CCR5 on human monocytes and enhance their susceptibility to infection by HIV type1. *J Inf Dis* 2000; 181:283-93. <http://amedeo.com/lit.php?id=10608777>
16. Singh AE, Romanowski B. Syphilis: Review with emphasis on clinical, epidemiologic, and some biologic features. *Clin Microbiol Rev* 1999; 12:187-209. <http://amedeo.com/lit.php?id=10194456>
17. Von Krogh G, Lacey CJN, Gross G, Barrasso R, Schneider A. European Course on HPV-Associated Pathology: Guidelines for the diagnosis and management of anogenital warts. *Sex Transm Inf* 2000; 76:162-168 <http://amedeo.com/lit.php?id=10961190>

## Gonorrhea

Gonorrhea, also called the clap, is caused by *Neisseria gonorrhoea*, a diplococcal bacterium. It is typically localized in the genitourinary mucosa, but infection may also occur orally or anally. Transmission is almost exclusively through sexual activity (exception: neonatal conjunctivitis), and the incubation period is about 2 to 10 days. Co-infection with *Chlamydia* occurs frequently.

## Symptoms

In men, primary symptoms are dysuria and urethral pain. A typical symptom is purulent secretion from the urethra, especially in the morning (“bonjour-drop”). Without treatment, the infection can ascend and cause prostatitis or epididymitis, leading to symptoms such as pain in the perineal region or scrotum or swelling of the scrotum.

In women, the course of gonorrhea is often asymptomatic, although vaginal discharge or purulent dysuria may occur. Involvement of the cervix and adnexa is rare,

but if left untreated, may lead to pelvic inflammatory disease with subsequent infertility.

Extragenital manifestations of gonorrhea occasionally cause pharyngitis or proctitis. Systemic infections with symptoms such as shivering, fever, arthritis or endocarditis are rare.

## Diagnosis

The diagnosis of gonorrhea is confirmed by microscopy. In a dye-staining test with methylene blue or gram stain, the intracellular diplococci of *Neisseria gonorrhoea* are traceable. This kind of diagnosis can directly be performed within several minutes at many sites. Other methods, such as serological examination, PCR or laboratory culture are also accurate, but are more complex and more expensive.

## Therapy

An isolated gonorrhea is usually treated with a single dose of ciprofloxacin 500 mg orally. Other effective antibiotics are Levofloxacin 250 mg or Ofloxacin 400 mg.

Recently, the American Centers for Disease Control and Prevention reported an increasing number of fluoroquinolone-resistant bacterial isolates. Consequently, the CDC suggests a single dose of cefixime 400 mg orally or ceftriaxone 125 mg as intramuscular injection for the treatment of gonorrhea in high-risk patients. Intramuscular administration of spectinomycin has been an option, but it is effective only in urogenital and anorectal infection, not in pharyngeal gonorrhea. For these reasons, a pragmatic and sufficient therapy seems to be a single dose of azithromycin 1 g or doxycycline 100 mg twice daily for 7 days. These therapeutic options also treat a possible co-infection with chlamydia species (see following chapter).

In all cases of gonorrhea, the sexual partners should also be screened for infection and treated if necessary.

## References

1. Anderson RMs, May RM. Epidemiological parameters of HIV transmission. *Nature* 1988; 333:514-9. <http://amedeo.com/lit.php?id=3374601>
2. CDC: Increases in Fluoroquinolone-Resistant *Neisseria gonorrhoeae* Among Men Who Have Sex with Men --- United States, 2003, and Revised Recommendations for Gonorrhea Treatment, 2004. *MMWR* 2004; 53:335-8 <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm5316a1.htm>
3. Handsfield HH, Dalu ZA, Martin DH, et al. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Azithromycin Gonorrhea Study Group. *Sex Transm Dis* 1994; 21:107-11. <http://amedeo.com/lit.php?id=9071422>
4. Harrison WO, Hooper RR, Wiesner PJ, et al. A trial of minocycline given after exposure to prevent gonorrhea. *N Engl J Med* 1979; 300:1074-8. <http://amedeo.com/lit.php?id=107450>
5. Rompalo AM, Hook EW 3rd, Roberts PL, et al. The acute arthritis-dermatitis syndrome. The changing importance of *Neisseria gonorrhoeae* and *Neisseria meningitidis*. *Arch Intern Med* 1987; 147:281-3. <http://amedeo.com/lit.php?id=3101626>
6. Roy K, Wang SA, Meltzer MI. Optimizing Treatment of Antimicrobial-resistant *Neisseria gonorrhoeae*. *Emerg Infect Dis*. 2005 Aug;11:1265-73. <http://amedeo.com/lit.php?id=16102317>

## Chlamydia infection

Infections with *Chlamydia trachomatis* are nearly twice as prevalent as gonococcal infections. The serovars D–K cause genitourinary infections and, if vertically transmitted, conjunctivitis or pneumonia in the newborn.

The serovars L1–3 cause Lymphogranuloma venereum. This disease is usually considered to be a tropical disease, rarely occurring in industrialized countries. However, for several years, Lymphogranuloma venereum has undergone a renaissance in Europe and USA: actually, the described outbreaks are under investigation by national and international surveillance authorities, which are working on management strategies.

### Symptoms

In men, a genital infection with *Chlamydia* is usually asymptomatic. If symptoms occur, they may be present as urethral discharge, burning or unspecific pain in the genital region. As in gonorrhea, an epididymitis, prostatitis or proctitis may occur. Reiter's syndrome with the triad reactive arthritis, conjunctivitis and urethritis is also possible.

In women, a chlamydial infection often does not cause any symptoms. But in about 20 % of female patients, unspecific symptoms such as discharge, burning or, more often, polyuria may occur as an expression of urethritis or cervicitis. Some of the patients also suffer from pelvic inflammatory disease involving the adnexa. This disease pattern can lead to later complications such as infertility or ectopic pregnancy due to tubal occlusions.

In Lymphogranuloma venereum, a primary lesion occurs at the entry location. Some weeks later, a tender lymphadenopathy develops which is mainly unilateral. These swollen lymph nodes may grow into large bubo that tend to ulcerate, possibly leading to scars and lymphedema.

### Diagnosis

A chlamydial infection may be suspected based purely on clinical symptoms. Gene amplification methods (PCR, LRC) are the best procedures for confirming the diagnosis. Sensitivity is superior to, while specificity is nearly equal to results obtained by culture. To achieve optimum results, a dry cotton wool wad should be used to collect some epithelioid cells, which should be sent to the laboratory in dry storage. This procedure is now a routine test in most labs.

Other direct tests such as ELISA or direct immunofluorescence are also possible, but there is a lack of sensitivity in populations with low prevalence.

### Therapy

The therapy of choice is doxycycline, 2 x 100 mg for 7 days. International guidelines also recommend 1 g azithromycin, given as a single dose, which is an equally potent therapy, but which costs nearly twice as much as doxycycline in many countries. Alternatively, ofloxacin 2 x 200 mg or erythromycin 4 x 500 mg for 7 days can be given.

Lymphogranuloma venereum requires a longer treatment, with doxycycline being administered for a minimum of 3 weeks.

## References

1. CDC: Some facts about Chlamydia. [http://www.cdc.gov/nchstp/dstd/Fact\\_Sheets/FactsChlamydiaInfo.htm](http://www.cdc.gov/nchstp/dstd/Fact_Sheets/FactsChlamydiaInfo.htm)
2. European Guidelines for the management of chlamydial infection. European STI-Guidelines. [http://www.iusti.org/sti/European\\_Guidelines.pdf](http://www.iusti.org/sti/European_Guidelines.pdf)
3. Gotz HM, Ossewaarde JM, Nieuwenhuis RF, et al. A cluster of lymphogranuloma venereum among homosexual men in Rotterdam with implications for other countries in Western Europe. *Ned Tijdschr Geneeskd*. 2004 Feb 28;148:441-2. <http://amedeo.com/lit.php?id=15038207>
4. Krosigk A, Meyer T, Jordan S, et al. Auffällige Zunahme des Lymphogranuloma venereum unter homosexuellen Männern in Hamburg. *JDDG* 2004; 8:676-80
5. Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. *N Engl J Med* 1992; 327:921-5. <http://amedeo.com/lit.php?id=1325036>
6. Morre SA, Spaargaren J, Fennema JS, de Vries HJ, Coutinho RA, Pena AS. Real-time polymerase chain reaction to diagnose lymphogranuloma venereum. *Emerg Infect Dis*. 2005 Aug;11:1311-2. <http://amedeo.com/lit.php?id=16110579>
7. Nieuwenhuis RF, Ossewaarde JM, van der Meijden WI, Neumann HA. Unusual presentation of early lymphogranuloma venereum in an HIV-1 infected patient: effective treatment with 1 g azithromycin. *Sex Transm Infect* 2003; 79:453-5. <http://amedeo.com/lit.php?id=14663119>
8. Paavonen J. Pelvic inflammatory disease. From diagnosis to prevention. *Dermatol Clin* 1998; 16:747-56, xii. <http://amedeo.com/lit.php?id=9891675>
9. RKI: Infektionen durch Chlamydien - Stand des Wissens. *Epid Bull* 1997; 18: 121-122. <http://www.rki.de/INFEKT/EPIBULL/97/9718.PDF>
10. Schachter J, Grossman M, Sweet RL, Holt J, Jordan C, Bishop E. Prospective study of perinatal transmission of Chlamydia trachomatis. *JAMA* 1986; 255:3374-7. <http://amedeo.com/lit.php?id=3712696>
11. Stamm WE, Cole B: Asymptomatic Chlamydia trachomatis urethritis in men. *Sex Transm Dis* 1986; 13:163-5. <http://amedeo.com/lit.php?id=3764626>

## Chancroid

Chancroid, also called *Ulcus molle*, is caused by *Haemophilus ducreyi*, a gram-negative bacterium. It is an endemic infection found primarily in tropical or subtropical regions of the world. In the industrialized countries, it appears to be mainly an imported disease, with only a few cases being reported by the national authorities.

## Symptoms

Usually, the incubation period is about 2–7 days. After transmission, one or more frayed-looking ulcers may appear at the entry location, usually in genitourinary or perianal locations. These ulcers are typically not indurated, unlike the primary ulcers of syphilis (therefore the Latin name *Ulcus molle*). Characteristically, they cause massive pain. In about half of the patients the inguinal lymph nodes are swollen and painful, mostly unilaterally. Balanitis or phimosis occurs less frequently.



## Diagnosis

Suspected chancroid is difficult to confirm. Clinically, other ulcer-causing STDs such as syphilis or herpes simplex infections have nearly the same symptoms. Microscopy of ulcer smears may demonstrate gram-negative bacteria, but diagnosis should be confirmed from a culture of scrapings from the ulcer or pus from a bubo. Sometimes, a biopsy from the ulcer becomes necessary to differentiate it from a malignoma.

## Therapy

Therapy should be conducted using a single dose of 1 g oral azithromycin. Ceftriaxone 250 mg intramuscularly, as a single dose, is equally potent. Alternative therapies are ciprofloxacin 2 x 500 mg for three days or erythromycin 4 x 500 mg for 4-7 days. In fluctuant buboes, needle-aspiration of pus may be indicated.

## References

1. Hammond GW, Slutchuk M, Scatliff J, et al. Epidemiologic, clinical, laboratory, and therapeutic features of an urban outbreak of chancroid in North America. *Rev Infect Dis* 1980; 2:867-79. <http://amedeo.com/lit.php?id=6971469>
2. Gesundheitsberichterstattung des Bundes. <http://www.gbe-bund.de/>
3. King R, Choudhri SH, Nasio J, et al. Clinical and in situ cellular responses to *Haemophilus ducreyi* in the presence or absence of HIV infection. *Int J STD AIDS* 1998; 9:531-6. <http://amedeo.com/lit.php?id=9764937>
4. King R, Gough J, Ronald A, et al. An immunohistochemical analysis of naturally occurring chancroid. *J Infect Dis* 1996; 174:427-30. <http://amedeo.com/lit.php?id=8699082>
5. Lewis DA. Chancroid: clinical manifestations, diagnosis, and management. *Sex Transm Infect.* 2003 Feb; 79:68-71. <http://amedeo.com/lit.php?id=12576620>
6. Martin DH, Sargent SJ, Wendel GD Jr, et al. Comparison of azithromycin and ceftriaxone for the treatment of chancroid. *Clin Infect Dis* 1995; 21:409-14. <http://amedeo.com/lit.php?id=8562752>
7. Naamara W, Plummer FA, Greenblatt RM, et al. Treatment of chancroid with ciprofloxacin. A prospective, randomized clinical trial. *Am J Med* 1987; 82:317-20. <http://amedeo.com/lit.php?id=3555055>
8. Ronald AR, Plummer FA. Chancroid and *Haemophilus ducreyi*. *Ann Intern Med* 1985; 102:705-7. <http://amedeo.com/lit.php?id=3872617>

## Condylomata acuminata

Condylomata acuminata are caused by human papillomaviruses (HPV). They are usually present as genital warts, but other locations (oral) are known to be involved. HIV-infected patients have a higher risk of acquiring genital warts.

The typical pathogens, human papillomavirus type 6 or type 11, are not normally considered to be cancerogenic. Although, in both male and female HIV-infected patients, epithelial atypia is seen more often than in uninfected persons.

Besides sexual intercourse, transmission of papillomavirus may be possible via smear infection and perhaps through contaminated objects. But the primary risk factor remains the number of sexual partners.

## Symptoms

Generally, genital warts remain asymptomatic. Pruritus, burning or bleeding is rare and generally caused by mechanical stress.

Malignant degeneration of genitourinary papillomavirus infections (HPV 16, 18, etc.) is the most important complication. In contrast to HPV-associated cervical carcinoma, genital or anal carcinoma rarely develops on underlying Condylomata.

## Diagnosis

Condylomata acuminata is a clinical diagnosis. Further diagnostic tests should be considered in case of persistence despite therapy or an early relapse. In addition to histological examination, direct HPV detection, including subtyping, is possible to differentiate between high and low risk types. Actually, this procedure is instrumental in gynecology in case of ambiguous histologies.

## Therapy

Treatment of genital warts is performed surgically by electrosurgery, cryotherapy, curettage, or laser. Chemical interventions with podophyllin or trichloroacetic acid are also possible. Other methods have been recommended. In daily clinical practice, a surgical intervention followed by adjuvant immunotherapy with interferon beta or (possibly more effective) with imiquimod reduces the rate of relapse and seems to be the best choice for patients.

## References

1. Gross G, Von Krogh G. Human Papillomavirus Infections in Dermatovenereology. CRC Press, Boca Raton, New York, London, Tokyo (1997).
2. Hagensee ME, Cameron JE, Leigh JE et al. Human papillomavirus infection and disease in HIV-infected individuals. *Am J Med Sci* 2004; 328: 57-63. <http://amedeo.com/lit.php?id=15254442>
3. Karlsson R, Jonsson M, Edlund K, et al. Lifetime number of partners as the only independent risk factor for human papillomavirus-infection: a population based study. *Sex Transm Dis* 1995; 22: 119-126. <http://amedeo.com/lit.php?id=7624813>
4. Koutsky L. Epidemiology of genital human papillomavirus infection *Am J Med* 1997; 102: 3-8. <http://amedeo.com/lit.php?id=9217656>
5. Ledger WJ, Jeremias J, Witkin SS. Testing for high-risk human papillomavirus types will become a standard of clinical care. *Am J Obstet Gynecol* 2000; 182:860-865. <http://amedeo.com/lit.php?id=10764463>
6. Leitlinien für Diagnostik und Therapie, Deutsche STD-Gesellschaft (DSTDG). Condylomata acuminata und andere HPV-assoziierte Krankheitsbilder des Genitale und der Harnröhre; 2000. <http://www.uni-duesseldorf.de/WWW/AWMF/II/std-001.htm>
7. Maw R. Comparing Guidelines for the management of anogenital warts. *Sex Transm Infect* 2000; 76:153. <http://amedeo.com/lit.php?id=10961187>
8. Quinn TC, Glasser D, Cannon RO, et al. HIV infection among patients attending clinics for sexually transmitted diseases. *N Engl J Med* 1988; 318:197-203. <http://amedeo.com/lit.php?id=3336411>
9. Ramsauer J, Plettenberg A, Meigel W: HIV-associated skin diseases. 1: Follow-up and epidemiology of HIV infection, pathogen-induced HIV-associated dermatoses. *Hautarzt* 1996; 47:795-813. <http://amedeo.com/lit.php?id=9036132>
10. Von Krogh G, Lacey CJN, Gross G, Barrasso R, Schneider A. European Course on HPV-Associated Pathology: Guidelines for the diagnosis and management of anogenital warts. *Sex Transm Inf* 2000; 76:162-168. <http://amedeo.com/lit.php?id=10961190>

## 23. HIV and Cardiac Diseases

Peter Krings und Till Neumann

Metabolic abnormalities are common side effects of antiretroviral therapy. It is expected that the incidence of premature cardiac and cardiovascular diseases will rise due to the elevated cardiovascular risk profile and increased life expectancy of HIV-infected patients (Fisher 2001, Neumann 2002a). Therefore, diagnosis and therapy of HIV-associated cardiovascular diseases should become an inherent part of current therapeutic concepts of HIV infection.

### Coronary artery disease (CHD)

Premature atherosclerosis in HIV-infected patients was described shortly after the introduction of antiretroviral therapy. The observation was supported by an autopsy trial, reporting a significant increase of atherosclerotic plaques over the last two decades in HIV-infected individuals (Morgello 2002). These data are further supported by the detection of increased coronary artery calcification scores in HIV patients treated with protease inhibitors (Robinson 2005, Meng 2002).

In contrast to case reports and autopsy trials analyzing the influence of antiretroviral therapy on myocardial infarction rate, the results of clinical observations appear to be inconsistent. At present, two major clinical trials have been published, and in one of these trials, a retrospective analysis of 36,500 patients, no rise in cardiac or cardiovascular events was detected (Bozzette 2003). Nevertheless, in the second trial, the most extensive prospective study to date, including more than 23,000 patients, a 26 % increase in the incidence of myocardial infarction was found with each year of antiretroviral therapy (Friis-Moller 2003).

However, the total incidence of myocardial infarction was small in both trials. Therefore, current treatment regimens for HIV infection might have no considerable impact on myocardial infarction rate and the concerns of cardiovascular complications have to be balanced against the marked benefits of antiretroviral treatment. Nevertheless, prevention of coronary heart disease should be integrated into current treatment procedures of HIV-infected patients.

### Prevention

Prevention is crucial, as the occurrence of cardiovascular disease is strongly related to lifestyles and modifiable risk factors. It has been shown that HIV-infected patients exhibit a marked cardiovascular risk profile (Neumann 2003, 2004a, 2004b). Most notably, in some countries the cigarette consumption is two- to three-fold higher than in the non-HIV-infected population.

Furthermore, an association between antiretroviral drugs and lipid concentrations, i.e. hypercholesterolemia and hypertriglyceridemia, has been reported (Stocker 1998, Sullivan 1997). These lipid alterations might jeopardize the benefits of antiretroviral therapy by increasing the risk of coronary disease (Grover 2005). Lipid alterations were first shown with protease inhibitors, but there is now evidence that some NRTIs and NNRTIs have an unfavorable effect on lipids too. In

addition to hyperlipidemia, insulin resistance has also been described in association with PIs (Behrens 1999, Noor 2001). However, new PIs such as atazanavir have a considerably more favorable lipid profile.

Prevention of coronary heart disease is based on the guidelines for non-HIV-infected patients (De Backer 2003; Table 1). Cessation of smoking and healthy food choices are the first steps in the therapy of hypercholesterolemia. The consumption of fruits, vegetables, whole grain bread and low fat dairy products in an energy balanced diet should be encouraged. The second step relies on lipid lowering drugs (Dube 2003). Good results were observed using a combination of statin (atorvastatin 10 mg/d) and fibrate (gemfibrozil 600 mg bid) (Henry 1998). However, an increased risk of rhabdomyolysis is suspected, and thus caution is required.

Furthermore, statin therapy might interact with the metabolism of common antiretroviral drugs. In particular, several PIs act as substrates for isoenzyme 3A4, a subgroup of the cytochrome p450 system. Inhibition of isoenzyme 3A4 by antiretroviral drugs can increase the blood concentration of statins and, therefore, induce side effects (Dube 2000). In contrast to most other statins, pravastatin and fluvastatin are not modulated by isoenzyme 3A4. Therefore, these two drugs are preferred by some authors for the therapy of HIV-infected patients being treated with antiretroviral drugs.

**Table 1: Prevention of coronary heart disease**

- 1) **Cease Smoking**
- 2) Make healthy food choices
- 3) Normalization of lipids
  - a. LDL-Cholesterol:
    - low risk (0-1 risk factors): < 160 mg/dl (4.14 mmol/l)
    - intermediate risk (2 or more risk factors): < 130 mg/dl (3.36 mmol/l)
    - high risk (i.e. CHD or diabetes mellitus): < 100 mg/dl (2.59 mmol/l)
  - b. HDL-Cholesterol: > 35 mg/dl (0.90 mmol/l) (increased risk > 40 mg/dl)
  - c. Triglycerides: < 200 mg/dl (5.17 mmol/l) (increases risk < 150 mg/dl)
- 4) Optimize blood glucose value (HbA1c < 6.5 %)
- 5) Reduce alcohol consumption (< 15 g/d)
- 6) Regular exercise training (1-2 h per week)
- 7) Normalization of weight (BMI of 21-25 kg/m<sup>2</sup>)
- 8) Optimize blood pressure (systolic: < 130 mmHg, diastolic < 85 mmHg)

## Diagnosis

HIV-infected patients with cardiovascular risk factors or of elevated age should undergo an annual cardiac check-up, including a resting ECG and estimation of the cardiovascular disease risk with the help of the SCORE system (De Backer 2003). The time between two cardiac controls should be shortened in case of high cardiovascular risks. Symptomatic patients also need further detailed cardiovascular examinations (exercise ECG, stress echocardiography, laboratory work-up and, in

some cases, scintigraphy of myocardium or coronary angiography). Clinical symptoms of coronary heart disease mostly occur due to a critical stenosis of more than 75 %. Therefore, the onset of new cardiac symptoms or an increase in gravity, duration or frequency, referred to as acute coronary syndrome, needs direct and immediate clarification (Erhardt 2002).

## Therapy

In randomized clinical trials, low-dose aspirin (100 mg/d), or in some cases clopidogrel (75 mg/d),  $\beta$ -blockers, ACE inhibitors, and statins, decreased the risk of mortality and re-infarction. A calcium antagonist and/or nitrate can be supplemented for symptomatic treatment.

The indication for vascular intervention (coronary angiography, including percutaneous transluminal catheter angioplasty and stent implantation) depends on the current guidelines (see <http://www.escardio.org/knowledge/guidelines>). Clear indications for invasive diagnosis are a documented exercise-induced ischemia, typical clinical symptoms together with ST-alterations in the ECG, increases in cardiac enzymes and/or a marked cardiovascular risk profile. It is worth emphasizing that HIV infection is not an exclusion criteria for invasive procedures. Successful cardiac interventions have been performed on HIV-infected patients, including catheter procedures and coronary artery bypass operations (Escaut 2003, Bittner 2003, Ambrose 2003).

## Congestive heart failure

Congestive heart failure includes a variety of myocardial alterations. In HIV-infected patients, the HIV-associated dilated cardiomyopathy is of major interest. It corresponds to a dilated and less contractile left ventricle.

## Etiology

Myocarditis is still the most thoroughly studied cause of dilated cardiomyopathy in HIV disease. Until now, a variety of pathogens has been found in the myocardial tissue of HIV-infected patients (Patel 1996, Wu 1992). Furthermore, human immunodeficiency virus itself appears to infect myocardial cells in a patchy distribution. Although it is unclear how HIV-1 enters CD4-receptor-negative cells such as cardiomyocytes, reservoir cells may play a role in the interaction between HIV-1 and myocytes.

In addition to a direct impact of the human immunodeficiency virus or other pathogens, dilated cardiomyopathy was reported in association with an autoimmune reaction. Cardiac-specific autoantibodies (anti- $\alpha$ -myosin antibodies) have been reported in up to 30 % of HIV-infected patients with cardiomyopathy. However, several studies also indicate that in HIV-infected patients, dilated cardiomyopathy is associated with cardiotoxic agents (e.g. pentamidine, interleukin-2, doxorubicin) or as the sequelae of malnutrition (Nosanchuk 2002). Furthermore, it is expected that antiretroviral therapeutic drugs may induce cardiac dysfunction due to mitochondrial toxicity (Lewis 2000, Frerichs 2002).

The frequency of clinical, symptomatic dilated cardiomyopathy is estimated to be between 1 and 5 %. However, in one study, only 30 % of HIV-infected individuals with ventricular malfunction could be identified by characteristic clinical symptoms (Roy 1999). Thus, reliance on clinical features of heart failure only, will fail to identify patients who might benefit from treatment.

## Diagnosis

The diagnosis of chronic heart failure is based on clinical findings and symptoms. In addition to exercise intolerance, patients often exhibit dyspnea and edema. Nocturia, nightly cough (cardiac asthma), peripheral cyanosis and an increase of weight may also occur. In these cases, ECG, chest x-ray and echocardiography may lead to the diagnosis of heart failure.

A new parameter in the diagnosis of heart failure is the b-type natriuretic peptide (BNP) or NTproBNP. This peptide has the power to distinguish between lung and cardiac malfunction.

Exercise intolerance can be determined by a 6-minute walk test, exercise ECG or spiroergometry. In some cases, further diagnosis can be performed with magnetic resonance tomography (MRT) or computer tomography (CT) revealing scar tissue or coronary artery calcification. Invasive diagnosis including myocardial biopsies is often recommended in unknown cases of chronic heart failure. Stable chronic heart failure patients in a low stage should be controlled annually. In a higher stage, the controls should include ECG, echocardiography and occasional BNP measurements every 6 months.

## Therapy

The therapy of congestive heart failure depends on current guidelines ([www.escardio.org/knowledge/guidelines](http://www.escardio.org/knowledge/guidelines)) and begins with moderate and regular exercise in combination with a healthy diet, including a reduced fluid and salt intake. Non-steroidal anti-rheumatics (NSAR), class I antiarrhythmics and calcium antagonists (verapamil, diltiazem and short-acting dihydropyridine derivatives) should be used carefully.

Treatment of congestive heart failure includes:

- from NYHA I (asymptomatic heart failure):  
ACE inhibitor (control blood pressure and renal function)  
beta-blocker for patients after myocardial infarction (beginning with low dose therapy under regular control of blood pressure and heart rate. If a low-dose therapy is tolerated, the beta-blocker medication should be increased slowly).
- from NYHA II (slight limitation of physical activity):  
beta-blockers for all patients, digitalis glycosides and diuretics.
- from NYHA III (marked limitation of physical activity):  
spironolactone (low dose with controlled potassium).
- from NYHA IV (unable to carry out any physical activity)  
reinforce medical treatment (combination of diuretics), consider heart transplantation, reconsider any surgical improvement and device implantation

NYHA III and NYHA IV require cooperation with a cardiologist. In the presence of ventricular arrhythmia, the indications for an implantable cardioverter defibrillator (ICD) have to be considered.

Therapeutic options that could eliminate the causes of heart failure (such as operative valve replacement in the case of a primary vitium or intensive antibiotic therapy for bacterial myocarditis) have priority. In these cases, cooperation with a specialized center is recommended.

## Prognosis

Chronic heart failure is associated with a reduced life expectancy. In cases of NYHA III-IV, the annual mortality rate rises by up to 30 %. While in some cases, a total recovery was described (Fingerhood 2001, Tayal 2001), the majority of patients with HIV-associated dilated cardiomyopathy still have a progression of left ventricular dysfunction (Felker 2000). It is still unclear whether antiretroviral medication has an influence on the recovery of ventricular function. Early diagnosis and conventional therapy seem to be the most promising ways to reduce the progression of disease.

## Pericardial effusion

Before effective antiretroviral drugs were available, pericardial effusion was the most frequent cardiac manifestation. In clinical trials, the incidence of pericardial effusions was recognized to be as high as 11 % per year (Heidenreich 1995). However, the majority of HIV-associated pericardial manifestations are described as asymptomatic. Nevertheless, the spectrum ranges from acute or chronic pericarditis to an acute pericardial tamponade (Silva-Cardoso 1999). Pericardial diseases could be caused by HIV itself, further pathogens, or neoplasms (Stotka 1989). In a recent report from South Africa, where pericardial effusion is obviously still more common than in Europe or North America, 96 % of HIV patients with large pericardial effusions had tuberculous pericarditis (Reuter 2005). However, non-HIV-associated causes of pericardial effusion, such as uremia, trauma, irradiation, and drugs, have to be considered. In some cases of lipodystrophy an increase in the cardiac lipid tissue could simulate an extensive pericardial effusion (Neumann 2002c).

Echocardiography is referred to as the standard method for diagnosis and control of pericardial diseases. Nevertheless, further diagnosis should be performed by computer tomography and/or magnetic resonance tomography when a neoplasm or an increase in the cardiac lipid tissue is suspected. Pericardial puncture has to be considered for symptomatic patients. If possible, a causative therapy should be applied. Pericardiotomy might be an option in palliative care.

## Cardiac arrhythmias

Cardiac arrhythmias can depend on medication. Antiretroviral drugs, e.g. efavirenz, foscarnet, pentamidine, or co-therapy with methadone, are expected to prolong the QT interval, an alteration in ECG, which might cause “Torsade de pointes” tachy-

cardia (Castillo 2002). Further drug combinations such as a macrolide and a chinolone may have the same effect on the QT interval.

Initiation or change of medication, which might influence the QT interval, should be controlled daily by ECG. In case of arrhythmias, electrolyte and glucose concentrations have to be determined and corrected if necessary. Magnesium may be used for termination of torsades de pointes tachycardia.

## Valvular heart disease

Valvular heart disease of HIV-infected patients occurs as a bacterial or mycotic endocarditis. In fact, the hypothesis that HIV infection alone makes a subject more susceptible to infective endocarditis could not be validated. However, intravenous drug abusers have a ten- to twelve-fold increased risk for infective endocarditis than non-intravenous drug abusers (Nahass 1990). The most frequent germ is staphylococcus aureus, being detected in more than 40 % of HIV-infected patients with bacterial endocarditis. Further pathogens include *Streptococcus pneumoniae* and *Hemophilus influenzae* (Currie 1995). Mycotic forms of endocarditis, which may also occur in patients who are not intravenous drug abusers, mostly belong to *Aspergillus fumigatus*, *Candida* species or *Cryptococcus neoformans* and are associated with a worse outcome (Martin-Davila 2005).

Even if non-drug-abusing HIV patients are not more susceptible to infective endocarditis, the clinical course of the infection is more severe and the outcome worse than in a non-HIV-infected population (Smith 2004).

Signs of infective endocarditis include fever (90 %), fatigue, and lack of appetite. An additional heart murmur may also be present (30 %). In these cases, repeated blood cultures should be taken and transesophageal echocardiography is mandatory (Bayer 1998). Due to the fact that the detection of the infectious agent is often difficult, an antibiotic therapy has to be started early, even without the microbiology results.

In most cases, previously damaged valves are affected. Therefore, antibiotic prophylaxis is recommended in all persons with a previously damaged endocardium and planned interventional procedure, e.g. dental work or operations on the respiratory or gastrointestinal tract. For diagnosis, antibiotic prophylaxis, and choice and length of antibiotic treatment, please refer to your local cardiologist and to the European guidelines for infective endocarditis (<http://www.esccardio.org/knowledge/guidelines/>).

## Further cardiac manifestations

Heart neoplasms are rarely found in HIV-infected patients. These manifestations occur predominantly in the advanced stages of the disease. On autopsy, the rates of cardiac-localized Kaposi's sarcoma and lymphoma are less than one percent.

Some infections of the heart in HIV-positive subjects may not only result in myocarditis but in abscesses. Several opportunistic pathogens including toxoplasma and trypanosomes have been reported to cause abscesses in the heart. These manifestations are believed to decrease with the introduction of HAART.



As well as neoplasms and abscesses, vascular alterations including vasculitis and perivasculitis have been described as further cardiovascular manifestations in HIV-infected patients. In particular, the function of the pulmonary vessels can deteriorate, resulting in pulmonary arterial hypertension and, consequently, right heart failure (Mehta 2000). For further information on pulmonary arterial hypertension see the chapter “HIV-associated pulmonary hypertension (PAH)”.

Table 2. Cardiac diseases in HIV-infected patients

#### Pericardial diseases

- Pericardial effusion
- Pericarditis (viral, bacterial, mycotic)
- Neoplasm (Kaposi's sarcoma, lymphoma)

#### Myocardial diseases

- HIV-associated dilated cardiomyopathy
- Myocarditis (acute or chronic)
- Neoplasm (Kaposi's sarcoma, lymphoma)
- Drug side-effects (especially by antiretroviral therapy)

#### Endocardial diseases

- Infective endocarditis (bacterial, mycotic)
- Nonbacterial thrombotic endocarditis

#### Vascular diseases

- Atherosclerosis
- Vasculitis, perivasculitis
- Pulmonary arterial hypertension

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## References

1. Ambrose JA, Gould RB, Kurian DC et al. Frequency of and outcome of acute coronary syndromes in patients with human immunodeficiency virus infection. *Am J Cardiol.* 2003;92:301-303.
2. Bayer AS, Bolger AF, Taubert KA et al. Diagnosis and management of infective endocarditis and its complications. *Circulation* 1998; 98: 2946-48. <http://amedeo.com/lit.php?id=9860802>
3. Behrens G, Dejam A, Schmidt H, et al. Impaired glucose tolerance, beta cell function and lipid metabolism in HIV patients under treatment with protease inhibitors. *AIDS* 1999, 13: F63-70. <http://amedeo.com/lit.php?id=10416516>
4. Bittner HB, Fogelson BG. Off-pump coronary artery bypass grafting in a patient with AIDS, acute myocardial infarction, and severe left main coronary artery disease. *J Cardiovasc Surg* 2003; 44: 55-7. <http://amedeo.com/lit.php?id=12627072>
5. Bozzette SA, Ake CF, Tam HK, et al. Cardiovascular and cerebrovascular events in patients treated for HIV infection. *N Engl J Med.* 2003; 348: 702-10. <http://amedeo.com/lit.php?id=12594314>
6. Castillo R, Pedalino RP, El-Sherif N, Turitto G. Efavirenz-associated QT prolongation and Torsade de Pointes arrhythmia. *Ann Pharmacother* 2002;26:1006-8. <http://amedeo.com/lit.php?id=12022902>
7. Currie PF, Sutherland GR, Jacob AJ, et al. A review of endocarditis in acquired immunodeficiency syndrome and human immunodeficiency virus infection. *Eur Heart J* 1995; 16: 15-8. <http://amedeo.com/lit.php?id=7671917>
8. De Backer G, Ambrosioni E, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: third joint task force of European and other societies on cardiovascular

- disease prevention in clinical practice. *Eur J Cardiovasc Prev Rehabil* 2003;10 (Suppl 1):S1-S78. <http://amedeo.com/lit.php?id=14555889>
9. Dube MP, Sprecher D, Henry WK, et al. Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with HIV and receiving antiretroviral therapy: recommendations of the adult ACTG cardiovascular disease focus group. *Clin Inf Dis* 2000; 31: 1216-24. <http://amedeo.com/lit.php?id=11073755>
  10. Dube MP, Stein JH, Aberg JA. Guidelines for the evaluation and management of dyslipidemia in human immunodeficiency virus (HIV)-infected adults receiving antiretroviral therapy. *Clin Infect Dis*. 2003; 37: 613-27. <http://amedeo.com/lit.php?id=12942391>
  11. Erhardt L, Herlitz J, Bossaert L, et al. Task force on the management of chest pain. *Eur Heart J* 2002;23:1153-1176. <http://amedeo.com/lit.php?id=12206127>
  12. Escout L, Monsuez JJ, Chironi G, et al. Coronary artery disease in HIV infected patients. *Intensive Care Med*. 2003; 29: 969-73. <http://amedeo.com/lit.php?id=12739013>
  13. Felker GM, Thompson RE, Hare JM, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. *N Engl J Med* 2000, 342: 1077-84. <http://amedeo.com/lit.php?id=10760308>
  14. Fingerhood M. Full recovery from severe dilated cardiomyopathy in an HIV-infected patient. *AIDS Read* 2001; 11: 333-5. <http://amedeo.com/lit.php?id=11449927>
  15. Fisher SD, Lipshultz SE. Cardiovascular abnormalities in HIV-infected individuals. In: Braunwald E, ed. *Heart disease: a textbook of cardiovascular medicine*. Philadelphia: Saunders 2001: 2211-21.
  16. Frerichs FC, Dingemans KP, Brinkman K. Cardiomyopathy with mitochondrial damage associated with nucleoside reverse transcriptase inhibitors. *N Engl J Med* 2002; 347: 1895-6. <http://amedeo.com/lit.php?id=12466522>
  17. Friis-Moller N, Sabin CA, Weber R et al. Combination antiretroviral therapy and the risk of myocardial infarction. *N Engl J Med* 2003; 349: 1993-2003. <http://amedeo.com/lit.php?id=14627784>
  18. Grover SA, Coupal L, Gilmore N et al. Impact of dyslipidemia associated with HAART on cardiovascular risk and life expectancy. *Am J Cardiol*. 2005;95:586-591 :
  19. Heidenreich PA, Eisenberg MJ, Kee LL, et al. Pericardial effusion in AIDS incidence and survival. *Circulation* 1995; 92: 3229-34. <http://amedeo.com/lit.php?id=7586308>
  20. Henry K, Melroe H, Huebesch J, et al. Atorvastatin and gemfibrozil for protease-inhibitor-related lipid abnormalities. *Lancet* 1998; 352: 1031-2. <http://amedeo.com/lit.php?id=9759748>
  21. Lewis W, Grupp IL, Grupp G, et al. Cardiac dysfunction occurs in the HIV-1 transgenic mouse treated with zidovudine. *Lab Invest* 2000; 80: 187-97. <http://amedeo.com/lit.php?id=10701688>
  22. Martin-Davila P, Navas E, Fortun J et al. Analysis of mortality and risk factors associated with native valve endocarditis in drug users: the importance of vegetation size. *Am Heart J*. 2005;150:1099-1106.
  23. Mehta NJ, Khan IA, Mehta RN, et al. HIV-related pulmonary hypertension. *Chest* 2000; 118: 1133-41. <http://amedeo.com/lit.php?id=11035689>
  24. Meng Q, Lima JA, Lai H, et al. Coronary artery calcification, atherogenic lipid changes, and increased erythrocyte volume in black injection drug users infected with human immunodeficiency virus-1 treated with protease inhibitors. *Am Heart J*. 2002;144:642-648.
  25. Morgello S, Mahboob R, Yakoushina T, et al. Autopsy findings in a HIV-infected population over 2 decades. *Arch Pathol Lab Med* 2002; 126: 182-90. <http://amedeo.com/lit.php?id=11825115>
  26. Nahass RG, Weinstein MP, Bartels J et al. Infective endocarditis in intravenous drug users: a comparison of HIV type 1-negative and -positive patients. *J Infect Dis*. 1990;162:967-970.
  27. Neumann T, Ross B, Hengge UR, et al. Kardiale Manifestationen der HIV-Infektion. *Med Klin* 2002a; 97: 659-65. <http://amedeo.com/lit.php?id=12434274>
  28. Neumann T, Canbay A, Barkhausen M, et al. Paracardial lipodystrophy versus pericardial effusion in HIV positive patients. *Heart* 2002c; 87: e4. <http://amedeo.com/lit.php?id=11997434>
  29. Neumann T, Woiod T, Neumann A, et al. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients: Part I: Differences due to the acquisition of HIV-infection. *Eur J Med Res* 2003; 8: 229-35. <http://amedeo.com/lit.php?id=12911871>
  30. Neumann T, Woiod T, Neumann A, et al. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients: Part II: Gender differences. *Eur J Med Res* 2004a; 9: 55-60. <http://amedeo.com/lit.php?id=15090290>
  31. Neumann T, Woiod T, Neumann A, et al. Cardiovascular risk factors and probability for cardiovascular events in HIV-infected patients: Part III: Age differences. *Eur J Med Res* 2004b; 9: 267-72. <http://amedeo.com/lit.php?id=15257881>
  32. Noor MA, Lo JC, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS* 2001; 15: F11-8. <http://amedeo.com/lit.php?id=11399973>

33. Nosanchuk JD. Fungal myocarditis. *Front Biosci* 2002; 7: d1423-38. <http://amedeo.com/lit.php?id=12045009>
34. Patel RC, Frishman WH. Cardiac involvement in HIV infection. *Med Clin North Am* 1996; 80: 1493-512. <http://amedeo.com/lit.php?id=8941233>
35. Remme WJ, Swedberg K. Guidelines for the diagnosis and treatment of chronic heart failure. Task Force Report. *Eur Heart J* 2001;22:1527-60. <http://amedeo.com/lit.php?id>
36. Reuter H, Burgess LJ, Doubell AF. Epidemiology of pericardial effusions at a large academic hospital in South Africa. *Epidemiol Infect.* 2005;133:393-399.
37. Robinson FP, Hoff JA, Kondos GT. Coronary artery calcium in HIV-infected men treated with highly active antiretroviral therapy. *J Cardiovasc Nurs.* 2005;20:149-154.
38. Roy VP, Prabhakar S, Pulvirenti J, Mathew J. Frequency and factors associated with cardiomyopathy in patients with HIV infection in an inner-city hospital. *J Natl Med Assoc* 1999; 91: 502-4. <http://amedeo.com/lit.php?id=10517069>
39. Silva-Cardoso J, Moura B, Martins L, et al. Pericardial involvement in human immunodeficiency virus infection. *Chest* 1999; 115: 418-22. <http://amedeo.com/lit.php?id=10027441>
40. Smith DT, Sherwood M, Crisel R et al. A comparison of HIV-positive patients with and without infective endocarditis: an echocardiographic study. *Am J Med Sci* 2004;328:145-149.
41. Stocker DN, Meier PJ, Stoller R, Fattinger KE. „Buffalo hump“ in HIV-1 infection. *Lancet* 1998; 352: 320-1. <http://amedeo.com/lit.php?id=9690434>
42. Stotka JL, Good CB, Downer WR, et al. Pericardial effusion and tamponade due to Kaposi's sarcoma in AIDS. *Chest* 1989; 95: 1359-61. <http://amedeo.com/lit.php?id=2721281>
43. Sullivan AK, Nelson MR. Marked hyperlipidaemia on ritonavir therapy. *AIDS* 1997; 11: 938-9. <http://amedeo.com/lit.php?id=9189227>
44. Swedberg K, Cleland J, Dargie H et al. Guidelines for the diagnosis and treatment of chronic heart failure: executive summary (update 2005): The Task Force for the Diagnosis and Treatment of Chronic Heart Failure of the European Society of Cardiology. *Eur Heart J.* 2005;26:1115-1140.
45. Tayal SC, Ghosh SK, Reaich D. Asymptomatic HIV patient with cardiomyopathy and nephropathy: case report and literature review. *J Infect* 2001; 42: 288-90. <http://amedeo.com/lit.php?id=11545577>
46. Wu TC, Pizzorno MC, Hayward GS, et al. In situ detection of human cytomegalovirus immediate-early gene transcripts within cardiac myocytes of patients with HIV-associated cardiomyopathy. *AIDS* 1992; 6: 777-85. <http://amedeo.com/lit.php?id=1329847>



## 24. HIV-associated Pulmonary Hypertension

Georg Friese, Mirko Steinmüller and Ardeschir Ghofrani

Pulmonary hypertension is a severe life-limiting disease, often affecting younger patients. The connection between HIV infection and the development of pulmonary hypertension is well documented (Mette 1992, Simonneau 2004). However, the underlying pathobiology still remains unclear. Given that the prognosis of HIV infection has been improved by HAART, severe pulmonary hypertension is becoming a life-limiting factor (Nunes 2002).

### Etiology, pathogenesis, classification

Pulmonary hypertension can be caused by vasoconstriction, reduction of arterial elasticity by structural remodeling of the vessel wall, obstruction of the vessel, and vessel rarefaction. All forms show the development of functional alterations (reversible vasoconstriction) and structural changes (vascular remodeling), and often occur in combination with intravascular thrombosis. The increase in right ventricular afterload induces right ventricular hypertrophy and/or dilatation.

Chronic pulmonary hypertension is classified using five groups according to the classification developed at the *World Symposium on Primary Pulmonary Hypertension* 1998 in Evian (modified in Venice 2003). HIV-associated pulmonary hypertension belongs to group number one (PAH):

### Pulmonary arterial hypertension (PAH)

#### 1.1 Primary pulmonary hypertension

- a) Sporadic disorder
- b) Familial disorder

#### 1.2 Associated with

- a) Collagen vascular disease
- b) Congenital (right-left) systemic-pulmonary shunt
- c) Portal hypertension
- d) **HIV-associated pulmonary hypertension**
- e) Drugs
- f) Persisting PAH of the newborn

Pulmonary hypertension is classified into three clinical stages:

**Latent pulmonary hypertension** is characterized when mean pulmonary arterial pressures (PAP) are below 21 mmHg with an exercise-induced increase to values above 30 mmHg. The patients suffer from dyspnea upon exercise. In **manifested pulmonary hypertension**, the mean PAP exceeds 25 mmHg at rest. Patients already suffer from dyspnea on light exercise. **Severe pulmonary hypertension** is characterized by a severely reduced cardiac output at rest, which cannot be increased upon exercise, due to the increase in right ventricular afterload. Thus, patients are unable to perform any physical activity without distress.

## Diagnosis

### Right heart catheterization

For diagnosis of chronic pulmonary hypertension, right heart catheterization is still considered to be the gold standard. It allows the essential parameters of pulmonary hemodynamics to be evaluated. The main parameter is pulmonary resistance, which can be abnormal even without affecting pulmonary arterial pressure. A test for reversibility of vasoconstriction should be performed at the stage of manifested pulmonary hypertension, to identify patients responding to vasodilative therapy. These “responders” are identified using oxygen insufflation or vasodilators during right heart catheterization. For example, during inhalation of nitric oxide, these patients show a decrease in pulmonary arterial pressure of 30 % and a simultaneous normalization of cardiac output.

### ECG

ECG alterations induced by pulmonary hypertension are present after a two-fold increase in right heart musculature. Typical signs are:

- right axis deviation (mean QRS-axis  $> +110^\circ$ )
- RS-ratio in lead V6  $< 1$
- S wave in lead I and Q wave in lead III
- S waves in lead I, II and III
- increased P-wave amplitude (not obligatory).

### Chest radiography

Pulmonary hypertension can be inferred by chest radiography observations:

- Enlarged right descending pulmonary artery (diameter  $> 20$  mm)
- Central pulmonary arterial dilatation in contrast to narrowed segmental arteries
- Pruning of peripheral pulmonary blood vessels
- Enlargement of transverse heart diameter and increase of retrosternal contact area of the right ventricle

## Echocardiography

Echocardiography allows recognition of right ventricular dilatation and estimation of systolic pulmonary arterial pressure. Typical signs are:

- right ventricular myocardial hypertrophy
- abnormal septum movements
- abnormal systolic intervals
- abnormal movement patterns of the pulmonary valve
- altered ejection flow profile of the right ventricle (transthoracic Doppler echocardiography).

## Ventilation-perfusion scan, pulmonary angiography and CT scan

These radiological techniques are used to identify or exclude chronic thromboembolic pulmonary hypertension (CTEPH) and may guide operative treatment. CTEPH is an important differential diagnosis in intravenous drug abusing HIV-patients suffering from recurring thromboembolisms (Figure 1).

## Therapy

### General treatment

Various modalities of general treatment have been established for the therapy of pulmonary hypertension on the basis of empirical data. These are:

#### 1. Diuretics

In the later stages of pulmonary hypertension, volume retention may cause an enormous increase in the right ventricular preload followed by congestive hepatomegaly, edema and ascites formation. Volume retention is not only caused by chronic right heart failure but also by stimulation of the renin-angiotensin system followed by elevated aldosterone levels. For this reason, a combination of loop diuretics (e.g. furosemide 20-80 mg per day) and aldosterone antagonists (e.g. aldactone 50-200 mg per day) has proved to be successful. The usual contraindications, as well as the risk of dehydration followed by a critical decrease of right ventricular preload, have to be considered. A preload of about 6-10 mmHg is needed for optimal right ventricular performance.

#### 2. Digitalis

The use of digitalis is still much debated. According to a randomized placebo-controlled double-blinded trial, only patients simultaneously suffering from Cor pulmonalis and decreased left ventricular function benefit from digitalis medication. However, digitalis medication is always justified in the case of tachycardic atrial arrhythmias. It has to be considered that digitalis has a high arrhythmogenic potential in combination with hypoxemia, which might lead to severe complications.

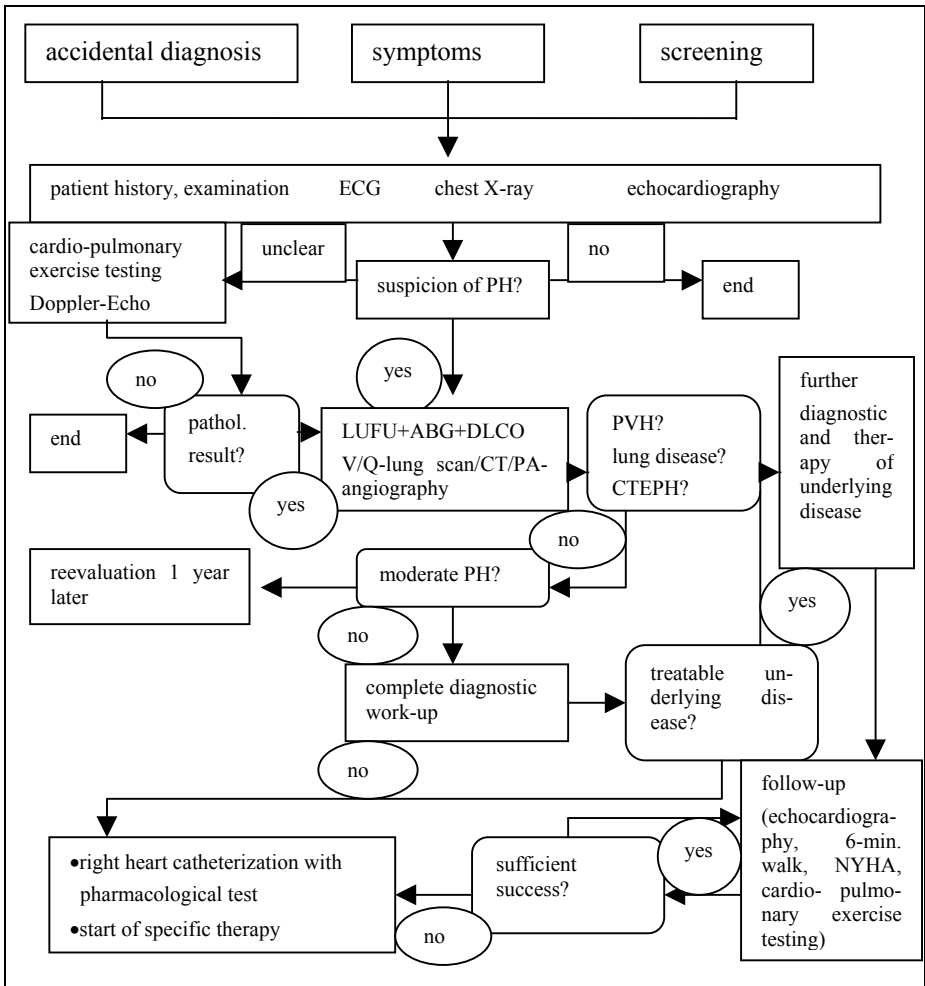


FIGURE 1. Diagnostic and therapeutic algorithm: suggestion for diagnostic procedures on suspicion of pulmonary hypertension (adapted from Arbeitsgemeinschaft Pulmonale Hypertonie). LUFU: lung function test; ABG: arterial blood gases; DLCO: CO diffusion capacity.

### 3. Anticoagulation

After considering the contraindications, the application of heparin or oral anticoagulants such as phenprocoumon and warfarin, are an established treatment for chronic pulmonary hypertension. Long-term anticoagulation therapy addresses the following aspects of the pathophysiology of PAH:

- increased risk of in-situ thrombosis caused by altered blood flow in narrowed and deformed pulmonary vessels
- increased risk of thrombosis caused by peripheral venous stasis, right ventricular dilatation and reduced physical exercise
- decreased levels of circulating thrombin and fibrinogen degradation products, which are supposed to act as growth factors in vascular remodeling processes.



The dose of anticoagulants should be adjusted to maintain the prothrombin time at an international normalized ratio (INR) of 2.5.

#### 4. HAART

HAART is considered as a general treatment for HIV-associated pulmonary hypertension. According to the CDC classification, pulmonary hypertension is a symptomatic complication and therefore classified as category B. This is independent of CD4 cell numbers and virus load, indicating an obligation for antiretroviral treatment. Evidence shows that the prognosis of HIV-associated pulmonary hypertension is improved upon effective antiretroviral therapy (Zuber 2004). Furthermore, the immune status of this high-risk group has to be stabilized to prevent systemic infection, especially pneumonia.

### Specific treatment

The aim of specific therapy is to decrease pulmonary arterial pressure, thereby reducing the right ventricular afterload. Substances that currently used for the treatment of pulmonary hypertension or tested in clinical studies are:

- Calcium channel blockers
- Prostanoids (intravenous, inhalative, oral, subcutaneous)
- Endothelin receptor antagonists (selective, none-selective)
- Phosphodiesterase-5 inhibitors

In addition to the immediate effect of muscle relaxation, some vasodilators (especially prostanoids and phosphodiesterase-5 inhibitors) seem to have a sustained antiproliferative effect.

#### 1. Calcium channel blockers

Currently nifedipine and diltiazem are the most commonly used calcium channel blockers. Around 5-10 % of primary pulmonary hypertension patients are so-called responders. The response to calcium channel blockers should be evaluated during right heart catheterization.

The major disadvantage of oral calcium channel blockers is their effects on the systemic circulation. Peripheral vasorelaxation causes hypotension and the negative inotropic effect of calcium channel blockers leads to a reduction in cardiac output. Furthermore, non-selective vasodilation in the pulmonary circulation may have disadvantageous effects on gas exchange by increasing ventilation-perfusion mismatches. For long-term therapy, up to 250 mg nifedipine or 720 mg diltiazem is used. The dose must be increased slowly over weeks to the correct treatment dosage.

#### 2. Intravenous prostacyclin

Reduction of endothelial prostacyclin synthesis in lung tissue has been described in patients suffering from pulmonary hypertension (Christman 1992, Tuder 1999). Therefore, substitution of exogenous synthetic prostacyclin is an obvious therapeutic option. Due to its short half-life, iloprost is continuously infused intravenously using a portable pump via a catheter or an implanted port. The intravenous dosage

of iloprost is slowly increased to a usual dose of between 0.5 and 2.0 ng per kg bodyweight per minute.

The treatment of outpatients with intravenous prostacyclin is today an established treatment for long-term therapy of severe pulmonary hypertension (Barst 1996, Sitbon 2002). Long-term therapy with intravenous prostacyclin induces a sustained hemodynamic benefit in the treatment of primary pulmonary hypertension (e.g. HIV-associated pulmonary hypertension).

The disadvantages of intravenous prostacyclin are:

- systemic side effects of non-selective vasodilators, e.g. arterial hypotension, orthostasis, skin hyperemia, diarrhea, jaw- and headache
- risk of acute right heart decompensation due to application failures
- possible catheter infection
- tachyphylaxis

Tachyphylaxis is observed in long-term application of intravenous prostacyclin and requires increased doses.

Conclusion: experiences with prostacyclin in HIV-associated pulmonary hypertension are based on smaller, uncontrolled trials. However, these studies suggest an improvement in the prognosis of affected patients (Aguilar 2000, Cea-Calvo 2003).

### 3. Inhalative prostanoids

Many disadvantages of intravenous application can be avoided by using aerosolized prostanoids (e.g. the recently approved prostanoid Ventavis™). Alveolar deposition of prostanoids stimulates a selective intrapulmonary effect. Repeated inhalation of iloprost has proved to be effective and safe in HIV-negative patients in a recent multi-centric, randomized placebo-controlled trial (Olschewski 2002). Iloprost-treated patients showed a significant improvement in exercise capacity, as measured by a six-minute walk test, as well as in NYHA classification.

The effect of this treatment on HIV-associated pulmonary hypertension was demonstrated in a further clinical trial at our center (Ghofrani 2004). Disadvantages of this form of therapy include the sophisticated aerosolization technology, the short duration of action after a single application (60-90 min), requiring frequent inhalations (6-9 per day), and the therapy-free interval during the night. Per day, 25-75 µg iloprost are given in 6-9 inhalations.

### 4. Endothelin receptor antagonists

Several experimental trials have proved the effectiveness of selective and non-selective endothelin antagonists. A phase III trial on the orally administered endothelin antagonist bosentan showed an improvement in physical exercise capacity and an increase in complication-free survival time of PPH patients (Rubin 2002). Applied doses vary between 62.5 and 125 mg twice daily. The major side effect of this therapy is an elevation of liver enzymes. Therefore, stringent controls of liver enzymes are necessary. The use of bosentan in patients suffering from HCV/HIV co-infection has to be considered carefully.

Based on these data, bosentan was approved for the treatment of pulmonary arterial hypertension in Europe. Due to the potential increase in liver enzymes, frequent controls of liver enzymes are required. Only physicians registered by the company Actelion and admitted to the prescription list are able to prescribe bosentan.

An uncontrolled study has reported initial experiences in using bosentan to treat HIV-associated pulmonary hypertension (Sitbon 2004).

### **5. Phosphodiesterase-5 (PDE5)-inhibitors**

Sildenafil (Revatio™) was the first phosphodiesterase-5 inhibitor to be approved for the therapy of pulmonary hypertension by the FDA last year, and at the beginning of this year by the EMEA in Europe. Revatio™ is also approved for use in HIV-associated pulmonary hypertension, although combination with protease inhibitors is not recommended because of possible interactions due to the same metabolic pathway (cytochrome P450 cyp 3A).

Considering the association of the groups of pulmonary arterial hypertension (Venice 2003), a similar therapeutic regime to that used for idiopathic pulmonary hypertension can be applied, depending on the clinical severity of the disease (Figure 2). A daily dose of 25-150 mg sildenafil is usually given in two or three single applications.

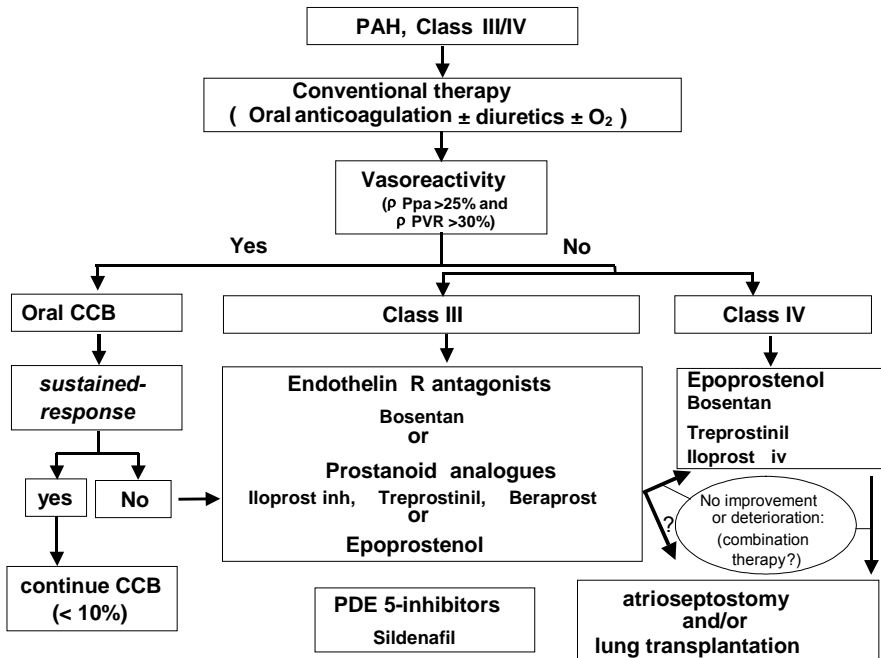


FIGURE 2. Therapeutic algorithm of pulmonary arterial hypertension depending on severity and vasoreactivity (adapted from World symposium on pulmonary hypertension, Venice 2003). Class I-IV: NYHA classification; Ppa: Pulmonary arterial pressure; PVR: pulmonary vascular resistance; CCB: Calcium channel blocker; PDE 5: Phosphodiesterase 5.

## Conclusion for clinicians

HIV-patients suffering from exercise-induced dyspnea should be tested for pulmonary hypertension when other pulmonary or cardiac diseases (e.g. restrictive or obstructive ventilation disorders, pneumonia, coronary heart disease) have been excluded. The incidence of pulmonary hypertension is elevated by a factor of 1,000 in HIV patients compared to the general population, excluding estimated numbers of unreported cases.

A suspected diagnosis of pulmonary hypertension can be substantiated by non-invasive diagnostic methods (e.g. echocardiography). Since new therapeutic options have recently become available, correct diagnosis is essential.

Further diagnosis and treatment of patients suffering from every kind of pulmonary hypertension should be performed in specialized centers with experience in the treatment of pulmonary hypertension and HIV infection.

## References and Internet addresses

1. Aguilar R, Farber H. Epoprostenol (prostacyclin) therapy in HIV-associated pulmonary hypertension. *Am.J.Respir.Crit Care Med.* 2000; 162: 1846-50. <http://amedeo.com/lit.php?id=11069824>

2. Barst R, Rubin L, Long W, McGoon M, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. The Primary Pulmonary Hypertension Study Group. *N Engl J Med* 1996; 334: 296-302. <http://amedeo.com/lit.php?id=8532025>
3. Bower M, Fox P, Fife K, et al. Highly active anti-retroviral therapy (HAART) prolongs time to treatment failure in Kaposi's sarcoma. *AIDS* 1999; 13:2105-11. <http://amedeo.com/lit.php?id=10546864>
4. Carlsen J, Kjeldsen K, Gerstoft J. Sildenafil as a successful treatment of otherwise fatal HIV-related pulmonary hypertension. *AIDS* 2002; 16:1568-9. <http://amedeo.com/lit.php?id=12131202>
5. Cea-Calvo L, Escribano S, Tello de M, et al. [Treatment of HIV-associated pulmonary hypertension with treprostinil]. *Rev.Esp.Cardiol.* 2003; 56: 421-5. <http://amedeo.com/lit.php?id=12689580>
6. Christman B, McPherson C, Newman J, et al. An imbalance between the excretion of thromboxane and prostacyclin metabolites in pulmonary hypertension. *N.Engl.J.Med.* 1992; 327: 70-5. <http://amedeo.com/lit.php?id=1603138>
7. Cooper, D. Immunological effects of antiretroviral therapy. *Antivir.Ther.* 3 1998; Suppl 4: 19-23. <http://amedeo.com/lit.php?id=10723505>
8. Ghofrani H, Wiedemann R, Rose F, et al. Combination therapy with oral sildenafil and inhaled iloprost for severe pulmonary hypertension. *Ann.Intern.Med.* 2002; 136: 515-22. <http://amedeo.com/lit.php?id=11926786>
9. Ghofrani H, Friese G, Discher T, et al. Inhaled iloprost is a potent acute pulmonary vasodilator in HIV-related severe pulmonary hypertension. *Eur.Respir.J.* 2004; 23: 321-6. <http://amedeo.com/lit.php?id=14979511>
10. McNaghten A., Hanson D, Jones J, et al. Effects of antiretroviral therapy and opportunistic illness primary chemoprophylaxis on survival after AIDS diagnosis. *Adult/Adolescent Spectrum of Disease Group.* *AIDS* 1999; 13: 1687-95. <http://amedeo.com/lit.php?id=10509570>
11. Mette, S, Palevsky H, Pietra G, et al. Primary pulmonary hypertension in association with human immunodeficiency virus infection. A possible viral etiology for some forms of hypertensive pulmonary arteriopathy. *Am.Rev.Respir.Dis.* 1992; 145: 1196-1200. <http://amedeo.com/lit.php?id=1586065>
12. Nunes H, Humbert M, Sitbon O, et al. Declining mortality from HIV-associated pulmonary arterial hypertension with combined use of highly active antiretroviral therapy and long-term epoprostenol infusion. *Am.J.Respir.Crit Care Med.* 2002; 165: A 412.
13. Olschewski H, Simonneau G, Galie N, et al. Inhaled iloprost for severe pulmonary hypertension. *N.Engl.J.Med.* 2002; 347: 322-9. <http://amedeo.com/lit.php?id=12151469>
14. Opravil M, Pechere M, Speich R, et al. HIV-associated primary pulmonary hypertension. A case control study. *Swiss HIV Cohort Study.* *Am.J.Respir.Crit Care Med.* 1997; 155: 990-5. <http://amedeo.com/lit.php?id=9117037>
15. Rubin L, Badesch D, Barst R, et al. Bosentan therapy for pulmonary arterial hypertension. *N.Engl.J.Med.* 2002; 346: 896-903. <http://amedeo.com/lit.php?id=11907289>
16. Schumacher Y, Zdebek A, Huonker M, et al. Sildenafil in HIV-related pulmonary hypertension. *AIDS* 2001; 15: 1747-8. <http://amedeo.com/lit.php?id=11546958>
17. Simonneau, G, Galie N, L. Rubin J, et al. Clinical classification of pulmonary hypertension. *J.Am.Coll.Cardiol.* 2004; 43: 5S-12S. <http://amedeo.com/lit.php?id=15194173>
18. Sitbon O, Gressin V, Speich R, et al. Bosentan for the treatment of human immunodeficiency virus-associated pulmonary arterial hypertension. *Am.J.Respir.Crit.Care Med.* 2004; 170: 1212-7. <http://amedeo.com/lit.php?id=15317666>
19. Sitbon O, Humbert M, Nunes H, et al. Intravenous infusion of epoprostenol in severe primary pulmonary hypertension (PPH): long-term survival and prognostic factors. *Am.J.Respir.Crit Care Med.* 2002; 165: A 517.
20. Tudor R, Cool M, Geraci M, et al. Prostacyclin synthase expression is decreased in lungs from patients with severe pulmonary hypertension. *Am.J.Respir.Crit Care Med.* 1999; 159: 1925-32. <http://amedeo.com/lit.php?id=10351941>
21. Zuber J, Calmy A, Evison J, et al. Pulmonary arterial hypertension related to HIV infection: improved haemodynamics and survival associated with antiretroviral therapy. *Clin. Infect. Dis.* 2004, 38: 1178-85. <http://amedeo.com/lit.php?id=15095226>



## 25. HIV and Pulmonary Diseases

Sven Philip Aries, Bernhard Schaaf

The spectrum of lung diseases in HIV-infected patients encompasses complications typical for HIV such as tuberculosis, bacterial pneumonia, lymphomas and HIV-associated pulmonary hypertension, but also includes typical everyday pulmonary problems like acute bronchitis, asthma, COPD and bronchial carcinomas (Table 1). Classical diseases such as PCP have become rarer as a result of HAART and chemoprophylaxis, so that other complications are on the increase (Grubb 2006). None other than acute bronchitis is the most common cause of pulmonary problems in HIV patients (Wallace 1997). However, particularly in patients with advanced immune deficiency, it is vital to take all differential diagnoses into consideration. Anamnestic and clinical appearance are often essential clues when it comes to telling the difference between the banal and the dangerous.

Table 1: Pulmonary complications in patients with an HIV infection

Infections	Neoplasia	Other
<b>Pneumocystis jiroveci</b>	Kaposi sarcoma	Lymphocytic interstitial pneumonia
<b>Bacterial pneumonia</b>	Non-Hodgkin's lymphoma	Non-specific interstitial pneumonia
<i>S. pneumoniae</i>	Hodgkin's lymphoma	Pulmonary hypertension
<i>S. aureus</i>	Bronchial carcinoma	COPD
<i>H. influenzae</i>		Bronchial hyperreactivity
<i>B. catarrhalis</i>		
<i>P. aeruginosa</i>		
<i>Rhodococcus equi</i>		
<i>Nocardia asteroides</i>		
<b>Mycobacteria</b>		
<i>M. tuberculosis</i>		
Atypical mycobacteria		
<b>Other</b>		
Cytomegalovirus		
<i>Aspergillus</i> spp.		
<i>Cryptococcus neoform.</i>		
<i>Histoplasma capsulatum</i>		
<i>Toxoplasma gondii</i>		

This chapter presents an outline of differential diagnoses in patients with respiratory complaints. PCP, mycobacterioses and pulmonary hypertension are covered in detail in chapters elsewhere.

## Anamnesis

### **What are the previous illnesses of the patient?**

Someone who has suffered from a PCP once is at a higher risk of having another one. A patient with hyperlipidaemia and carotid stenosis might have coronary heart disease.

### **What medication does the patient take?**

Taking cotrimoxazol regularly makes a PCP unlikely, and the risk of bacterial pneumonia may also be reduced (Beck 2001). In the case of PCP prophylaxis with Pentamidine inhalation, however, atypical, often apically pronounced manifestations of a PCP are to be expected.

### **Has the patient recently started HAART?**

Particularly HAART can induce pulmonary problems:

During a newly begun course of treatment with abacavir, asthma could also be due to hypersensitivity. Dyspnea (13 %), cough (27 %) and pharyngitis (13 %) are common symptoms (Keiser 2003). Some patients even develop pulmonary infiltrates.

T-20 seems to increase the risk of bacterial pneumonia, at least among smokers.

Dyspnea and tachypnea are also seen in lactic acidosis secondary to nuke therapy.

In addition, pulmonary symptoms after institution of HAART might result from the Immune Reconstitution and Inflammatory Syndrome (IRIS). The list of etiologies includes a number of infective and non-infective causes (Grubb 2006). Low CD4+ T-cell count and high viral load are risk factors. In a retrospective analysis, IRIS was seen in 30 % of patients with TB, atypical mycobacteriosis and cryptococcosis (Shelburn 2005).

### **Does the patient smoke?**

Although smoking is more harmful to HIV-positive than to HIV-negative persons, it is still more common among HIV-positives (Royce 1990). All HIV-associated and HIV-independent pulmonary diseases are more common in smokers than in non-smokers. This starts with bacterial pneumonia and PCP, but also applies to asthma, COPD and pulmonary carcinomas (Hirschtick 1996). Smoking promotes the formation of a local immune deficit in the pulmonary compartment: it reduces the number of alveolar CD4+ cells and the production of important pro-inflammatory cytokines such as IL-1 and TNF- $\alpha$  (Wewers 1998). Furthermore, smoking suppresses the phagocytosis capacity of alveolar macrophages. This effect is more pronounced in HIV patients than in HIV-negative patients. HIV infection itself, however, does not seem to have any direct influence on the capability for bacterial killing (Elssner 2004).

Motivating the patient to restrict nicotine intake is thus an important medical task, particularly in HIV consultation. Strategies which promise success and are supported by the evidence of studies include participation in motivational groups, nicotine substitutes and taking Bupropion, whereby interactions, particularly with Ritonavir, should be taken into consideration.



### Where does the patient come from?

Another important question is that of the travelling history and/or the origin of the patient. There are places where disease such as histoplasmosis and coccidiomycosis occur endemically. Histoplasmosis, for example, is more widespread in certain parts of the USA and in Puerto Rico than PCP, while it is rare in Europe.

Tuberculosis plays a greater role among immigrants.

### How did the patient become infected with HIV?

Intravenous drug users suffer more often from bacterial pneumonia or tuberculosis (Hirschtick 1995). Pulmonary Kaposi's sarcomas are almost exclusively found in MSM (men who have sex with men).

### What are the symptoms?

Occasionally, some valuable information can be gained above the more uniform symptoms such as coughing and shortness of breath, which might be useful for differentiation between PCP and bacterial pneumonia. Thus, for example, it is typical for the onset of bacterial pneumonia to be more acute. Patients usually go to the doctor after only 3-5 days of discomfort, whereas patients with PCP suffer from symptoms for an average of 28 days (Kovasc 1984). PCP patients typically have dyspnea and a non-productive cough. A large quantity of discoloured sputum is more likely to indicate a bacterial cause or a combination of infections.

### What does the chest X-ray look like?

Table 2: Chest X-ray findings and differential diagnosis

Chest X-ray	Typical differential diagnosis
Without pathological findings	PCP, asthma, KS of the trachea
Focal infiltrates	Bacterial pneumonia, mycobacteriosis, lymphoma, fungi
Multifocal infiltrates	Bacterial pneumonia, mycobacteriosis, PCP, KS
Diffuse infiltrates	PCP (centrally pronounced), CMV, KS, LIP, cardiac insufficiency, fungi
Miliary image	Mycobacteriosis, fungi
Pneumothorax	PCP
Cavernous lesions	Mycobacteriosis (CD4 > 200), bacterial abscess (Staph., Pseudomonas)
Cystic lesions	PCP, fungi
Pleural effusion	Bacterial pneumonia, mycobacteriosis, KS, lymphoma, cardiac insufficiency
Bihilar lymphadenopathy	Mycobacteriosis, KS, sarcoidosis

### The most important question: What is the immune status?

The number of CD4+ T-cells provides an excellent indication of the individual risk of a patient to suffer from specific opportunistic infections. More important than the nadir is the current CD4+ T-cell count. In patients with more than 200/ $\mu$ l, infection with typical opportunistic HIV-associated diseases is very unlikely. Here, as with HIV-negative patients, one generally tends to expect more „normal“ problems like acute bronchitis and bacterial pneumonia. However, tuberculosis should always be considered. Although the risk of becoming infected with tuberculosis grows along

with increasing immunodeficiency, more than half of all tuberculosis infections in HIV patients occur at a CD4+ T-cell count of above 200/ $\mu$ l (Lange 2004, Wood 2000).

At less than 200 CD4+ T-cells/ $\mu$ l, PCP and, more rarely, pneumonia/pneumonitis with cryptococci, occurs. At this stage too, however, bacterial pneumonia is the most common pulmonary disease overall.

Below 100 CD4+ T-cells/ $\mu$ l, there is an increase in the number of pulmonary Kaposi sarcomas and toxoplasma gondii infections. At a cell count of under 50/ $\mu$ l, infections with endemic fungi (histoplasma capsulatum, Coccidioides immitis), non-endemic fungi (Aspergillus, Candida species), atypical mycobacteria and different viruses (mostly CMV) occur. Especially in patients with advanced immunodeficiency, it must be remembered that pulmonary illness may only represent an organ manifestation of a systemic infection. Rapid, invasive diagnostic procedure is thus advisable in such patients.

## Pulmonary complications

### Bacterial pneumonia

Bacterial pneumonia occurs more often in HIV-positive than in HIV-negative patients, and, like PCP, leaves scars in the lung. This often results in a restriction of pulmonary function which goes on for years (Alison 2000). Although bacterial pneumonia occurs in the early stages of HIV infection, the risk grows along with increasing immunosuppression. A case of bacterial pneumonia significantly worsens the long-term prognosis of the patient (Osmond 1999). Thus, contracting bacterial pneumonia more than once a year is regarded as AIDS defining. The introduction of HAART went hand in hand with a significant reduction in the occurrence of bacterial pneumonia (Jeffrey 2000).

Clinically and prognostically speaking, there is no great difference between bacterial pneumonia in HIV-infected patients and pneumonia in an immunocompetent host. However, the HIV-patient more often presents with less symptoms and a normal leucocyte count (Feldman 1999). Etiologically, pneumococci and haemophilus infections are most common. In comparison with immunocompetent patients, infections with *Staphylococcus aureus*, *Branhamella catarrhalis*, and in the later stages (< 100 CD4+ T-cells/ $\mu$ l) *Pseudomonas spp.* occur more often. In the case of slow-growing, cavitating infiltrates, there is also the possibility of rare pathogens such as *Rhodococcus equi* and nocardiosis. Polymicrobial infections and co-infections with *Pneumocystis jiroveci* are common (10-30 %), which makes clinical assessment difficult (Miller 1994).

What is also important for the risk stratification of the patient, in addition to the usual criteria (pO<sub>2</sub>, extent of infiltrate, effusion, circulatory condition, extrapulmonary involvement and confusion of the patient) is the CD4+ T-cell count. The mortality of patients with < 100 cells/ $\mu$ l is increased more than sixfold. Therefore it probably makes sense when dealing with patients with a pronounced immune defect not to rely on the risk scores validated for immunocompetent patients and to admit apparently less severely ill patients to the hospital for treatment (Cordero 2000).

Should there be no suspicion of mycobacteriosis, a calculated antibacterial treatment of patients with a CD4+ T-cell count of  $> 200/\mu\text{l}$  with medication effective against *S. pneumoniae*, *H. influenzae* and *S. aureus* is indicated. However, there are no controlled studies available to support this. In accordance with recommended therapies for community acquired pneumonia with co-morbidity, the prescription of a Group 2 Cephalosporin such as Cefuroxim or group 3a such as Cefotaxim/Ceftriaxon, or an aminopenicillin with betalactamase inhibitor (Ampicillin/Sulbactam or Amoxicillin/clavulanic acid, e.g. Augmentan™ 875/125 mg, twice daily) can be recommended. In the case of regionally increased incidence of legionella infection, combination with a macrolide is advisable (e.g. Klacid™ 500 mg twice daily). Once positive culture results have been obtained, the patient should receive further specific treatment. With advanced immunodeficiency (CD4+ T-cells  $< 200/\mu\text{l}$ ), primary consideration should be given to bronchoscopic diagnostics, due to the broader spectrum of pathogens (Dalhoff 2002). In patients with a high risk of pseudomonas infection (low CD4 count, nosocomial infection, sepsis) initial therapy should include antibiotics active against pseudomonas.

Pneumococcus vaccination is recommended. At a CD4+ T-cell count lower than  $200/\mu\text{l}$ , however, there is no proof of vaccination benefit. Due to the frequency of secondary bacterial infections, an annual influenza vaccination is also advisable.

### **Which diagnostic strategy makes sense with pulmonary infiltrates?**

The intensity of the diagnostic workup in a patient with pulmonary infiltrates is based on the HIV stage and the expected spectrum of pathogens. With a CD4+ T-cell count of  $> 200/\mu\text{l}$ , non-invasive basic diagnostics and a calculated antibiotic therapy are justified. This basic diagnostic investigation includes taking two blood cultures and a microscopic and cultural sputum examination. The bacteremia rate seems to be higher than in immunocompetent patients (Miller 1994). The main value of sputum culture is the demarcation of mycobacterial and aspergillus infections.

In individual cases the possibility of antigen detection in the urine should be considered (e.g. pneumococcus, legionella, cryptococcus, histoplasma). The determination of the cryptococcus antigen in serum has a high predictive value for the detection of invasive cryptococcosis (Saag 2000). A chest CT is sometimes helpful in the diagnostic workup (high-resolution CT, HR-CT). A PCP, for example, might be depicted in an HR-CT, but might be missed in a conventional chest X-ray.

In advanced stages ( $< 200$  CD4+ T-cells/ $\mu\text{l}$ ), bronchoscopic investigation is primarily recommended (Dalhoff 2002). The diagnostic success rate of a bronchoscopy in HIV-infected patients with pulmonary infiltrates is 55-70 % and rises to 89-90 % when all techniques including the transbronchial biopsy are combined (Cadranel 1995). The sensitivity of a bronchoalveolar lavage (BAL) amounts to 60-70 % in bacterial pneumonia (patients without previous antibiotic treatment), and 85-100 % in PCP (Baughman 1994). Due to the high sensitivity of the BAL, transbronchial biopsy with possible complications is only recommended in the diagnosis of PCP if there is a negative initial diagnostic workup and in patients taking chemoprophylaxis (Dalhoff 2002). If invasive pulmonary aspergillosis or CMV is considered, a transbronchial biopsy should be the preferred method in order to differentiate be-

tween colonisation and tissue invasion. Surgical open biopsies and CT-controlled trans-thoracic pulmonary biopsies are rarely necessary.

## **Asthma bronchiale**

One would think that an immunosuppressing disease like HIV infection would at least protect patients from manifestations of exaggerated immune reaction such as allergies and asthma. However, the opposite is the case: in a study from Canada concerning HIV-infected men, more than 50 % had suffered an episode of wheezing within the previous 12 months, and nearly half of those showed evidence of bronchial hyperreactivity. These findings were particularly distinct among smokers (Poirer 2001). As the disease progresses, it probably comes to an imbalance between too few „good“ TH1 cells producing interferon and Interleukin 2, and too many „allergy-mediating“ TH2 cells with an increased total IgE. In cases of unclear coughing, dyspnoea or recurrent bronchitis, the possibility of bronchial hyperreactivity, asthma or emphysema should be kept in mind.

## **Emphysema**

Smokers with HIV infection develop pulmonary emphysema more often than non-infected smokers. It is possible that a pathogenetic synergy arises from smoking and the pulmonary infiltration with cytotoxic T-cells due to HIV infection (Diaz 2000). Smoking crack increases the risk of pulmonary emphysema even more. Here, it seems that superficial epithelial and mucosal structures are destroyed (Fliegil 1997). Furthermore, cocaine can lead to unusual manifestations with pneumothorax or alveolar infiltrates.

## **Lymphoid interstitial pneumonia (LIP):**

LIP is a form of pneumonia which takes a chronic or subacute course and is extremely rare in adults. Radiologically, its reticulonodular pattern makes it similar to PCP. This illness occurs paraneoplastic, rarely, idiopathic and as in HIV and EBV disease parainfectious. In contrast to PCP, patients with LIP usually have a CD4+ T-cell count of > 200/μl and normal LDH values. A CD8-dominated lymphocytic alveolitis with no pathogen detection is characteristic. Definite diagnosis often calls for an open pulmonary biopsy. LIP is considered sensitive to steroids. The role played by HAART is unclear, especially as LIP has occasionally been observed in the context of immune reconstitution during HAART.

## **Bronchial carcinoma**

HIV patients are at considerably higher risk of bronchial carcinoma. A retrospective analysis covering 8,400 patients from the years 1986-2001 showed an eightfold increased incidence of bronchial carcinoma in the period after 1996 than that for the normal smoking population. Interestingly, the majority of bronchial carcinomas are, histologically, adenocarcinomas, which results in discussion of whether HIV infection itself leads to a genetic instability (Bower 2003). Patients with bronchial carcinomas and HIV are younger, the disease is often more advanced at presentation and takes a more aggressive course than in HIV-negative patients (White 1996, Karp 1993). Whether to treat with chemotherapy, and what kind, has to be decided for

each case individually. A small cohort study has shown that HIV-infected patients with advanced bronchial carcinoma have a similarly bad prognosis to that of HIV negative patients, regardless of immune status during HAART and chemotherapy (Powles 2003).

## Less common opportunistic infections

The detection of CMV in BAL repeatedly gives rise to discussion regarding clinical relevance. Seroprevalence is high (90 %), and colonisation of the respiratory tract is common. CMV pneumonia is the primary reason for 3.5 % of pulmonary infiltrates in AIDS patients. The significance of the pathogen in the later stages may well be underestimated, since histological examination of autopsy material showed pulmonary CMV infections in up to 17 % (Afessa 1998, Waxman 1997). Regarding invasive pulmonary aspergillosis, which only occurs in the late stages and usually in conjunction with additional risk factors such as neutropenia or steroid therapy (Mylonakis 1998), please refer to the OI-Chapter.

## References

1. Afessa B, Green W, Chiao J, et al. Pulmonary complications of HIV infection: autopsy findings. *Chest* 1998;113:1225-1229. <http://amedeo.com/lit.php?id=9596298>
2. Baughman R, Dohn M, Frame P. The continuing utility of bronchoalveolar lavage to diagnose opportunistic infection in AIDS patients. *Am J Med* 1994;97:515-522. <http://amedeo.com/lit.php?id=7985710>
3. Beck JM, Rosen MJ, Peavy H. Pulmonary Complications of HIV. Report of the fourth NHLBI Workshop. *Am J Respir Crit Care Med* 2001; 164: 2120-2126. <http://amedeo.com/lit.php?id=11739145>
4. Bower M, Powles T, Nelson M, et al. HIV-related lung cancer in the era of highly active antiretroviral therapy. *AIDS* 2003;17:371-375. <http://amedeo.com/lit.php?id=12556691>
5. Cadranet J, Gillet-Juvin K, Antoine M, et al. Site-directed bronchoalveolar lavage and transbronchial biopsy in HIV-infected patients with pneumonia. *Am J Respir Crit Care Med* 1995;152:1103-1106. <http://amedeo.com/lit.php?id=7663791>
6. Conley LJ, Bush TJ, Buchbinder SP, et al. The association between cigarette smoking and selected HIV-related medical conditions. *AIDS* 1996; 10:1121-1126. <http://amedeo.com/lit.php?id=7651475>
7. Cordero E, Pachon J, Rivero A, et al. Community-acquired bacterial pneumonia in human immunodeficiency virus-infected patients: validation of severity criteria. *Am J Respir Crit Care Med* 2000;162:2063-8. <http://amedeo.com/lit.php?id=11112115>
8. Dalhoff K, Ewig S, Hoffken G, et al. Recommendations for the diagnosis, therapy and prevention of pneumonia in the immunocompromised host. *Pneumologie* 2002;56:807-831. <http://amedeo.com/lit.php?id=12486620>
9. Diaz P, King M, Pacht E, et al. Increased susceptibility to pulmonary emphysema among HIV-seropositive smokers. *Ann Intern Med* 2000;132:369-372. <http://amedeo.com/lit.php?id=10691587>
10. Elssner A, Carter J, Yungler T, Wewers M. HIV-1 infection does not impair human alveolar macrophage phagocytic function unless combined with cigarette smoking. *Chest* 2004;125:1071-1076. <http://amedeo.com/lit.php?id=15006971>
11. Feldman C, Glatthaar M, Morar R, et al. Bacteremic pneumococcal pneumonia in HIV-seropositive and HIV-seronegative adults. *Chest* 1999;116:107-114. <http://amedeo.com/lit.php?id=10424512>
12. Fligel S, Roth M, Kleerup E, et al. Tracheobronchial histopathology in habitual smokers of cocaine, marijuana, and/or tobacco. *Chest* 1997;112:319-326. <http://amedeo.com/lit.php?id=9266864>
13. Grubb JR, Moorman AC, Baker RK, Masur H. The changing spectrum of pulmonary disease in patients with HIV infection on antiretroviral therapy. *AIDS* 2006, 12:1095-1107. <http://amedeo.com/lit.php?id=16691060>
14. Hirschtick R, Glassroth J, Jordan M, et al. Bacterial pneumonia in persons infected with the human immunodeficiency virus. *N Engl J Med* 1995; 333:845-851.
15. Hirschtick R, Glassroth J, Jordan M, et al. Bacterial pneumonia in patients with HIV infection. *N Engl J Med* 1995;333:845-851. <http://amedeo.com/lit.php?id=7651475>

## 646 HIV and Pulmonary Diseases

16. Karp J, Profeta G, Marantz P, et al. Lung cancer in patients with immunodeficiency syndrome. *Chest*. 1993;103:410-413. <http://amedeo.com/lit.php?id=8432128>
17. Keiser P, Nassar N, Skiest D, et al. Comparison of symptoms of influenza A with abacavir-associated hypersensitivity reaction. *Int J STD AIDS*. 2003;14:478-481. <http://amedeo.com/lit.php?id=12869229>
18. Kovacs JA, Hiemenz JW, Macher AM, et al. Pneumocystis carinii pneumonia: A comparison between patients with the AIDS and patients with other immunodeficiencies. *Ann Intern Med* 1984, 100:663-671. <http://amedeo.com/lit.php?id=6231873>
19. Lange C, Schaaf B, Dalhoff K. HIV and lung. *Pneumologie* 2004; 58:416-427. <http://amedeo.com/lit.php?id=15216435>
20. Miller R, Foley N, Kessel D, et al. Community acquired lobar pneumonia in patients with HIV infection and AIDS. 1994 *Thorax*; 49:367-368. <http://amedeo.com/lit.php?id=8202910>
21. Morris A, Huang L, Bacchetti P, et al. Permanent declines in pulmonary function following pneumonia in HIV-infected persons. *Am J Resp Crit Care Med* 2000, 162: 612-6. <http://amedeo.com/lit.php?id=10934095>
22. Mylonakis E, Barlam TF, Flanigan T, et al. Pulmonary aspergillosis and invasive disease in AIDS: review of 342 cases. *Chest*. 1998;114:251-262. <http://amedeo.com/lit.php?id=9674477>
23. Osmond D, Chin D, Glassroth J, et al. Impact of bacterial pneumonia and Pneumocystis carinii pneumonia on HIV disease progression. *Clin Infect Dis* 1999;29:536-543. <http://amedeo.com/lit.php?id=10530443>
24. Poirer C, Inhaber N, Lalonde R, et al. Prevalence of bronchial hyperresponsiveness among HIV-infected men. *Am J Resp Crit Care Med* 2001; 164: 542-5. <http://amedeo.com/lit.php?id=11520712>
25. Powles T, Thirwell C, Newsom-Davis T, et al. HIV adversely influence the outcome in advanced non-small-cell lung cancer in the era of HAART? *Br J Cancer* 2003; 89:457-459. <http://amedeo.com/lit.php?id=12888811>
26. Royce R, Winkelstein W Jr. HIV infection, cigarette smoking and CD4+ T-lymphocyte counts: preliminary results from the San Francisco Men's Health Study. *AIDS* 1990;4:327-333. <http://amedeo.com/lit.php?id=1972021>
27. Saag M, Graybill R, Larsen R, et al. Practice guidelines for the management of cryptococcal disease. *IClin Infect Dis*. 2000 30:710-718. <http://amedeo.com/lit.php?id=10770733>
28. Shelburne SA, Visnegarwala F, Darcourt J, et al. Incidence and risk factors for immune reconstitution inflammatory syndrome during highly active antiretroviral therapy. *AIDS* 2005;19:399-406. <http://amedeo.com/lit.php?id=15750393>
29. Sullivan J, Moore R, Keruly J, et al. Effect of antiretroviral therapy on the incidence of bacterial pneumonia in patients with advanced HIV infection. *Am J Respir Crit Care Med* 2000; 162: 64-7. <http://amedeo.com/lit.php?id=10903221>
30. Wallace J, Hansen N, Lavange L, et al. Respiratory disease trends in the pulmonary complications of HIV Infection Study cohort. *Am J Respir Crit Care Med* 1997;155:72-80. <http://amedeo.com/lit.php?id=9001292>
31. Waxman A, Goldie S, Brett-Smith H, et al. Cytomegalovirus as a primary pulmonary pathogen in AIDS. *Chest* 1997;111:128-134. <http://amedeo.com/lit.php?id=8996006>
32. Wewers M, Diaz P, Wewers M, et al. Cigarette Smoking in HIV Infection Induces a Suppressive Inflammatory Environment in the Lung. *Am J Respir Crit Care Med* 1998;158:1543-1549. <http://amedeo.com/lit.php?id=9817706>
33. White DA. Pulmonary complications of HIV-associated malignancies. *Clin Chest Med*. 1996;17:755-761. <http://amedeo.com/lit.php?id=9016376>
34. Wood R, Maartens G, Lombard C. Risk factors for developing tuberculosis in HIV-1-infected adults from communities with a low or very high incidence of tuberculosis. *J Acquir Immune Defic Syndr*. 2000; 23:75-80. <http://amedeo.com/lit.php?id=10708059>

## 26. HIV-1 associated Encephalopathy and Myelopathy

Christian Eggers and Thorsten Rosenkranz

### HIV encephalopathy

The primary cause of HIV encephalopathy (HIVE) is the infection of the CNS caused by HIV. If untreated, some 15-20 % of patients will eventually develop the disease. Since the introduction of highly active antiretroviral therapy (HAART) the incidence of the disorder has decreased. Other terms used for this condition with largely the same significance are AIDS dementia complex, AIDS dementia, HIV dementia, and HIV associated cognitive motor complex. HIVE only occurs in the later stages of the HIV infection when there is a profound immune suppression (CD4+ T-cells < 200/ $\mu$ l). The incidence of HIVE will likely increase in the developed countries as a consequence of increasing life expectancy (Valcour 2004).

In HIVE there is a high level of replication of HIV in macrophages and microglial cells of the brain. Neuronal cells have not consistently been shown to be infected. However, different immunopathological mechanisms lead to functional and structural damage of these cells. With respect to viral replication and viral quasispecies the CNS is partially independent from the hematolymphatic compartment (Eggers 2003). In HIVE the viral load in the brain parenchyma and the cerebrospinal fluid have been shown to be high, and to loosely correlate with the extent of the disease.

### Clinical manifestation

HIVE is considered to be a subcortical dementia. HIVE emerges over the course of weeks and months. Acutely developing symptoms point out to another etiology. Fever, exhaustion, the effects of tranquilizers and reduced physical condition, e.g. with opportunistic infection, may all mimic dementia. In these cases, diagnosis of HIVE can only be made after repeated examinations when the condition mimicking dementia has improved.

Symptoms are occasionally noted earlier by relatives than by the patient himself. This is why a history given by these persons is of utmost importance. Typical complaints are slowing of reasoning, forgetfulness, difficulties concentrating, lack of energy drive, mild depressive symptoms and emotional blunting. For symptoms and signs see Tables 1 and 2.

Impairment of alertness, neck stiffness and focal or lateralising neurological signs (e.g. hemiparesis, aphasia) are not typical for HIVE. Psychotic symptoms without cognitive or motor disturbance do not warrant a diagnosis of HIVE. The coincidence of psychosis with HIVE is rare. Focal and generalized epileptic seizures are rare manifestations of HIVE.

The severity of HIVE may functionally be categorized according to the Memorial Sloan Kettering scale (Table 3) (Price 1988).

## 648 HIV-1 associated Encephalopathy and Myelopathy

Table 1: Symptoms of HIVE including history given by close relatives or companions

Cognition	Forgetfulness, difficulties concentrating, mental slowing (apprehension, processing)
Emotional	Loss of drive and initiative, withdrawal from social activities, failure to manage the financial and administrative aspects of one's life. Depressive mood, emotional blunting
Motor	Slowing and impairment of fine movements (e.g. typing, buttoning up), and disturbance of gait
Autonomous	Impaired micturition (urgency), loss of sexual libido, erectile dysfunction

Table 2: Signs with HIVE

Neurological findings	<p>Early stages: impaired gait, slowing of rapidly alternating movements, hypomimia, occasionally tremor and short stepped gait</p> <p>Later: brisk tendon reflexes, positive Babinski sign, slowing of gaze saccades, sphincter impairment including incontinence. Palmomental, grasp and glabella reflexes. Occasionally accompanying polyneuropathy</p> <p>In the terminal stages spastic tetraplegia and dual incontinence</p>
Neuropsychological findings	Slowing of psychomotor speed (e.g. naming the months in reverse), impairment of short term memory (recall of verbally presented items, digit span), and mental flexibility (spelling simple words backwards)
Psychological findings	<p>Early stages: emotional blunting, disappearance of strong personality traits, distractability, loss of initiative</p> <p>Later: problems with recalling events in the correct time order, disorientation to time, space and situation. Finally mutism</p>

Table 3: Severity of HIVE

Stage 0:	(normal) normal mental and motor function.
Stage 0,5:	(equivocal/subclinical) no impairment of work or capacity to perform activities of daily living (ADL); normal gait; slowing of ocular movements and movements of extremities may be present
Stage 1:	(mild) able to perform all but the more demanding aspects of work or ADL, but with unequivocal signs or symptoms of functional, intellectual or motor impairment; can walk without assistance
Stage 2:	(moderate) able to perform basic activities of self-care, but cannot work or maintain the more demanding aspects of daily life; able to walk, but may require a single prop
Stage 3:	(severe) major intellectual incapacity (cannot follow news or personal events, cannot sustain complex conversation, considerable psychomotor slowing); motor disability (cannot walk without assistance, usually manual slowing and clumsiness)
Stage 4:	(end stage) almost mutistic. Intellectual and social comprehension and output are at a rudimentary level; almost or completely mute; paraparetic or paraplegic with urinary and fecal incontinence



## Diagnostic workup

Making an HIV diagnosis requires a synopsis of clinical information and the results of laboratory tests. No laboratory test result on its own warrants the diagnosis of HIV. Rather, the diagnosis requires the exclusion of other conditions (Table 3).

Clinically, the cognitive and psychological signs and symptoms are invariably accompanied by motor signs, although these may be subtle (Table 2). The International HIV dementia scale (Sacktor 2005) is an easy-to-use bedside instrument for the detection and quantification of the cognitive impairment of HIV.

Laboratory tests are mainly employed to exclude differential diagnoses. MRI should be preferred to CT. MRI often shows patchy, diffuse, hyperintense and relatively symmetrical lesions in the white matter. These changes indicate leukoencephalopathy. In addition, atrophy with enlargement of the ventricles and the extra-ventricular CSF spaces may be seen. However, none of these findings are specific for HIV, and the disease may be present with a normal MRI. Unlike in PML the white matter lesions do not affect the cortical U-fibers, i.e. they don't reach the cortical ribbon. Edema and space occupying lesions are not typical for HIV and should raise suspicion of other conditions. There may be some faint contrast enhancement symmetrically in the basal ganglia.

CSF analysis shows a normal to even decreased white cell count. In contrast, total protein and albumin concentrations may be slightly elevated (blood-brain-barrier disruption). Oligoclonal bands and increased IgG-index indicate autochthonous immunoglobulin production within the CNS. However, these findings are unspecific and are frequently present in the asymptomatic stages of HIV infection. Although there is a statistically significant correlation of a higher CSF viral load with HIV, this association is of little value in the context of an individual patient. The EEG shows no or only mild signs of generalized slowing. Moderate or severe slowing or focal arrhythmic delta activity are atypical for HIV.

## Treatment

According to the pathogenesis of HIV, treatment should aim at suppressing the viral replication in the CNS. It is an unresolved issue whether the antiviral compounds need to penetrate into the CSF. A variety of clinical (Letendre 2004), virological (de Luca 2002), pathological and electrophysiological studies suggest that substances reaching higher CSF concentrations are more effective. In contrast, we found no association of the number of CNS-penetrating substances and their CSF levels with the magnitude of CSF viral load suppression (Eggers 2003). HAART-induced neurocognitive improvement correlates more closely with viral load suppression in the CSF than in the plasma (Marra 2003).

In the absence of prospective, controlled, and randomized studies with clinical end points, we consider it important that any antiretroviral regimen in patients with HIV includes as many as possible CNS-penetrating substances. We suggest any of the following: zidovudine, lamivudine (high concentrations in *ventricular* CSF; unpublished observations), nevirapine and indinavir. With the substances approved for clinical use in the recent years, CNS penetration is low or unknown.

## 650 HIV-1 associated Encephalopathy and Myelopathy

Table 4: Differential diagnoses of HIV encephalopathy and diagnostic workup

<b>Condition</b>	<b>adequate diagnostic step (commentary)</b>
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >15/ $\mu$ l) (serological findings may be atypical for active neurosyphilis)
CMV encephalitis	CSF (pleocytosis, potentially granulocytic; decreased glucose elevated total protein)  PCR for CMV in CSF, CMV antigen (pp65) in blood antibody testing in blood and CSF (IgG and antibody index may be increased)  MRI (potentially subependymal hyperintensity and contrast enhancement)  Occurs mostly in association with manifestation of other organs (retinitis, colitis, pneumonitis, esophagitis)
Toxoplasmosis	CT / MRI (single or multiple lesions found most frequently in basal ganglia or thalamus, space occupying effect, edema, frequently with contrast enhancement (patchy or ring-shaped))  Presence of toxoplasma specific IgG in blood and CSF (rarely total seronegativity)  (may rarely pass as diffuse microglial nodule encephalitis)
Primary CNS lymphoma	CT / MRI (single or multiple lesions most frequently adjacent to ventricles, space occupying effect, edema, almost invariably intense contrast enhancement (patchy more than ring-shaped))  CSF cytology  EBV PCR in CSF (HIV-associated CNS lymphomas EBV induced)  PET or SPECT (tracer enhancement in lesion)
VZV encephalitis	CSF (marked inflammatory signs)  VZV specific IgG in blood and CSF (IgM may be absent)  VZV PCR in CSF  Mostly antecedent or accompanying cutaneous zoster lesions
Cryptococcal meningitis	CSF (opening pressure frequently elevated, cell count and protein may be normal), India ink stain  Cryptococcal antigen in blood and CSF, fungal culture
Tuberculous meningitis and other bacterial infections	CSF, culture, PCR for mycobacteria  appropriate tests
Progressive multifocal leukoencephalopathy (PML)	MRI (single or multiple lesions of white matter, no space occupying effect, no edema, no contrast enhancement)  PCR for JC virus in CSF
Intoxication	Determination of drug levels / screening for illicit drugs
Metabolic encephalopathy and impaired general physical condition	Determination of electrolytes, renal and hepatic markers, hormones (thyroid, cortisol), blood count  Hypoxaemia? (blood gas analysis)  Reduced physical state? (bed ridden, wasting, pyrexia)
Depression with „pseudo dementia“	Psychiatric examination
Other „subcortical“ dementia forms	Normal pressure hydrocephalus, Parkinsonian syndroms, other neurodegenerative conditions, subcortical arteriosclerotic encephalopathy

A number of small studies investigated the effect of Selegelin, Nimodipin, Lexipafant, and valproic acid for treatment of HIVE. These drugs act on the molecular pathogenesis of HIVE and are used in conjunction with antiretroviral treatment. Although a trend for clinical and neuropsychologic improvement was seen with some substances, none of them can be recommended for clinical routine.

**Prognosis:** An optimal HAART may lead to significant clinical improvement of HIVE. The extent of improvement includes restoration of working ability in patients previously dependent on caregivers. This effect can be observed for up to four years, in parallel with sufficiently suppressed plasma viraemia (Cysique 2006). During the first months of treatment, the radiological signs of leukoencephalopathy may become more prominent, but eventually regress over the following one to two years.

Autopsy studies and clinical case series show, however, that some patients develop a clinically apparent CNS disease despite effective HAART-induced suppression of plasma viral load (Brew 2002; own unpublished observations). Even with rapid decrease of plasma viraemia during HAART, many HIVE patients show a significantly protracted decrease of the CSF viral load (Eggers 2003). On these grounds we recommend that in patients with HIVE, the CSF viral load should be determined during the first one or two years of HAART. Modification of the antiviral regimen should be considered when clinical and virologic studies suggest ongoing CNS viral replication with complete suppression of plasma viraemia.

## **HIV-associated myelopathy**

### **Clinical characteristics**

HIV-infected patients may develop a myelopathy without the neuropsychological signs and symptoms of HIVE, labelled HIV associated myelopathy (HIVM). The histopathological hallmark are vacuoles most prominent in the cervical and thoracic parts of the spinal cord and lipid-laden macrophages, hence the term “vacuolar myelopathy” (Petito 1985). These changes are reminiscent of severe combined degeneration and may occur with HIV-negative patients. As HIV viral products have only inconsistently been shown to be part of the lesions, the role of the virus for the disease is uncertain. Pathogenetically, a disturbance of cobalamin-dependent transmethylation has been discussed. Like HIVE, HIVM occurs mainly with advanced immunosuppression. Only a proportion of patients with the autoptic finding of vacuolar myelopathy shows clinically apparent myelopathy during life (dal Pan 1994).

### **Diagnostic workup**

A patient may be suspected of having HIVM if he has a spastic-atactic gait, hyperreflexia with positive Babinski sign, disturbance of sphincter control, erectile dysfunction, and slight signs of sensory dysfunction in a glove and stocking distribution. The diagnosis of an independent HIVM should only be made when a concomitant cognitive impairment is significantly less prominent than the myelopathy. Electrophysiological tests which show increased latencies of somatosensory evoked

potentials (SEP) and the motor evoked potentials on transcranial magnetic stimulation are compatible with the diagnosis. CSF, microbiological and spinal imaging studies are inconspicuous or unspecific, and they have their importance in the exclusion of differential diagnosis, as listed in Table 4. Spinal imaging should include MRI of the cervical and, possibly the thoracic cord.

Table 5: Differential diagnoses of HIV myelopathy and diagnostic workup

condition	adequate diagnostic step (commentary)
Mechanic compression of the myelon (cervical myelopathy, disk herniation)	degenerative changes of the cervical spine MRI shows reduced CSF spaces around the spinal cord with hyperintense lesions of the cord parenchyma
Neurosyphilis	Antibody testing and CSF analysis (pleocytosis >45/3) (serological findings may be atypical for active neurosyphilis)
CMV myelopathy	CSF (signs of inflammation) PCR for CMV in CSF antibody testing in blood and CSF (IgG and antibody index may be increased)
Toxoplasmosis	contrast enhancing cord lesion on MRI
VZV myelitis	CSF (marked inflammatory signs) VZV specific IgG in blood and CSF (IgM may be absent) VZV PCR in CSF Mostly antecedent or accompanying cutaneous zoster lesions
HSV myelitis	CSF (inflammatory signs may be absent), HSV PCR in CSF
HTLV-1 (tropical spastic paraparesis)	travel to the Carribean, West Africa or East Asia slow evolution of symptoms, bladder dysfunction characteristic, CSF inflammation, HTLV-1 specific antibodies
Severe combined degeneration	Vitamin B12 levels, increased erythrocyte volume
heredo-degenerative diseases (hereditary spastic paraparesis, adrenoleukodystrophy, Friedreich ataxia etc.)	appropriate tests

## Treatment

Early observations of significant improvement with zidovudine monotherapy (Oksenhendler 1990) were later confirmed with HAART. This is why any patient with HIVM should be offered effective HAART. A controlled trial showed L-methionin to bring about improvement on electrophysiological but not clinical parameters.

## References

1. Brew B, Fulham M, Garsia R. Factors Associated with AIDS Dementia Complex. 9<sup>th</sup> CROI 2002, Seattle. <http://www.retroconference.org/2002/Abstract/13381.htm>
2. Cysique L, Maruff P, Brew B. Variable benefit in neuropsychological function in HIV-infected HAART-treated patients. *Neurology* 2006;66:1447-1450. <http://amedeo.com/lit.php?id=16682686>

3. dal Pan GJ, Glass JD, McArthur JC. Clinicopathologic correlations of HIV-1-associated vacuolar myelopathy: an autopsy-based case-control study. *Neurology* 1994; 44:2159-2164. <http://amedeo.com/lit.php?id=7969977>
4. de Luca A, Ciancio BC, Larussa D, et al. Correlates of independent HIV-1 replication in the CNS and of its control by antiretrovirals. *Neurology* 2002; 59:342-347. <http://amedeo.com/lit.php?id=12177366>
5. Eggers C, Hertogs K, Stuerenburg HJ, van Lunzen J, Stellbrink HJ. Delayed CNS virus suppression during HAART is associated with HIV encephalopathy, but not with viral drug resistance or poor CNS drug penetration. *AIDS* 2003; 17:1897-1906. <http://amedeo.com/lit.php?id=12960822>
6. Letendre SL, McCutchan JA, Childers ME, Woods SP, Lazzaretto D, Heaton RK, Grant I, Ellis RJ. Enhancing antiretroviral therapy for human immunodeficiency virus cognitive disorders. *Annals of Neurology* 2004;56:416-423. <http://amedeo.com/lit.php?id=15349869>
7. Marra CM, Lockhart D, Zunt JR, Perrin M, Coombs RW, Collier AC. Changes in CSF and plasma HIV-1 RNA and cognition after starting potent antiretroviral therapy. *Neurology* 2003;60:1388-1390. <http://amedeo.com/lit.php?id=12707454>
8. Oksenhendler E, Ferchal F, Cadranet J, Sauvageon-Martre H, Clauvel JP. Zidovudine for HIV-related myelopathy [letter]. *Am J Med* 1990; 88:65N-66N.
9. Petitto CK, Navia BA, Cho ES, Jordan BD, George DC, Price RW. Vacuolar myelopathy pathologically resembling subacute combined degeneration in patients with the acquired immunodeficiency syndrome. *NEJM* 1985; 312:874-849. <http://amedeo.com/lit.php?id=3974673>
10. Sacktor N, Wong M, Nakasujja N, Skolasky R, Selnes O, Musisi S, Robertson K, McArthur JC, Ronald A and Katabira E. The International HIV Dementia Scale: a new rapid screening test for HIV dementia. *AIDS* 2005;19:1367-1374. <http://amedeo.com/lit.php?id=16103767>
11. Price RW, Brew BJ. The AIDS dementia complex. *J Infect Dis* 1988; 158:1079-1083. <http://amedeo.com/lit.php?id=3053922>
12. Valcour V, Shikuma C et al. Higher frequency of dementia in older HIV-1 individuals: the Hawaii Aging with HIV-1 Cohort. *Neurology* 2004;63:822-827. <http://amedeo.com/lit.php?id=15365130>



## 27. Neuromuscular Diseases

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### **Polyneuropathy and polyradiculopathy**

Peripheral neuropathies may complicate all stages of HIV infection. During the early asymptomatic stages peripheral neuropathies are uncommon, but electrodiagnostic testing reveals subclinical evidence of peripheral nerve involvement in about 10 % of cases. In later stages, symptomatic neuropathies occur in some 30-50 % of patients. Neuropathological studies have shown pathological changes with a prevalence approaching 100 % in patients with AIDS.

The neuropathies can be classified as primary HIV-associated or as secondary diseases caused by neurotoxic substances or opportunistic infections. Although neuropathies related to HIV infection have been on the decline since the introduction of HAART, there has been an increase in the prevalence of toxic neuropathies (Authier 2003). Different types of peripheral neuropathies can be distinguished on the basis of when they occur with respect to the stage of HIV disease, and by the clinical course, major symptoms and electrophysiological and neuropathological features.

### **Clinical features**

#### **Acute inflammatory demyelinating polyneuropathy (AIDP), Guillain-Barré syndrome (GBS)**

AIDP usually occurs at seroconversion or at asymptomatic stages of HIV infection. In addition, it seems to be rarely associated with immune reconstitution (Piliero et al. 2003). The typical clinical presentation is that of areflexia, symmetrical ascending weakness and relative sparing of sensory nerve fibers. Involvement of cranial nerves and cervical and thoracic spinal nerves leads to respiratory insufficiency, dysarthria and dysphagia. Parasympathetic and sympathetic nerve involvement may cause life threatening cardiac arrhythmias and severe arterial hypo- or hypertension.

Cerebrospinal fluid (CSF) typically shows a raised concentration of protein caused by the dysfunction of the blood-brain-barrier. In contrast to HIV-negative patients with AIDP, a moderate pleocytosis of up to 50 leucocytes/ $\mu$ l CSF is found in most HIV-positive patients.

The progressive stage is followed by a few days or weeks of stable disease until recovery begins. If secondary axonal damage has occurred, recovery can last up to two years. A persistent disability of varying degrees develops in about 30 %.

Table 1: Polyneuropathies and polyradiculopathies in HIV infection

Type	HIV infection	Clinical features	Findings
<b>Primary HIV-associated polyneuropathies</b>			
Acute, inflammatory, demyelinating polyneuropathy (Guillain-Barré syndrome, GBS)	Seroconversion, asymptomatic, no or beginning immunosuppression	Symmetrical weakness > sensory loss, areflexia	ENG with demyelinating features, elevated CSF protein and moderate CSF-pleocytosis (< 50 c/μl)
Chronic demyelinating inflammatory polyneuropathy (CIDP)	Asymptomatic beginning immunosuppression, rarely AIDS	Distal and proximal weakness > sensory loss, areflexia	ENG with demyelinating features, elevated CSF protein and moderate CSF-pleocytosis (< 50 c/μl)
Vasculitic neuropathy	Asymptomatic no or beginning immunosuppression, rarely AIDS	Mostly asymmetric, acute loss of function of single nerves, rarely distal symmetrical sensory and motor disturbances	Elevation of ANA, cryoglobulinemia, hepatitis C virus coinfection; vasculitis in nerve biopsy but also in muscle, kidney and other organs
Neuropathy in diffuse, infiltrative leukocytosis syndrome (DILS)	Moderate immunosuppression	Mostly asymmetrical weakness and sensory loss, rarely distal symmetrical disturbances	Disease resembling Sjögren's syndrome; CD8+ cells > 1200/μl
Distal symmetrical sensory polyneuropathy (DSSP)	AIDS or advanced immunosuppression	Distal symmetrical sensory loss, paresthesia and pain of the legs	ENG with axonal features predominantly involving sensory nerves of the legs
<b>Secondary polyneuropathies</b>			
Medication-related toxic neuropathy	Beginning or advanced immunosuppression	Distal symmetrical sensory loss, paresthesia and pain of the lower legs	Treatment with ddl, ddC, d4T, vincristine, dapson
Acute neuromuscular weakness syndrome	Beginning or advanced immunosuppression	Acute progressive tetraparesis	Lactic acidosis during NRTI treatment, axonal nerve damage, additional myopathy
Mononeuritis multiplex in CMV-infection or non-Hodgkin lymphoma	AIDS	Asymmetric, acute loss of function of single nerves	CMV infection of other organs, CMV DNA detection in plasma; non-Hodgkin lymphoma
Polyradiculitis in CMV or M. tuberculosis infection or due to meningeal lymphoma	AIDS	Flaccid paraparesis, sensory loss, bladder dysfunction	CMV or mycobacterial infection at other sites, detection of mycobacteria in CSF, malignant cells in CSF



### **Chronic, inflammatory, demyelinating polyneuropathy (CIDP)**

Whereas AIDP is a monophasic, self-limiting disease, the course of CIDP is chronic progressive or relapsing-remitting. Weakness and sensory disturbances commonly develop over several months. In some cases, relapses, incomplete remissions and periods of stable disease alternate with each other.

In CIDP, as in AIDP, the CSF is abnormal with an elevated protein level. A moderate pleocytosis is often found instead of the classical acellularity. The underlying pathological mechanisms of both AIDP and CIDP seem to be macrophage and complement-mediated demyelination. The reason why a chronic persistence of the autoimmune process occurs in CIDP is unknown.

CIDP is a rare complication of seroconversion or the early stages of infection before AIDS.

### **Vasculitic neuropathy**

Necrotizing vasculitis with involvement of peripheral nerves is a rare cause of neuropathy in HIV infection. Most patients develop a mononeuritis multiplex characterized by acute, relapsing dysfunction of individual peripheral nerves. The prognosis of the disease is determined by the involvement of other organs such as heart, kidneys or muscles in the vasculitic process. An immune complex attack associated with Hepatitis C virus infection or cryoglobulins appears to play an essential role in the pathological mechanism.

### **Diffuse infiltrative lymphocytosis syndrome (DILS)**

DILS is a rare cause of distal symmetrical and often painful neuropathy. It resembles Sjögren's syndrome, but has multivisceral infiltration characterized by CD8 hyperlymphocytosis (CD8+ T-cell count  $>1000/\mu\text{l}$ ). Sicca syndrome with parotidomegaly, lymphadenopathy, splenomegaly, pneumonitis and renal dysfunction may occur in association with axonal neuropathy (Gherardi 1998).

### **Distal symmetrical sensory polyneuropathy (DSSP)**

DSSP is the most common neuropathy in HIV-positive patients and becomes symptomatic in the later stages of infection when the CD4+ T-cell count is at or below  $200/\mu\text{l}$ . The clinical course is predominated by slowly progressive sensory symptoms such as numbness, dys- and paresthesia of feet and lower legs (Table 2). Approximately 30-50 % of patients complain of burning, lacerating or stabbing pain. It mainly involves toes and soles and sometimes makes walking difficult. Leading clinical findings are depressed or absent ankle reflexes, an elevated vibration threshold at toes and ankles and decreased sensitivity to pain and temperature in a stocking distribution, whereas proprioception is usually normal. Weakness and atrophy of intrinsic foot muscles are mild and are not features of the disease. The fingers and hands are rarely involved.

Involvement of the upper legs and trunk, significant weakness of leg muscles or decreasing proprioception are not typical for DSSP and should raise suspicion of other disorders, for instance a conjoined myelopathy. Loss and dysfunction of small sympathetic and parasympathetic nerve fibers may cause postural hypotension, erectile dysfunction, gastroparesis and alterations of skin or nails in many DSSP patients.

Table 2: Clinical features of distal symmetrical sensory polyneuropathy

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Numbness, pain, dys- and paresthesia of the feet and lower legs
Decreased or absent deep ankle tendon reflexes
Decreased or absent vibratory sense of the toes and ankles
No or only minimal motor dysfunction
No or only minimal involvement of the hands and arms
Slowly progressive course
Electrodiagnostic studies with features of axonal nerve damage
Autonomic dysfunction: orthostatic hypotension, erectile dysfunction

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### Medication-related toxic neuropathy

A distal symmetrical sensory peripheral neuropathy occurs in about 10-30 % of patients treated with ddI, d4T or ddC. It is indistinguishable from HIV-induced DSSP on clinical examination or in electrodiagnostic studies. The only difference is in the exposure to neurotoxic nucleoside antiretroviral medication. Brew et al. (Brew 2003) found an elevation of serum lactate in over 90 % of patients with d4T-related neuropathies.

Nucleoside neuropathy develops after a mean of 12–24 weeks of treatment. After withdrawal, there can be a temporary worsening for 2–4 weeks and improvement usually begins after 6–12 weeks. In several cases the restitution remains incomplete. In these cases there may have been an additional pre-existent damage to the peripheral nerves due to the HIV infection. Subclinical disturbance of peripheral nerve function confirmed by pathological findings in electrodiagnostic studies elevates the risk of developing NRTI-related neuropathy.

In the American TORO-1 study, 11 % of patients treated with T-20 (enfurvitide) developed neuropathy versus 5 % in the control group (Lalezari 2003), but the European TORO-2 study did not confirm these results (Lazzarin 2003). Whether protease inhibitors (indinavir, saquinavir, ritonavir, and atazanavir) increase the risk of neuropathy, is still a matter of debate (Crabb 2004, Pettersen 2006)

Table 3: Neurotoxic drugs frequently used in HIV medicine

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NRTI	ddI, ddC, d4T
Antibiotic	dapsone, metronidazole, isoniazid
Cytotoxic	vincristine

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### Acute neuromuscular weakness syndrome

In the course of a NRTI-induced lactic acidosis a life threatening tetraparesis resembling AIDP may occur. In most cases axonal peripheral nerve damage was found, but in a few patients demyelination was also detected. In addition, muscle biopsy revealed myositis or mitochondrial myopathy in some cases (Simpson 2004).

Table 4: Diagnostic work-up

Procedure	Findings	Condition
<b>Basic examinations (recommended for all cases)</b>		
Medical history	Drugs	Medication-related toxic PNP
	Opportunistic diseases	Neuropathy associated with CMV infection or lymphoma
	Alcohol abuse	Alcoholic PNP
Neurological examination	Clinical type of PNP (distal symmetrical, mononeuritis multiplex, etc.)	Symptoms not due to myelopathy or myopathy
Electromyography Electroneurography	Confirmation of neuropathy	Symptoms not due to myelopathy or myopathy
	Demyelinating features	AIDP, CIDP
	Axonal features	DSSP, Multiplex Neuropathy, DILS
Blood tests	HbA1c, glucose	Diabetic polyneuropathy
	Vit B12, B1, B6, Fe, ferritin	PNP due to malnutrition or malabsorption
	ANA, cryoglobulins, HCV-serology, circulating immune complexes, ANCA	Vasculitic neuropathy
	TPHA	Neurosyphilis
	CD8+ T-cells > 1200/ $\mu$ l	Neuropathy associated with DILS
	lactate	NRTI-induced toxic neuropathy
	CMV DNA (if CD4+ T-cells < 100/ $\mu$ l)	Mononeuritis multiplex due to CMV-infection
<b>Additional tests (necessary only in particular cases)</b>		
CSF	Elevated total protein	AIDP, CIDP
	Pleocytosis (granulocytes), CMV DNA	Polyradiculitis due to CMV infection
	Lymphoma cells, EBV DNA	Lymphomatous meningitis
	Elevated IgA, acid fast bacilli, mycobacterial DNA	Tuberculous polyradiculitis
Autonomic tests (sympathetic skin reaction, heart rate variability)	Involvement of sympathetic or parasympathetic nerves	Additional autonomic neuropathy
MRI (lumbar spine)	Compression of the cauda equina	Spinal lymphoma Spinal toxoplasmosis
Nerve and muscle biopsy	Necrotizing vasculitis	Vasculitic neuropathy
	Perivascular CD8 infiltration without necrosis	DILS-associated neuropathy

### **Polyneuropathy and polyradiculopathy due to other diseases**

In patients with advanced HIV disease, mononeuritis multiplex may be caused by CMV infection or non-Hodgkin lymphoma. Acute or subacute polyradiculopathies of the cauda equina with rapidly progressive flaccid paraparesis of the legs, bowel dysfunction and sensory disturbances occur in the course of opportunistic infections (CMV, *M. tuberculosis*) or meningeal non-Hodgkin lymphoma. Other important causes of a polyneuropathy are alcohol abuse, diabetes mellitus, malnutrition in patients with long lasting gastrointestinal diseases, neoplastic diseases or cachexia.

### **Diagnosis**

A diagnosis of neuropathy can usually be made based on medical history and clinical examination. Electrodiagnostic studies may be performed for confirmation and for differentiation from other diseases such as myelopathy. Cerebrospinal fluid analysis may be necessary if there is a suspicion of infection with, for example, CMV or syphilis. Sural nerve and muscle biopsy may only be necessary in atypical cases – for instance painful DSSP with a high CD4+ T-cell count and low viral load and without neurotoxic medication or other risk factors. Table 4 gives some recommendations for practical purposes in clinical practice.

### **Treatment**

Causative treatment options only exist for some of the rare neuropathies or polyradiculopathies. Intravenous immunoglobulins and plasmapheresis have been proved effective in the therapy of AIDP. Corticosteroids are also effective in CIPD. In clinical trials on the treatment of CIDP, no difference in the efficacy of immunoglobulins, plasmapheresis or corticosteroids has been shown. However, an individual patient may just respond to one out of the three procedures. In patients who only respond to higher dosages of corticosteroids, other immunosuppressive agents such as azathioprine, low dose weekly methotrexate or cyclosporin may replace long term steroid therapy. We have seen CIDP patients who were in partial remission after temporary steroid therapy and who have remained stable for years with ART alone.

In medication-related neuropathy the offending agent should be withdrawn. However, replacement of ddI or d4T might be difficult in some cases of multiple drug-resistant HIV infection. In this situation, the reduction in the quality of life by neuropathic symptoms must be balanced against the risk of deterioration of immunological and viral parameters. A small open-label study with 2 x 3,500 mg L-acetylcarnitine resulted in peripheral nerve regeneration, demonstrated in skin biopsies, and in improvement of neuropathic symptoms induced by neurotoxic NRTI (Hart 2004). Two small open studies confirmed the effectiveness of L-acetyl-carnitine in reducing pain in patients with neurotoxic neuropathy (Herzmann 2005, Osio 2006), but a randomized controlled trial is still lacking.

A causative treatment for DSSP does not exist. ART might improve the function of sensory nerves in a few cases, and therefore starting ART or optimizing a current ART should be considered in newly diagnosed DSSP. In most cases the neuropathic symptoms still persist.

Symptomatic treatment is directed at irritative symptoms such as pain and paresthesia. It is not effective against deficits of nerve function including sensory loss or weakness.

Table 5: Causative treatment of polyneuropathies and polyradiculopathies

Condition	Treatment
AIDP	Intravenous immunoglobulins 0.4 g/kg daily for 5 days or: plasmapheresis (5 x in 7-10 days)
CIDP	Intravenous immunoglobulins 0.4 g/kg daily for 5 days or: plasmapheresis (5 x in 7-10 days) or: prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12-16 weeks
Vasculitic neuropathy	Prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12-16 weeks
Neuropathy due to DILS	Start or improvement of ART <u>plus</u> prednisone 1-1.5 mg/kg daily for 3-4 weeks with subsequent tapering for 12-16 weeks
Distal symmetrical sensory polyneuropathy	A causative treatment is not known, ART may improve nerve function, for symptomatic treatment. See table 6
Medication-related toxic neuropathy	Withdrawal of the neurotoxic substances, if possible.
Mononeuritis multiplex or polyradiculitis due to CMV-infection	Intravenous foscarnet 2 x 90 mg/kg daily <u>plus</u> intravenous ganciclovir 2 x 5 mg/kg daily.
Lymphomatous meningitis	Start or improvement of ART <u>plus</u> intrathecal methotrexate (intraventricular shunt or lumbar puncture) 12-15 mg 2 x/weekly until CSF is free of malignant cells, subsequently 1 x/week for 4 weeks and subsequently 1 x/month <u>plus</u> 15 mg oral folinate after each injection <u>plus</u> systemic treatment of lymphoma (see chapter "Malignant Lymphoma")
Polyradiculitis due to infection with <i>M. tuberculosis</i>	Treat tuberculosis (see chapter "OIs")

The agents listed in table 6 are recommended because they have proved useful in daily practice and because they interfere only slightly and in a predictable way with ART. A controlled study showed that lamotrigine was effective in reducing the symptoms of neurotoxic neuropathy (Simpson 2003). The drug is well tolerated if one adheres to the slow dose escalation regimen and stops treatment or reduces the dose when a skin reaction occurs. In a small study, gabapentin was shown to be effective in reducing DSSP-induced pain (Hahn 2004). The advantages of this substance are good tolerability and lack of interference with ART.

A randomized controlled trial could not detect a therapeutic benefit of lidocaine 5 % gel for the treatment of pain in HIV-associated neuropathy (Estanislao 2004).

Table 6: Symptomatic treatment of painful neuropathy

	<b>Treatment</b>	<b>Adverse effects</b>
Step 1:	Physical therapy, supporting measures (wide shoes, etc.), L-acetyl-carnitine 2 x 2–4 g	Rarely allergy, mild diarrhea
Step 2:	Temporarily 3–4 x 1000 mg paracetamol <i>or</i> 2–3 x 50 mg diclofenac <i>or</i> 4 x 40 drops novaminsulfone for 10–14 days	Nausea, vomiting, allergy (rarely)
Step 3:	Gabapentin 300 mg at night, dose escalation of 300 mg a day every third day up to a maximum of 3 x 1200 mg <i>or</i>	Sedation, nausea, dizziness, rarely pancreatitis
	Pregabalin 2 x 75 mg for 1 week, dose escalation to 2 x 150 in 2 <sup>nd</sup> week, possible escalation up to 2 x 300 mg <i>or</i>	Nausea, vomiting, diarrhea, allergic drug rash
	Lamotrigine 25 mg at night, dose escalation of 25 mg every 5 days up to 300 mg <i>or</i>	Allergy, sedation, cephalgia, nausea
	Amitriptyline 25 mg at night, dose escalation of 10–25 mg every 2–3 days up to 3 x 50 mg <i>or</i>	Sedation, orthostatic hypotension, constipation, dizziness, dry mouth, dysrhythmia, retention of urine, caveat: glaucoma
	Nortriptyline 25 mg in the morning, dose escalation of 25 mg every 2–3 days up to 2–3 x 50 mg	Orthostatic hypotension, constipation, dizziness, dry mouth, dysrhythmia, retention of urine, caveat: glaucoma
Step 4:	Flupirtine 3 x 100, dose escalation up to 3 x 600 mg <i>or</i>	Sedation, constipation, nausea
	Retarded morphine 2 x 10 mg gradual escalation up to 2 x 200 mg	Sedation, constipation, nausea
General practice	<p>Proceed one step if symptoms persist.</p> <p>Substances within step 3 may be combined (for instance an anticonvulsant and an antidepressant), substances of step 3 and step 4 may also be combined (for instance flupirtine and an anticonvulsant).</p> <p>If a rapid relief of symptoms is necessary, treatment should be started with step 4 substances and a low dose step 3 drug should simultaneously be started with slow escalation.</p> <p>The slower the escalation the greater the possibility of reaching an effective dosage.</p>	

The tricyclic antidepressants amitriptyline and nortriptyline both have significant anticholinergic side effects. The dose necessary for reducing neuropathic pain is in the same range as for treating depression and many patients do not tolerate these dosages. However, lower dosages have proved ineffective in DSSP. Nortriptyline has no sedative side effects. We use this substance with good success rates, although clinical trials for its use in HIV-associated neuropathy are lacking. The anti-

convulsant carbamazepine is widely used for the treatment of neuropathic pain. However, it induces some enzymes of the CYP450 system and interferes significantly with ART. Thus its use in HIV medicine is very limited. Pregabalin, an anti-convulsant drug similar to gabapentin, has recently been approved for the treatment of painful neuropathy. It effectively relieves pain in studies of patients with painful diabetic peripheral neuropathy. Like gabapentin, it does not interfere with ART and is well tolerated. We are successfully treating an increasing number of patients with DSSP and neurotoxic neuropathy with this new substance.

Potent opioids may be used to manage moderate or severe pain if a slow dose escalation of an antidepressant or anticonvulsant is not possible and an immediate analgesic effect is desired (Sindrup 1999). Even in cases of substituted or non-substituted drug abuse, opioids should be used (Breitbart 1997). Sometimes, the dosage of methadone must only be moderately increased for a sufficient analgesic effect.

## Myopathy

Myopathies occur in 1-2 % of all HIV patients. They may appear at any stage of the disease. Table 7 gives a synopsis of the most important types of myopathy in HIV infection.

Polymyositis mediated by cytotoxic T-cells is the most common HIV-associated myopathy. AZT-induced myopathy occurs very infrequently with the AZT dosages used today. Some substances commonly used in HIV medicine (ddI, co-trimoxazole, pentamidine, sulfadiazine, lipid lowering drugs) may rarely cause acute rhabdomyolysis with tetraparesis and marked elevation of serum CK levels. Notably, PIs raise the serum concentration of statins increasing the risk of statin-induced myopathy and rhabdomyolysis (Hare 2002).

An elevated serum CK activity is frequently observed during treatment with TDF, especially in patients with HBV- or HCV-coinfection. This is due to a type 2 macroenzyme creatine kinase (Macro CK) and must not lead to suspicion of ischemic or muscular disease. The accumulation of this liver-derived isoenzyme seems to be the result of an insufficient Macro CK2 clearance capacity mediated by TDF (Schmid 2005).

## Clinical features

Myopathy in HIV infection usually presents with exercise-induced myalgia of proximal muscles followed by slowly progressive, symmetrical weakness and atrophy of proximal muscles. Limb girdle muscles are most commonly involved, but distal muscles and muscles of trunk, neck, face or throat may also be affected.

## Diagnosis

Myalgia, fatigue and elevated serum CK levels are frequently found in HIV infection. But these unspecific symptoms and signs on their own do not warrant the diagnosis of myopathy. The diagnosis of probable myopathy requires weakness, muscle atrophy or myopathic features demonstrated by electromyography. A muscle

biopsy confirms the diagnosis and may give some additional clues to the classification and pathogenesis of the muscle disease.

Table 7: Myopathies in HIV infection

Primary HIV-associated	Secondary
Polymyositis	AZT myopathy
Nemaline (rod body) myopathy	Vasculitic myopathy
Vacuolar myopathy	Lymphomatous muscle infiltration
Inclusion body myositis	Infectious myositis
	Medication-related toxic rhabdomyolysis

## Treatment

Moderate myalgia may respond to non-steroidal anti-inflammatory drugs.

Prednisone (100 mg daily for 3-4 weeks, subsequent tapering) or intravenous immunoglobulin (0.4 g/kg for 5 days) have been shown to be effective in treatment of polymyositis (Espinoza 1991, Viard 1992).

The treatment of AZT myopathy is cessation of the drug. Myalgia usually resolves within 1-2 weeks. If symptoms persist for 4-6 weeks, prednisone as described above may be effective.

## References

1. Authier FJ, Gherardi RK Peripheral neuropathies in HIV-infected patients in the era of HAART. *Brain Pathol* 2003, 13: 223-228
2. Breitbart W, Rosenfeld B, Passik S, et al. A comparison of pain report and adequacy of analgesic therapy in ambulatory AIDS patients with and without a history of substance abuse. *Pain* 1997, 235-243. <http://amedeo.com/lit.php?id=9272808>
3. Brew BJ, Tisch S, Law M. Lactate concentrations distinguish between nucleoside neuropathy and HIV neuropathy. *AIDS* 2003, 17: 1094-1096. <http://amedeo.com/lit.php?id=12700465>
4. Childs EA, Lyles RH, Selnes OA, et al. Plasma viral load and CD4 lymphocytes predict HIV-associated dementia and sensory neuropathy. *Neurology* 1999, 52:607-613. <http://amedeo.com/lit.php?id=10025796>
5. Cupler EJ, Danon MJ, Jay C, et al. Early features of zidovudine-associated myopathy: histopathological findings and clinical correlations. *Acta Neuropathol* 1995, 90:1-6. <http://amedeo.com/lit.php?id=7572071> Espinoza LR, Aguilar JL,
6. Espinoza C, et al. Characteristics and pathogenesis of myositis in HIV infection. Distinction from Azidithymidine-induced myopathy. *Rheum Dis Clin North Am* 1991, 17:117-129. <http://amedeo.com/lit.php?id=2041882>
7. Estanisloa L, Carter K, McArthur J et al. A randomized controlled trial of 5% lidocaine gel for HIV-associated distal symmetric polyneuropathy. *J Acquir Immune Defic Syndr* 2004, 37:1584-1586.
8. Gherardi RK, Chrétien F, Delfau-Larue MH, et al. Neuropathy in diffuse infiltrative lymphocytosis syndrome. *Neurology* 1998, 50:1041-44. <http://amedeo.com/lit.php?id=9566392>
9. Hahn K, Arendt G, Braun JS et al. A placebo-controlled trial of gabapentin for painful HIV-associated sensory neuropathies. *J Neurol* 2004; 251:1260-1266.
10. Hare CB, Vu MP, Grunfeld C, Lampiris HW. Simvastatin-nelfinavir interaction implicated in rhabdomyolysis and death. *Clin Infect Dis* 2002; 35:e111-2. <http://amedeo.com/lit.php?id=12410494>
11. Hart AM, Wilson ADH, Montovani C et al. Acetyl-L-carnitine: a pathogenesis based treatment for HIV-associated antiretroviral toxic neuropathy. *AIDS* 2004, 18 :1549-1560
12. Herzmann C, Johnson MA, Youle M. Long-term effect of acetyl-L-carnitine for antiretroviral toxic neuropathy. *HIV Clin Trials* 2005, 6:344-50



13. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant HIV infection in North and South America. *N Engl J Med* 2003; 348:2175-85. <http://amedeo.com/lit.php?id=12637625>
14. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; 348:2186-95. <http://amedeo.com/lit.php?id=12773645>
15. Martin C, Solders G, Sönnnerborg A, et al. Antiretroviral therapy may improve sensory function in HIV-infected patients. *Neurology* 2000, 54:2120-27. <http://amedeo.com/lit.php?id=10851375>
16. Osio M, Muscia F, Zampini L et al. Acetyl-L-carnitine in the treatment of painful antiretroviral toxic neuropathy in human immunodeficiency virus patients: an open label study. *J Peripher Nerv Syst* 2006, 11:72-76
17. Pettersen JA, Jones G, Worthington C, et al. Sensory neuropathy in human immunodeficiency virus/acquired immunodeficiency syndrome patients: protease inhibitor-mediated neurotoxicity. *Ann Neurol* 2006, 59:816-24
18. Piliro PJ, Fish DG, Preston S, et al. Guillain-Barré syndrome associated with immune reconstitution. *Clin Infect Dis* 2003, 36:e111-e114.
19. Schifitto G, Yiannoutsos C, Simpson DM, et al. Long-term treatment with recombinant nerve growth factor for HIV-associated sensory neuropathy. *Neurology* 2001, 57:1313-16. <http://amedeo.com/lit.php?id=11591856>
20. Simpson DM, Slasor P, Dafnia U, et al. Analysis of myopathy in a placebo-controlled zidovudine trial. *Muscle and Nerve* 1997, 20:383-385. <http://amedeo.com/lit.php?id=9052824>
21. Simpson DM, Haidich AM, Schifitto G, et al. Severity of HIV-associated neuropathy is associated with plasma HIV-1 RNA levels. *AIDS* 2002, 16:407-12. <http://amedeo.com/lit.php?id=11834952>
22. Simpson DM, McArthur JC, Olney MD et al. Lamotrigine for HIV-associated painful sensory neuropathies. *Neurology* 2003, 60:1508-14. <http://amedeo.com/lit.php?id=12743240>
23. Simpson DM, Estanislao L, Evans et al. HIV-associated neuromuscular weakness syndrome. *AIDS* 2004, 18:1403-12
24. Sindrup S, Jensen TS. Efficacy of pharmacological treatments of neuropathic pain: an update and effect related to mechanism of drug action. *Pain* 1999, 83:389-400. <http://amedeo.com/lit.php?id=10568846>
25. Schmid H, Mühlbayer D, Bogner JR et al. Macroenzyme creatine kinase type 2 accumulation in sera of HIV-infected patients: significant association with tenofovir DF (TDF) treatment. 12<sup>th</sup> Conference on Retroviruses and Opportunistic Infections, 2005, Boston, Poster No. 827
26. Viard JP, Vittecoq D, Lacroix C, et al. Response of HIV-1 associated polymyositis to intravenous immunoglobulin. *Am J Med* 1992, 92:580-581. <http://amedeo.com/lit.php?id=1580311>



## 28. HIV and Psychiatric Disorders

Susanne Tabrizian and Oliver Mittermeier

Psychiatric disorders occur frequently in HIV-infected patients but the reported prevalence rates differ considerably, depending on the stage of infection and study population. Fact is, though, that there are multiple factors that can have an impact on comorbid psychiatric illness: psychiatric disorders, e.g. substance abuse, can be an independent risk factor for HIV infection. Furthermore, there are the neuropathological effects of the virus itself, and there is evidence that the infection of microglia leads to neuronal damage due to the excretion of neurotoxins. Additionally, opportunistic infections and some of the antiretroviral drugs may cause psychiatric symptoms.

Apart from the affection of the patient's well-being, psychiatric disorders may lead to problems in antiretroviral therapy: adherence to antiretroviral medication becomes poorer. Therefore, early diagnosis and therapy of psychiatric disorders are of vital importance for HIV-positive individuals (Angelino 2001).

### Major depression

Major depression is the most frequently occurring psychiatric disorder in HIV patients. Reports on prevalence rates differ substantially and reach up to 40 % (Angelino 2001). Major depression is a severe illness with serious complications: up to 15-20 % of all patients with recurrent depressive episodes commit suicide. Further common complications are physical, social or role model function impairment (Low-Beer 2000).

Major depression interferes with all aspects of being and may have a severe impact on quality of life. It is characterized by depressed mood, decreased energy and loss of interest. Patients tend to be unable to experience joy or satisfaction in activities that would usually generate these feelings; they may feel ill, lack energy and experience a sense of doom. Also feelings of guilt, a lack of self-esteem and self-reproach are frequent (Angelino 2001). Additionally, neurovegetative symptoms such as loss of appetite and sleep disturbances with so-called early morning wakening or fatigue are common. Furthermore, depressed patients describe somatic symptoms such as pain or vertigo. Often the severity of symptoms changes during the day with greater severity in the morning and relief in the evening. Poor concentration and cognitive impairment, the so-called pseudodementia in depression may also occur. The individual presentation of these symptoms varies notably and may therefore make diagnosis difficult.

Two simple questions, though, may provide valuable hints:

1. During the past month have you often been bothered by feeling down, depressed or hopeless?
2. During the past month have you often been bothered by little interest or pleasure in doing things?

These two questions are being recommended by the U.S. Preventive Services Task Force for screening for depression in primary care. If at least one of the two questions is confirmed by the patient, further diagnostic testing is recommended (Pignone 2002). This screening can be improved by simply inquiring whether help is needed. Asking “is this something with which you would like help?” improves the specificity of general practitioners diagnosis for major depression significantly (Arroll 2005).

The following criteria of ICD-10 should be explored when making a diagnosis of depression:

- a) *Pervasive low mood (see above)*
- b) *Loss of interest and enjoyment (see above)*
- c) *Reduced energy, diminished activity*
- d) Disturbed or increased sleep
- e) Diminished or increased appetite
- f) Poor concentration and attention
- g) Poor self-esteem and self-confidence
- h) Ideas of guilt and unworthiness
- i) Psychomotor retardation or agitation
- j) Ideas or acts of self-harm or suicide

Therapy is indicated if symptoms last for more than two weeks and when at least two of the first three symptoms in addition to at least one of the other symptoms are reported by the patient.

All of these symptoms might occur as a reaction to a stressful life event or sad circumstances. In these cases treatment is not immediately necessary. If the symptoms persist for an unreasonable period of time – more than a couple weeks – a depressive episode might have been triggered. This should then be treated accordingly (Ebert 2001). Aggressive treatment is also obviously necessary in suicidality. HIV-positive patients are more at risk than the general population. The highest rate of suicidal thoughts and attempts occur approximately one to two years after diagnosis of HIV infection. Altogether, though, the rate of suicide among HIV patients has dropped recently – probably due to the improvement of therapy since the beginning of the HAART era (Einsiedel 2001).

## **Treatment**

Treatment of depression is based on two principles: medication and psychotherapy. Since we cannot discuss different aspects of psychotherapy in this article, we will focus on pharmacological treatment. In general, treatment of depressed HIV-infected patients does not differ from that of other patients. It is shown in various studies, that antidepressant medication is efficacious in treating depression among depressed, HIV-positive individuals (Himmelhoch 2005). Medication should therefore always be part of a therapeutic regimen. It should consist of acute phase therapy, maintenance therapy and prophylaxis of a relapse of depression. The goal of treatment should be the complete remission of depressive symptoms. After allevia-

tion, treatment should be continued for at least six months. At the end of treatment, medication should be reduced slowly over a period of weeks.

Once antidepressant medication has been initiated, it may take two weeks for patients to experience a benefit. Side effects, however, might occur earlier, and patients should be informed about this. A non-response to treatment is considered when – given a standard dose of medication or therapeutic serum levels have been attained – there is no relevant benefit for the patient after four to six weeks (Benkert 2003).

At such time, a switch to an antidepressant of another class should be considered. Another period of two to four weeks latency for the therapeutic effect has to be taken into account. Alternatively, an augmentation strategy – added medication with e.g. lithium or thyroid preparations – could be started, since effects might be seen earlier. Sometimes the combination of two antidepressants might bring relief. These strategies should only be provided by experienced therapists. Without thorough experience in treating psychiatric disorders, one should concentrate on three to four antidepressant drugs. In this way, side effects and therapeutic benefits can be more easily observed.

The choice of the appropriate antidepressant can be based on the side effect profile, e.g. sedating vs. activating. Previous therapies are important too: a drug that previously had beneficial results in a patient will be effective in this patient again (Ebert 2001).

### **Selective serotonin (5-HT) re-uptake inhibitors**

So-called serotonin (5-HT) re-uptake inhibitors (SSRI) are considered to be first-line medication in depressed HIV-positive patients since they are effective and well tolerated. Starting with low doses reduces the probability of adverse effects.

Recently, there have been reports on SSRI medication precipitating suicide, especially in children and adolescents. When looking at available data though, these findings are not consistent and are not easily transferable to adults. In most countries, population suicide rates have fallen in the last years even though significantly more antidepressants - and especially SSRIs - have been prescribed. Furthermore, it is difficult to show effects of medication on suicide since suicide is rare, even among depressed patients, and it is therefore difficult, especially in short clinical trials, to assess the risks of medication-related suicides statistically. However, long-term studies are required to gain further information on benefits and risks of antidepressant medication (Gunnell 2004).

Overall, the risk of suicide for adults does not seem to be increased by medication with SSRIs. This is for instance supported by a recent Swedish database study, examining nearly 15000 suicides that found no increased risk for the treatment of depressed individuals with SSRIs (Isacson 2005). Nonetheless, doctors should closely monitor patients with psychiatric disorders, regardless of their medication, for suicide risk, and, if indicated, ask for suicidal thoughts or self-harm in order to react promptly.

## 670 HIV and Psychiatric Disorders

Table 1: Selective Serotonin (5-HT) Re-uptake Inhibitors (SSRI) \*

<b>Drug (Trade name™)</b>	<b>Dosage / day (generally once daily administration)</b>	<b>a) Interactions with HAART b) Evaluation / comments c) Selected side effects</b>
Citalopram (Cipramil™, Sepram™)	20 mg in the morning, therapeutic dose is 20-60 mg	a) Lopinavir/r, ritonavir increase citalo- pram levels b) effective, well tolerated, non-sedating antidepressant c) Initially diarrhea, nausea, decreased sexual arousal / erection
Fluoxetine (e. g. Fluctin™, Prozac™)	10 mg in the morning for 2-3 days, then 20 mg	a) Increased levels of amprenavir, de- lavidine, efavirenz, indinavir, lopinavir/r, nelfinavir, ritonavir and saquinavir. Nevirapine decreases fluoxetine levels b) Activating; most clinical trials con- ducted with fluoxetine c) see above
Fluvoxamine (Fevarin™, Fluvox- amin-neuraxpharm™)	50 mg in the morning, after 3-4 days increase dose to 100-200 mg	a) Increased levels of amprenavir, de- lavidine, efavirenz, indinavir, lopinavir/r, nelfinavir, ritonavir and saquinavir. Nevirapine decreases fluoxetine levels b) Potent inhibitor of CYP1A2 c) see above
Paroxetine (Seroxat™, Tagonis™)	10 mg in the morning for 2-3 days, therapeutic dose is 20 mg	a) Lopinavir/r, ritonavir increase par- oxetine levels b) Somewhat sedating, administration at bedtime if possible c) see above
Sertraline (Gladem™, Zoloft™)	25-50 mg in the morn- ing, lowest effective dose 50 mg, maximum 150 mg	a) Lopinavir/r, ritonavir increase ser- traline levels b) Non-sedating. In agitation, akathisia, or insomnia, combination with benzodia- zepine possible – applicable for all SSRIs c) see above

\* Note: SSRIs should not be combined with monoamine oxidase inhibitors (MAOI) e.g. Moclobemid (Aurorix™). Adjustment of dosage is required in renal or hepatic disorder. (Angelino 2001, Benkert 2001, Einsiedel 2001)

### Tricyclic antidepressants

Tricyclic antidepressants (TCAs) – named after their chemical structure which contains three rings – are effective and, in HIV patients, well studied agents. However, side effects are more frequent in this class of antidepressants. Their anticholinergic effects need to be pointed out: they are contraindicated in patients with urinary retention and closed-angle glaucoma and they should be avoided in patients with bundle branch blocks. Furthermore, TCAs are easier to under- or overdose than SSRIs. Serum levels should therefore be obtained if possible.

Table 2: Tricyclic antidepressants

<b>Drug (Trade name™)</b>	<b>Dosage/day</b>	<b>a) Interactions with HAART b) Evaluation/comments c) Selected side effects</b>
Amitriptyline (e. g. Saroten™, Laroxyl™, Novo-protect™, Amineurin™)	Initially 2-3 x 25 mg usual therapeutic dose 3 x 50 mg or 2 x 75 mg	a) Lopinavir/r, ritonavir increase amitriptyline levels b) Promotes sleep. Weight gain, constipation – might be desired side effects c) Delirious syndrome when fast dose increase
Clomipramine (Anafranil™, Hydiphen™)	2-3 x 25 mg for three days usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase clomipramine levels b) Initially possible agitation, combination with benzodiazepine possible, also see above c) Effective in chronic pain
Doxepin (Aponal™, Siquan™)	Initially 3 x 25 mg usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase doxepin levels b) see above c) Often orthostasis
Imipramine (Tofranil™, Pryleugan™)	2-3 x 25 mg for three days usual therapeutic dose 3 x 50 mg or 3 x 75 mg	a) Lopinavir/r, ritonavir increase imipramine levels b) see above c) Especially at the start of therapy anticholinergic adverse effects

For further reading see Angelino 2001, Benkert 2001, Einsiedel 2001

### Other drugs / therapies

There are numerous other antidepressants but at the time being there is not much data on their use in HIV-infected patients. These include the noradrenergic and serotonergic drug mirtazapine (unlike SSRIs and tricyclic agents, there are so far no reports on sexual dysfunction with this drug) and the combined serotonin-noradrenaline re-uptake inhibitor venlafaxine. The selective noradrenaline re-uptake inhibitor reboxetine seems to be interesting in the therapy of HIV-infected patients since it is not metabolized via cytochrome P450 (CYP450) (Carvalho 2003).

Table 3: Other antidepressants

<b>Drug (Trade name)</b>	<b>Dosage / day</b>	<b>a) Interactions with HAART b) Evaluation / comments c) Selected side effects</b>
Mirtazapine (Remeron™)	Initially 15 mg at bedtime  usual therapeutic dose 30-45 mg	a) not known b) Sedating, promotes sleep, weight gain no sexual dysfunction c) Cave!: not in leukopenia!
Reboxetine (Edronax™)	Initially 2 to 4 mg maintenance ther- apy 8 mg to 12 mg	a) not known b) not sedating c) Dry mouth, insomnia, sweating, tremor and urinary retention. Cave!: Dose reduction (2 x 2 mg) in renal or hepatic insufficiency
Venlafaxine (Trevilor™)	Initially 37.5 mg in the morning  administer twice daily  maintenance ther- apy 75 to 375 mg/day	a) Lopinavir-ritonavir, ritonavir increase ven- lafaxine levels b) Extended release formulation with lesser side effects. Effective in anxiety c) Initially high rates of gastrointestinal side effects. RR ↑, allergic skin reactions, delayed ejaculation

For further reading see Angelino 2001, Benkert 2003

New formulations of existing antidepressants are being developed: intravenous formulations with a faster onset of antidepressant action or a once-weekly administered SSRI. (Norman 2004). Furthermore, single enantiomers have been introduced in several countries, e.g. the S-enantiomer of the SSRI citalopram, escitalopram. It is more than twice as potent at inhibiting serotonin uptake and is supposed to maintain therapeutic efficacy at a lower effective dosage. Pharmacokinetic interaction with ritonavir – a CYP3A4 substrate and prototype CYP3A4 inhibitor – which may potentially affect plasma concentrations of escitalopram, was not clinically significant (Gutierrez 2003). None of these agents, however, will be a sovereign remedy, and one should, especially when experience in psychiatric care is limited, only use a few drugs and know them well instead of trying all available substances.

In addition to the above, herbal medicines are also in use, even though there is an ongoing discussion about their effectiveness. There were great expectations espe-



cially about St. John's wort – a herbal substance without serious adverse effects – when clinical trials demonstrated an antidepressant effect in mild to moderate depression (Linde 1996). Unfortunately hopes have fallen somewhat since St. John's wort did not show an advantage above placebo in further clinical trials (Hypericum Depression Trial Study Group 2002). Remarkably enough, though, the SSRI in this trial was not very effective either and merely showed a positive trend above placebo in effectiveness.

In addition to the above, there are more therapeutic options aside from medication, e.g. controlled sleep withdrawal, where the patient has to stay awake throughout the night. Following this procedure, there is a significant reduction of symptoms the next day in about one half of treated patients– but only until the next night's sleep. Repeated sleep withdrawal, though, might reduce the duration of a depressive episode. Phototherapy, especially in seasonal depression, and electroconvulsive therapy carried out in specialized centers for non-responding patients, are therapeutic options too. There are no data on these therapies in HIV patients. Evidence does exist, however, from small clinical trials for a therapeutic effect of exercise in HIV patients (Neidig 2003). Three times a week jogging for half an hour is a good antidepressant and a therapeutic chance that is possibly not tried often enough.

## Psychotic disorders

*Psychotic* means the occurrence of delusions or prominent hallucinations, and typically the patient has no insight into their pathologic character. The prevalence of psychotic disorders in individuals with HIV or AIDS is rather unclear: rates vary between 0.2 and 15 % (Sewell 1996). Basically, psychotic disorders can be classified into two different forms:

### Primary psychotic disorders

Psychosis that occurs independently of infection with HIV is to be seen as a comorbid condition. Diseases such as schizophrenia, schizophreniform disorder and brief psychotic disorder can be classified into this group. Typical symptoms are delusions, hallucinations, disorganized speech (e.g. frequent derailment or incoherence) or grossly disorganized or catatonic behavior. Etiopathogenetically, a biopsychosocial concept, the vulnerability-stress-coping model, is assumed. It is thought that genetic and psychosocial factors determine a predisposition or an increased vulnerability for psychotic decompensation.

Therefore, an infection with a neuropathological virus such as HIV could trigger a pre-existing psychosis (Einsiedel 2001).

### Secondary psychotic disorders

Characteristic symptoms of a secondary psychotic disorder are prominent hallucinations or delusions. They are caused by an organic disorder of the central nervous system (CNS) as a consequence of a general medical condition. In HIV patients this could, for example, be an opportunistic infection, cerebral lymphoma or HIV encephalopathy. In addition to that, psychotic symptoms can be caused by medications or drug-drug interactions e.g. in HAART (Foster 2003). Therefore an exact

history of medication and especially recent changes in medication are of vital interest.

The occurring delusional themes are numerous, including somatic delusions, delusions of grandeur, religious delusions, and, most frequently, paranoia or persecutory delusions. Diseases that affect subcortical structures or the temporal lobes are more frequently associated with delusions than others. In hallucinations, every sensory quality (auditory, visual, olfactory, gustatory or tactile) might be affected.

Patients with a previously undiagnosed general medical condition, such as HIV infection, might develop an acute psychiatric condition due, for example, to HIV encephalopathy, brain damage from an opportunistic CNS infection such as toxoplasmosis, neoplasms involving the CNS, or metabolic dysfunction. In all acute psychotic disorders, a magnetic resonance image of the brain (more sensitive than computed tomography) and examination of cerebral spinal fluid should therefore be carried out as soon as possible. HIV infection does not show any specific psychopathological findings (Röttgers 2000).

## Treatment

While in organic psychosis, the causative general medical condition must be treated first, in primary psychosis, according to its multifactorial etiology, therapy should consist of a combination of pharmacological, psychotherapeutic, psycho-educational and sociopsychiatric intervention.

Symptomatic treatment with neuroleptics is initially the most important line of treatment in the acute phase of primary psychotic disorders. In principle, the pharmacological treatment of HIV patients does not differ much from that of other populations, but it should be started at low doses and titrated cautiously (Farber 2002), since a dysfunction of the blood brain barrier and consequently a higher rate of medication side effects is to be expected: start low, go slow!

In acute psychotic disorder, regardless of the etiology, the use of a conventional antipsychotic agent, e.g. haloperidol 5 mg PO or IM, is usually successful. For additional sedation in cases with more severe agitation, comedication with a benzodiazepine is possible. When aggressive behavior is present, diazepam 5 to 10 mg PO or IM is a good choice; if fear or anxiety is the leading symptom, lorazepam up to 2.5 mg is indicated. In the further course of treatment, change to an atypical antipsychotic agent (see below) is recommended.

In less acute symptomatic psychotic disorders and in primary comorbid psychosis the use of atypical antipsychotic agents is again the treatment of choice, due to various reasons: atypical antipsychotic agents cause significantly less extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) than typical antipsychotic drugs. Furthermore, they might provide an advantage in non-responding patients and in the treatment of negative symptoms: *asociality*, the withdrawal from relationships; *avolition*, the loss of initiative and drive; *affective flattening* or inappropriateness; *alogia*, a poverty of speech production and content; *anhedonia*, difficulty experiencing pleasure. These are often the most debilitating symptoms in psychotic disorders. Because of the lower risk of developing EPS and TD – for which HIV-infected patients are more susceptible than others – treatment with atypical antipsychotic agents might improve adherence to psychopharmacological treatment

too. In case of insufficient effectiveness, a different atypical antipsychotic agent should be selected after approximately four weeks.

Table 4: Atypical antipsychotic agents

<b>Drug (Trade name)</b>	<b>Dosage/day</b>	<b>a) Interactions with HAART b) Evaluation/comments c) Selected side effects</b>
Amisulpirid (Solian™)	twice daily positive symptoms: 400-800 mg negative symptoms: 50-300 mg maintenance therapy: 200-400 mg	a) No interaction to be expected b) Nearly complete renal elimination, poses advantage in patients with liver damage c) EPS in doses > 400 mg/d possible, usually not severe
Clozapine (Leponex™)	prescribing doctor needs to register at manufacturers start with 6.25-12.5 mg, increase every 1-2 days by 25 mg to max. 600 mg. maintenance therapy: 100-400 mg	a) Because of risk of agranulocytosis (1-2 %) in HIV patients not recommended b) Atypical antipsychotic agent with significance for non-responding schizophrenia and in patients with non-tolerable EPS c) Agranulocytosis; seizures; sedation; weight gain and hyperglycemia
Olanzapine (Zyprexa™)	starting dose 5 mg h.s. maintenance 5-20 mg  when sedation during daytime is wanted: two to three doses/day	a) No interaction with PIs b) Good antipsychotic effect. Few EPS when < 20 mg. Trials with HIV patients available. Side effects, weight gain (depending on dosage) and/or sedation might be favorable. c) In 1-10 %: EPS (e.g. akathisia), drowsiness, orthostasis, liver enzymes↑. Cave!: hyperglycemia possible
Quetiapine (Seroquel™)	start with 25 mg slow titration to 300 to 450 mg divided into two doses/day	a) Contraindication in combination with ritonavir, macrolide antibiotics and ketoconazole. b) No trials with HIV patients published. c) Common (>10 %) sedation, drowsiness. Occasionally orthostasis, liver enzymes↑, weight gain. Cave!: Leukopenia
Risperidone (Risperdal™)	slow titration over one week start with 0.5-2 mg maintenance dose: 4-6 mg divided into two doses/day in renal or hepatic insufficiency do not exceed 4 mg/day !	a) NRTIs increase risperidone plasma level. b) Good antipsychotic effectiveness. Dose dependent EPS: seldom when ≤ 6 mg. Trials with HIV patients published. No influence on blood count, no increase in seizures. First atypical antipsychotic agent available in long acting formulation (twice weekly). c) Orthostasis, especially in the beginning and at high doses – titrate slowly!

Table 4: Atypical antipsychotic agents

Drug (Trade name)	Dosage/day	a) Interactions with HAART b) Evaluation/comments c) Selected side effects
Ziprasidone (Zeldox™)	start with 2 x 20 mg Maximum dose is 2 x 80 mg IM administration possible.	a) Not examined b) So far no trials with HIV population. Contraindicated in patients with long QT interval, cardiac arrhythmias, myocardial infarction. EPS rates not higher than in placebo. Only minimal weight gain. c) Cave: QTc prolongation! > 1 %: drowsiness, hypotension, sedation

## Acute treatment in psychiatric emergency

Most important: de-escalation by “talking down” – this includes measures such as staying in contact with the patient, taking him seriously and adopting a non-confrontational position. Should the use of restraints be necessary, stay calm but act firmly. Always leave the patient the chance to correct inappropriate behavior and always use the least possible restrictive method of restraint.

Table 5: Psychiatric emergency (Benkert 2003; Currier 2004)

Diagnosis	Psychopharmacological treatment
Agitation in acute psychosis	Haloperidol 5-10 mg PO or IM, may be repeated after 30 min, maximal 50 mg in the first 24 hrs. Cave: EPS – then 2.5-5 mg (1/2-1 Amp.) biperidene (Akinethon™) IV or IM.
Agitation and aggression in mania	<b>plus</b> oral or IV application of 2 mg lorazepam, when panic is predominant; maximum dose 10 mg / day (inpatient) or diazepam, when stronger sedation is needed; in aggressive patients: 10 mg PO, IM or slowly IV. Repetition after 30 min possible. Maximum dose 40-60 mg parenteral or 60-80 mg oral (inpatient). Cave: hypotension, respiratory depression
Acute intoxication with psychoactive drug	<b>alternatively</b> oral treatment with 2 mg of risperidone plus 2 mg of lorazepam (Currier 2004)
Delirium due to general medical condition (e.g. infection, excruciation, electrolyte metabolism disorder)	treatment of general medical condition if necessary antipsychotic agent e.g. melperone 50-100 mg for sedation or haloperidol (especially in psychotic symptoms) 2-5 mg PO or IM.
Drug-induced delirium (e.g. antidepressants, antibiotics, rarely efavirenz or others)	change or reduce causative substance in accordance to severity of symptoms, if necessary antipsychotic agent e.g. melperone 50-100 mg for sedation or haloperidol 2-5 mg PO or IM  in hospitalized patients if necessary clomethiazole 2 capsules every 2 hours, maximum dose 20 capsules/day. Cave: respiratory depression, hypersecretion; strictly for inpatients only!

## References

1. Angelino AF, Treisman GJ. Management of psychiatric disorders in patients infected with HIV. *Clin Infect Dis* 2001; 33: 847–56. <http://amedeo.com/lit.php?id=11512090>
2. Arroll B, Goodyear-Smith F, Kerse N, Fishman T, Gunn J. Effect of the addition of a "help" question to two screening questions on specificity for diagnosis of depression in general practice: diagnostic validity study. *BMJ*. 2005 Oct 15;331(7521):884. <http://amedeo.com/lit.php?id=16166106>
3. Benkert O, Hippus H. *Kompendium der Psychiatrischen Pharmakotherapie*, 4. Auflage, Springer-Verlag Berlin Heidelberg 2003.
4. Berzewski H. Juristische Aspekte des psychiatrischen Notfalls. *psycho25*(1999), Sonderausgabe III/99,125-32
5. Carvalhal AS, de Abreu PB, Spode A, Correa J, Kapczinski F. An open trial of reboxetine in HIV-seropositive outpatients with major depressive disorder. *J Clin Psychiatry* 2003; 64: 421-4.
6. Currier GW, Chou JC, Feifel D et al. Acute treatment of psychotic agitation: a randomized comparison of oral treatment with risperidone and lorazepam versus intramuscular treatment with haloperidol and lorazepam. *J Clin Psychiatry*. 2004 Mar;65(3):386-94. <http://amedeo.com/lit.php?id=15096079>
7. Ebert D. *Psychiatrie systematisch* 4. Auflage - Bremen UNI-MED, 2001.
8. Einsiedel RW von, Berger T, Weisbrod M, Unverricht S, Hartmann M. HIV-Patienten mit psychiatrischen Krankheiten. Behandlungsstrategien und Medikamenteninteraktionen. *Nervenarzt* 2001; 72: 204-15. <http://amedeo.com/lit.php?id=11268765>
9. Farber EW, Mc Daniel JS. Clinical management of psychiatric disorders in patients with HIV disease. *Psychiatr Q* 2002; 73: 5-16. <http://amedeo.com/lit.php?id=11780597>
10. Foster R, Olajide D, Everall IP. Antiretroviral therapy-induced psychosis: case report and brief review of the literature. *HIV Med*. 2003 Apr;4(2):139-44. <http://amedeo.com/lit.php?id=12702135>
11. Gunnell D, Ashby D. Antidepressants and suicide: what is the balance of benefit and harm. *BMJ* 2004; 329; 34-8. <http://amedeo.com/lit.php?id=15231620>
12. Gutierrez MM, Rosenberg J, Abramowitz W. An evaluation of the potential for pharmacokinetic interaction between escitalopram and the cytochrome P450 3A4 inhibitor ritonavir. *Clin Ther* 2003; 25: 1200-10. <http://amedeo.com/lit.php?id=12809966>
13. Himmelhoch S, Medoff DR. Efficacy of antidepressant medication among HIV-positive individuals with depression: a systematic review and meta-analysis. *AIDS Patient Care STDS*. 2005 Dec;19(12):813-22. <http://amedeo.com/lit.php?id=16375613>
14. Hypericum Depression Trial Study Group; Effect of *Hypericum perforatum* (St John's Wort) in Major Depressive Disorder. *JAMA* 2002; 287: 1807-14. <http://amedeo.com/lit.php?id=11939866>
15. Isacson G, Holmgren P, Ahlner J. Selective serotonin reuptake inhibitor antidepressants and the risk of suicide: a controlled forensic database study of 14,857 suicides. *Acta Psychiatr Scand*. 2005 Apr;111(4):286-90. <http://amedeo.com/lit.php?id=15740464>
16. Linde K, Ramirez G, Mulrow CD, Pauls A, Weidenhammer W, Melchart D. St John's wort for depression. *BMJ* 1996; 313: 253-258. <http://amedeo.com/lit.php?id=8704532>
17. Low-Beer S, Chan K, Hogg RS, et al. Depressive symptoms decline among persons on HIV protease inhibitors. Depressive symptoms decline among persons on HIV protease inhibitors. *J Acquir Immune Defic Syndr* 2000; 23: 295-301. <http://amedeo.com/lit.php?id=10836751>
18. Neidig JL, Smith BA, Brashers DE. Aerobic exercise training for depressive symptom management in adults living with HIV infection. *J Assoc Nurses AIDS Care* 2003; 14: 30-40.
19. Norman TR, Olver JS. New formulations of existing antidepressants. *CNS Drugs* 2004; 18: 505-20. <http://amedeo.com/lit.php?id=15182220>
20. Pignone MP, Gaynes BN, Rushton JL, et al. U.S. Preventive Services Task Force. Screening for depression: Recommendations and rationale. *Ann Intern Med* 2002; 136: 765-76. <http://amedeo.com/lit.php?id=12020146>
21. Röttgers HR, Weltermann BM, Evers S, Husstedt IW. Psychiatrische Akutsymptomatik als Erstmanifestation einer HIV-Infektion. *Nervenarzt* 2000; 71: 404-10. <http://amedeo.com/lit.php?id=10846717>
22. Sewell D. Schizophrenia and HIV. *Schizophr Bull* 1996; 22: 465-73.



## 29. Sexual Dysfunction in HIV/AIDS

Christoph Mayr and U. Fritz Bredeek

### Introduction

The “Multinational Survey of Aging Males” (MSAM), an international study of 14,254 men aged 40 to 70 years, showed a continuous vital interest in sexual activity in that age group: 83 % classified their sexual desire and interest as an important or very important component of their life and the average frequency of sexual activity was 5.8x /month. From other studies it is known that erectile dysfunction has a serious impact on the quality of life for men (Feldman 1994).

Many factors affect sexual function and sexual experience, with a key role being age (Feldman 1994). HIV infection can lead to sexual dysfunction because of the well-known interactions of the reproductive system with the immune system, the endocrine and the neuroendocrine systems. HIV infection has a significant psychological impact, and furthermore long-term antiretroviral therapy might have a negative psychological effect on the sexual experience. In patients on HAART, features of the lipodystrophy syndrome resemble the characteristics of the classic metabolic syndrome with raised insulin resistance, excess weight (abdominal girth > 102 cm), dyslipidemia and hypertension (> 130/85 mmHg). The clear association between metabolic syndrome and erectile dysfunction (ED) makes ED a predictive marker of the metabolic syndrome (Shabsigh in 2005).

The data relevant to sexual dysfunction in HIV patients is discussed in the following pages, with the acknowledgment that many questions remain regarding its causes and treatment.

### Definitions

Erectile dysfunction or Impotentia coeundi is defined as the “constant or repeated appearance of an inability to attain or maintain an erection which is sufficient for the satisfactory execution of sexual intercourse,” (NIH 1993). The diagnosis is made if the problem has existed for a minimum of 6 months, and if at least 70 % of attempts to carry out sexual intercourse have been unsuccessful.

It is important to clearly separate ED from libido disturbance, defined as a decreased or entirely absent sexual drive or desire, and ejaculation disturbance, clinically apparent most frequently as Ejaculatio praecox or Ejaculatio tarda.

### Etiology of sexual dysfunction in HIV/AIDS

The causes of sexual dysfunction (SD) are plentiful. A paradigm shift has taken place since 1980: improved diagnostic tests and better knowledge of the aging processes in men have led to the belief that 80 % of the cases have some organic involvement and 50 % of cases are exclusively organic in nature. A monopsychological cause is responsible for only 20 % of the cases (NIH in 1993). In HIV a “disease-specific” peculiarity lies in the fact that the probability of an SD is

not only increased by the chronic illness but by the comorbidities that are associated with HIV and the aging patient population, the psychosocial stress factors and the need for polypharmacy (Crum 2005).

## Age

The most important biological cause of ED is age. ED exists in variable degrees, from light (17 %) to moderate (17-34 %) to complete (5-15 %) in 52 % of all men aged 40 to 70 years (Feldman 1994). The overall prevalence of ED ranges from 7 % in men aged 18-29 years (Laumann 1999) to 85 % in men aged 76-85 years.

Both the increased lifespan and the higher quality of life have a growing influence on the incidence of SD in HIV patients. Furthermore, biological changes, such as the declining testosterone production, decreasing sensitivity of the erectile tissues secondary to the decreasing neural or hormonal stimuli, and circulatory problems occurring with age, are further boosted in the context of HIV infection and HIV therapy.

## Risk factors: diseases and comorbidities

Important ED risk factors coexist frequently in HIV patients, including excessive alcohol consumption, smoking and other recreational drug use; metabolic disorders (hyperlipidemia, diabetes mellitus); and cardiovascular disease, with hypertension being of particular importance. Pathophysiologically, most cases of ED are caused by neuronal (polyneuropathy) and vascular (micro- and macroangiopathy) changes; however, ED can also be an early sign of a metabolic syndrome.

Other possible risk factors are endocrine disorders, various neurological illnesses (i.e. disc prolapse) and infectious diseases. A frequent cause of ED in young men is chronic kidney or liver dysfunction (hepatitis, cirrhosis). Psychosocial problems, relationship conflicts and psychiatric illnesses (e.g., depression) are frequently related to sexual dysfunction. As a consequence, HIV patients have an increased risk for erectile dysfunction.

Table 1: Substances/Substance classes which may cause Erectile Dysfunction

Alcohol	Nicotine
Antihypertensives	Antidepressants
Diuretics	Antirheumatics (NSAR)
Lipid lowering agents	H2-Antagonists, proton pump inhibitors
Anticonvulsants	Tranquilizers
Opiates	Gestagens/estrogens
Chemotherapeutics, HAART	Amphetamines, hallucinogens

## Medication

Many drugs have a negative influence on sexual function, predominantly on the libido and the ability to gain an erection. See Table 1 for an overview of the relevant substance classes in this context. Antiretroviral medications are also associated with SD; and both the duration and the combination of therapies have an accelerat-



ing effect. In a standardized survey on 78 HIV-infected men who have sex with men (MSM), conducted by Cove in London in 2004, 69 % reported at least one sexual partial dysfunction and 38 % indicated ED. All antiretroviral drugs can decrease sexual function. Some studies (Colson 2002, Schrooten 2001, Martinez 1999) showed PIs to be the main culprit, however, at least one study found no effects of specific drug classes (Lallemant 2002). Our own observations suggest that combinations of NRTIs and PIs work synergistically.

## Ongoing research

An increasing prevalence of SD of up to 50 % was seen in HIV-infected men during the early 1990s (Meyer-Bahlber 1991, Catalan 1992, Tindall 1994). Similar results were observed in HIV-infected women (Brown 1993, Pergami 1993, Goggin 1998). In a prospective study (Lamba 2004) a clear increase in the prevalence of libido loss (48 %) and ED (25 %) was seen in HIV positive MSM on HAART, compared to HIV positive MSM not on antiretroviral therapy (26 % both) or HIV negative MSM (2 and 10 % respectively).

A survey of 904 HIV-infected men and women in 10 European countries (Schrooten 2001) showed that libido loss and ED existed significantly more frequently in patients on therapy containing a PI compared to patients naïve to PIs (40 vs. 16 % for LL and 34 vs. 12 % for ED, respectively). In a multivariate analysis, the following factors were identified for libido loss: current or previous use of a PI, symptomatic HIV infection, age, and MSM. Additionally, taking tranquilizers was found to be an independent risk factor for ED.

The impact of PIs in SD was also seen by Collazos (2002) in a prospective study of 189 patients. No correlation could be found between measured sex hormone levels and incidence of SD. Interestingly, in subjects taking a PI-containing regimen, testosterone levels were significantly higher compared to NNRTI-containing regimens in which 17 $\beta$ -estradiol levels were significantly elevated.

In a standardized questionnaire of 156 MSM, no role for PIs as the cause of SD could be ascertained (Lallemant 2002). 71 % of the participants indicated signs of SD since initiation of ART; however, in therapy stratified groups (PI: 71 %, without PI: 65 %, no PI in the last 4 weeks: 74 %) there were no significant differences seen between patients taking or not taking a PI. 18 % of the participants had already suffered from SD before the diagnosis of HIV infection, and 33 % before the initiation of ART. The impact of psychological factors is highlighted by one study, in which the rate of HIV-positive MSM with ED rose from 38 to 51 % with the use of condoms (Cove in 2004).

More recent research impressively underscores the positive effect of testosterone substitution in HIV-infected hypogonadotropic men (Rabkin 2000, Grinspoon 1998). Testosterone deficiency can cause weight loss, loss of muscle mass, osteopenia, and depression (Grinspoon 1996, Huang 2001, Rietschel 2000).

## Diagnosis of sexual dysfunction

A diagnostic work-up for the causes of SD is required before therapy. This includes a complete anamnesis with emphasis on sexual, social and family history and

should include potential social (recreational drug use) and familiar risk factors (i.e. diabetes mellitus), as well as a complete medication history. A thorough physical examination is obligatory. A diagnostic test of the morning blood level of testosterone is of central importance to determine the testicular endocrine function. The calculated index of free testosterone is the recommended parameter to follow, since this index reflects the real biological activity of testosterone. The direct determination of free testosterone by the lab has been identified as being unreliable ([www.issam.ch](http://www.issam.ch)).

Table 2: Laboratory diagnostics for erectile dysfunction

Special hormone diagnostics	General work-up
Testosterone (free circulating testosterone)	Cbc
Luteotropic hormone	Glucose, HbA1c
Follicular stimulating hormone	Lipid panel
Poss. LHRH	
Poss. HCG	possible: TSH
Poss. prolactin, PSA	Urine analysis

Low testosterone level requires determination of LH and FSH. Further work-up may require a LH or FSH stimulating test, usually handled by an endocrinologist, to exclude secondary hypogonadism. NPT (nocturne penile tumescence measurement) is considered as minimally invasive and measures nocturnal erections. 3-6 erections per night of at least 70 % rigidity, lasting 10 minutes, are considered normal values. The question of morning erections can serve as critical criterion for the sexual anamnesis.

Further andrological diagnostics include sonography of the scrotum and, if the mammary glands are enlarged or involvement of the hypophysis is suspected (i.e. by an increased prolactin or estrogen level), an MRI of the Sella turcica is indicated. Other diagnostic tests used for the vascular work-up include Doppler sonography of the penis and pharmacocavernosography; and for the neuro-physiological work-up a Caverosum EMG, vibrometry, sphincter- and N. pudendus-EMG. These are rarely necessary and left to the urologist.

## Therapy for sexual dysfunction

### General overview

Phosphodiesterase 5 inhibitors (PDE-5 inhibitors: sildenafil, vardenafil, tadalafil) have substantially improved the therapy of ED. They are simple to take, effective and, in general, relatively well tolerated. However, with the exception of a few private insurance companies, PDE-5 inhibitors are not covered by insurance plans. and so must be paid for by the patients themselves. With the introduction of PDE-5 inhibitors, intra-cavernous erectile tissue injection or the intra-urethral application of vasoactive prostaglandins has clearly receded into the background. Today, surgical interventions, such as penile vein surgery, revascularization surgery or prosthodontics, also no longer play a role.

For the HIV physician, it is important to know the interactions between PDE-5 inhibitors and HAART (particularly protease inhibitors and the NNRTI delavirdine). Through an inhibition of the cytochrome p450 enzyme system (CYP3A4) the level of PDE-5 inhibitors in the plasma is increased. This needs to be discussed with the patient. In particular, for patients using a boosted PI regimen PDE-5 inhibitors need to be started at a low dose. We specifically recommend a mini test dose at the beginning (e.g., 1/4 of a tablet of sildenafil 50 mg) and increase according to the success and side effects. Our experience indicates that a significant proportion of patients have the desired success with such a low dose. However, some patients do not achieve any effect with these low dosages (HIV infection of several years, multimorbidity, and psychological overlap). In these patients, the approved maximum dose should not be exceeded. Simultaneous administration of nitrate containing medications or substances containing nitrites (“poppers”!) is contraindicated since it may cause therapy-resistant hypotension.

Sexual activity is physically tiring and can be a strain on the cardiovascular system. If it is not clear whether a patient has an underlying cardiovascular problem, it is advised to screen for it before prescribing ED drugs. This is particularly true if unstable angina is suspected.

Apomorphine is a centrally effective dopamine receptor agonist. It is less effective and so is less important in the treatment of ED, but should be considered in patients with contraindications to PDE-5 inhibitors (APO-go ampullae, max. 100 mg s.c.). Apomorphine seems to be particularly helpful in psychogenic ED and light organic ED. Miscellaneous herbal substances (Yohimbine, Maca, *Turnera diffusa*) might have a positive effect on sexual function. However, systematic studies have not been performed. These substances have little side effects, however, monitoring, especially for possible interactions with HAART, is advisable. For psychosocial problems, relationship conflicts or depressive disorders, psychotherapeutic support and if necessary a sexual-medical discussion are advised.

## **PDE-5 inhibitors**

### **Sildenafil (Viagra™)**

Sildenafil was licensed in the USA in 1998, and shortly afterwards in Europe, as the first PDE-5 inhibitor. Sildenafil is available in dosages of 25, 50 and 100 mg. The first effects are seen between 12 and 40 mins (mean 25 mins) after taking the medication. This can be delayed if a fatty meal or alcohol is consumed simultaneously. The maximum plasma concentration is reached after approx. one hour, the clinical time of effectivity lies within approx. 8 – 12 hours.

The response rate is dependent on the etiology of ED, but varies between 43 and 83 %. The most frequent side effects seen are headaches (11 %), flushes (11 %), dyspepsia (3 %), dizziness (3 %), rhinitis (2 %) and color blindness (1 %).

Because of synergistic effects of PDE-5 inhibitors with nitrates and NO-donators (e.g. molsidomin) the simultaneous consumption of those two substance classes can lead to vasodilatation and therefore to severe hypotension. The combination is absolutely contraindicated. Clarification with the patient is needed, since the use of amyl nitrates (“poppers”), or similar substances used as sexual stimulants, is

prevalent in some of the groups more affected by the HIV epidemic (i.e. the gay scene).

Epidemiologic studies have so far not shown a statistically increased likelihood of angina pectoris, myocardial infarct or deaths under sildenafil use.

### **Vardenafil (Levitra™)**

Vardenafil was licensed in 2003. Phosphodiesterase 5 or the hydrolysis from cGMP is restrained approx. tenfold greater than by sildenafil, but the bioavailability, at 15 %, is low. Vardenafil is available in a dosage of 10 and 20 mg. First effects are seen approx. 15 to 30 mins after taking the medication; maximum plasma concentrations are reached after 60 mins. The clinical effect can last up to 12 hours.

Randomized, placebo-controlled studies, evaluating satisfaction with the amount of erection, showed a response rate of between 48 and 80 %. The response rate for successful sexual intercourse with ejaculation was approx. 75 %. Vardenafil is well tolerated by patients on antihypertensive therapy and is effective in these patients.

The same contraindication for the combination with nitrates and NO-donators exists. Adverse events include – as with sildenafil – headache (10-21 %), erythema (5-13 %), dyspepsia (1-6 %) and rhinitis (9-17 %).

### **Tadalafil (Cialis™)**

Tadalafil was licensed in 2003. Dosages of 10 and 20 mg are available. Compared to other PDE-5 inhibitors the maximum plasma concentration is reached at 2 hours, the first effect is noticeable after 15 to 20 minutes. Since the plasma half-life is approx. 17.5 hours, the medication is effective up to 36 hours after intake. Personal observations point to the fact that these circumstances promote the popularity of tadalafil in the gay scene (“weekend pill”).

Headache (7-21 %), dyspepsia and heartburn (1-17 %), myalgia (3-7 %), back pains (4-9 %), rhinitis (5 %) and flushes (1-5 %) are the most frequently observed side effects. Clinical influences on the cardiovascular system could not be observed; an increased incidence of myocardial infarction was not seen in any study.

Recent studies with MSM suggest a connection between the intake of drugs, the intake of PDE-5 inhibitors and sexual risk behavior (Swearingen in 2005, Jackson in 2005).

### **Testosterone**

Substitution therapy is clearly indicated for a documented lack of testosterone with clinical symptoms. Possible options are intramuscular injections (testosterone depot 250 mg i.m. with an interval of 14 to 21 days) or application in the form of a gel (e.g., testogel 25 mg/50 mg daily). Oral substitution is possible (e.g., andriol testocaps), but has not proved itself in clinical everyday life. The depot injection of 1,000 mg testosteroneundecanoat (Nebido™) has recently been recommended in intervals of 3 months with an increasing dose 6 weeks after the initial one. The advantages of the depot injection lie in the more even serum concentrations of testosterone. In times of limited recourses, it is advisable to document the testosterone deficit and the appropriate clinical symptoms precisely.

It has been pointed out that testosterone injections may promote growth of a carcinoma in situ of the prostate. A yearly PSA measurement appears to be advisable during therapy, as well as a baseline physical examination before starting substitution. However, this is not covered by health insurances. Moreover, with a positive family anamnesis, a urological consultation is advisable before the beginning of the substitution.

Hair loss, skin irritation (with the gel!), increase in serum liver enzymes, the lipid panel and the e-phoresis, as well as water retention in tissues, have been described as relevant side effects.

## References

- Braun M, Wassmer G, Klotz T et al. Epidemiology of erectile dysfunction: results of the 'Cologne Male Survey'. *International Journal of Impotence Research* 2000; 12: 305-11
- Brown GR, Rundell JR. A prospective study of psychiatric aspects of early HIV disease in women. *Gen Hosp Psychiatry* 1993; 15: 139-47
- Catalan J, Klimes I, Bond A et al. The psychosocial impact of HIV infection in men with hemophilia. *J. Psychosom Res.* 1992; 36: 409-16 <http://amedeo.com/lit.php?id=1483162>
- Collazos J, Martinez E, Mayo J et al. Sexual Dysfunction in HIV-infected Patients Treated with highly active antiretroviral therapy. *JAIDS* 2002; 31:322-26. <http://www.medscape.com/viewarticle/449091>
- Colson AE, Keller MJ, Sax PE et al. Male sexual dysfunction associated with antiretroviral therapy. *J AIDS* 2002; 30:27-32. <http://amedeo.com/lit.php?id=12048360>
- Cove J, Petrak J. Factors associated with sexual problems in HIV-positive gay men. *Int. J. STD & AIDS* 2004; 15: 732-6. <http://amedeo.com/lit.php?id=15537458>
- Crum NF, Furtek KJ, Olson PE et al. A Review of Hypogonadism and Erectile Dysfunction Among HIV-Infected Men During the Pre- and Post-HAART Eras: Diagnosis, Pathogenesis, and Management. *AIDS Patient Care STDS* 2005; 19:655-71. <http://amedeo.com/lit.php?id=16232050>
- Feldman HA, Goldstein I, Hatzichritou DG et al. Impotence and it's medical and psychosozial correlates: results of the Massachusetts Male Aging Study. *J Urol* 1994; 151: 54-61. <http://amedeo.com/lit.php?id=8254833>
- Goggin K,.. et al. The relationship of mood, endocrine, and sexual disorders in HIV+ women: an exploratory study. *Psychosom. Med.* 1998; 60:11-6. <http://amedeo.com/lit.php?id=9492233>
- Grinspoon S, Corcoran C, Lee K et al. Loss of lean body and muscle mass correlates with androgen levels in hypogonadal men with AIDS and wasting. *J Clin Endocrinol Metab* 1996; 81: 4051-8. <http://amedeo.com/lit.php?id=8923860>
- Grinspoon S, Corcoran C, Askari H et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1998; 129:18-26. <http://amedeo.com/lit.php?id=9652995>
- Huang JS, Wilkie SJ, Sullivan MP et al. Reduced bone density in androgen-deficient women with acquired immune deficiency syndrome wasting. *J Clin Endocrinol Metab* 2001, 86:3533-9. <http://amedeo.com/lit.php?id=11502775>
- Jackson G. PDE 5 inhibitors and HIV risk: current concepts and controversies. <http://amedeo.com/lit.php?id=16236072>
- Lallemant F, Salhi Y, Linard F et al. Sexual dysfunction in 156 ambulatory HIV-infected men receiving highly active antiretroviral therapy combinations with and without protease inhibitors. *JAIDS* 2002; 30: 187-90. <http://amedeo.com/lit.php?id=12045681>
- Lamba H, Goldmeier D, Mackie NE, et al. Antiretroviral therapy is associated with sexual dysfunction and with increased serum oestradiol levels in men. *Int J STD AIDS* 2004; 15:234-7. <http://amedeo.com/lit.php?id=15075015>
- Martinez E, Collazos J, Mayo J et al. Sexual dysfunction with protease inhibitors. *Lancet* 1999; 353:810-1. <http://amedeo.com/lit.php?id=10459968>
- Meyer-Bahlber HF et al. Sexual risk behaviour, sexual functioning and HIV disease progression in gay men. *J Sex Res* 1991; 28:3-27
- NIH Consensus Conference. Impotence. NIH Consensus Development Panel on Impotence. *JAMA* 1993;270:83-90. <http://amedeo.com/lit.php?id=8510302>
- Pergami A, Gala C, Martini S et al. The psychosocial impact of HIV infection in women. *J Psychosom Res* 1993; 37: 687-96. <http://amedeo.com/lit.php?id=8229900>

## 686 Sexual Dysfunction in HIV/AIDS

20. Schrooten W, Colebunders R, Youle M, et al. Sexual dysfunction associated with protease inhibitor containing highly active antiretroviral treatment. *AIDS* 2004; 15:1019-23. <http://amedeo.com/lit.php?id=11399984>
21. Shabsigh R et al. Erectile dysfunction as a predictor for metabolic syndrome. Results from the Massachusetts male aging study (MMAS). Abstract 1236, 100. Annual Meeting of the Am. Urol. Association 2005, San Antonio.
22. Swearingen SG, Klausner JD. Sildenafil use, sexual risk behavior, and risk for sexually transmitted diseases, including HIV infection. *Am J Med* 2005; 118:569-70 <http://amedeo.com/lit.php?id=15922685>
23. Tindall B, Forde S, Goldstein D et al. Sexual dysfunction in advanced HIV disease. *Aids Care* 1994; 6:105-7. <http://amedeo.com/lit.php?id=8186272>

## 30. HIV and Wish for Parenthood

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### Introduction

Since 1996, the optimization of antiretroviral therapy has led to great improvements in both the quality of life and life expectancy of people living with HIV/AIDS, at least in countries where HAART is widely available. A growing number of men and women living with HIV/AIDS feel encouraged to include parenthood in the planning of their lives. Procreation without risk, or at very low risk of infection for the uninfected partner or prospective child, is now an option for couples in which one or both partners are HIV-infected. The low materno-fetal transmission rate that can be achieved today has added to the acceptance of planned motherhood in seropositive women. Ethical and legal controversies have also been overcome in many countries.

Procreative options for HIV-affected couples theoretically vary from unprotected intercourse to several techniques of assisted reproduction, donor insemination or adoption. Usually, couples are advised against unprotected intercourse, as the priority is to prevent infection in the uninfected partner or child.

Transmission rates for unprotected heterosexual intercourse range from 1/1000 per contact (male to female) to < 1/1000 (female to male). These numbers are hardly useful in individual counseling situations. They can vary greatly depending on the stage of HIV disease, viral load or presence of other sexually transmittable diseases (Wawer 2005). Viral load in semen or genital secretions does not always correlate with that in plasma, and HIV can be detected in semen even when viral load in blood plasma is below the limit of detection. In other words, couples should not risk unprotected intercourse on the basis of the infected partner having an undetectable load. Consistent use of condoms can decrease the transmission risk in heterosexual relationships by 80-85 % (Davis 1999) and abstention from condom use, restricted to the time of ovulation, has been proposed as an option for discordant couples. Mandelbrot et al. (1997) reported a transmission rate of 4 % in 92 couples using carefully timed, but unprotected intercourse to conceive. Infections were restricted to couples who also reported inconsistent use of condoms outside the fertile period. In a small retrospective Spanish study (Barreiro et al. 2004) no infections occurred in a cohort of 74 HIV discordant couples who conceived by timed intercourse. However, data from couples who did not conceive were not available. The data so far cannot support unprotected intercourse limited to ovulation time as being a safe option for couples.

Donor insemination is an alternative safe option for a small number of couples, but due to legal restrictions it is only offered in a minority of centers. In the UK, for example, there are no restrictions on donor insemination, whereas in Germany the access is limited. In addition, most couples wish for a child that is the biological offspring of both parents. Adoption in many countries is merely a theoretical option: HIV infection of one partner usually renders this procedure very difficult, or even impossible in most countries (e.g. in Germany).

To minimize the risk of HIV transmission, the following options are recommended:

- Self-insemination or assisted reproduction in case of infection in the female partner
- Assisted reproduction with processed sperm in case of infection in the male partner

In several European countries, as well as in the US and Japan (Kato 2006), reproductive assistance for couples affected by HIV has been set up in the past few years. Equal access for HIV-positive women and men is granted in most, but not all of these countries.

## The safety of sperm washing

The technique of processing sperm from HIV-positive men prior to the insemination of their HIV-negative partners was first published by Semprini et al. in 1992. The first inseminations with sperm, washed free of HIV, were carried out in Italy and Germany as early as 1989 and 1991, respectively. Up to mid 2003, more than 1,800 couples had been treated in about 4,500 cycles, applying various techniques of assisted reproduction. More than 500 children have been born with no single seroconversion reported in the centers closely following the protocol of washing and testing the sperm prior to assisted reproductive techniques.

Native ejaculate mainly consists of three fractions: spermatozoa, seminal plasma and nuclear concomitant cells. HIV progenome and virus has so far been detected in the seminal plasma, the concomitant cells, and occasionally in immobile spermatozoa. Several studies have indicated that viable, motile spermatozoa are not likely to be a target for HIV infection (Pena 2003, Gilling-Smith 2003).

Motile spermatozoa can be isolated by standardized preparation techniques. After separation of the spermatozoa from plasma fractions and NSC (non-spermatozoa cells), the spermatozoa are washed twice with culture medium and resuspended in fresh culture medium. Incubation for 20–60 minutes allows motile sperm to “swim-up” to the supernatant. To be more certain that it is not contaminated with viral particles, an aliquot of the sample should be tested for HIV nucleic acid using highly sensitive detection methods (Weigel 2001, Gilling-Smith 2003, Pasquier 2006). Depending on the method, the lowest limit of detection is 10 cp/ml. After having studied the effectiveness of several methods of sperm processing, Anderson (2005) concluded that the combination of gradient density centrifugation and swim-up allows a 10,000-fold decrease of HIV-1 concentration in sperm. Since HIV could theoretically remain undetected, sperm washing is currently regarded as a very effective risk reduction, but not a risk-free method.

Several studies have shown that sperm washing can also reduce the risk of HCV in couples with male HCV-coinfection (Gilling-Smith 2003, Chu 2006).

Most of the European centers that offer assisted reproduction to HIV-discordant couples are part of the CREATHE-network, which aims to optimize treatment and safety of the methods as well as to compile an extensive database. There are high hopes that soon sufficient clinical cases can be reported to demonstrate the safety and reliability of sperm washing.



## Pre-conceptual counseling

The initial counseling of the couple should not only consider extensive information on all reproductive options available, diagnostics and prerequisites for reproductive treatment, but also the psychosocial situation of the couple. Important issues to discuss are the financial situation, current psychosocial problems, the importance of a network of social support from family or friends, and planning and perspectives about the future as a family, including possible disability or death of one of the partners (Nakhuda 2005). A supporting, empathic and accepting mode of counseling is advisable, as many couples feel distressed if their motives for, or entitlement to, parenthood are questioned. The risks of unprotected intercourse or improper condom use, not only during reproductive treatment but at all times, should be discussed (Sauer 2006). In cases where professional psychosocial services are not integrated, co-operation with organizations in the AIDS counseling system or self-help groups is advisable.

Possible stress occurring during the work-up and treatment of the couple should be discussed as well as doubts or fears of the couple. Many couples for example are afraid that their test results might indicate that parenthood is impossible.

If the male partner is HIV-infected, the couple need to know that the risk of HIV infection can be minimized, but not excluded. HIV-positive women have to be informed about the risks of vertical transmission and the necessary steps to avoid it. In any case, couples should know that even using state-of-the-art reproductive techniques, achieving a pregnancy cannot be guaranteed.

Table 1: Pre-treatment investigations

General	Comprehensive medical and psycho-social history
Female examination	Gynecological examination, sonography, tubal patency test, basal temperature if necessary, endocrine profile, cervical smear (cytology, microbiology) (UK: 2-5 FSH/LH and mid-luteal progesterone to evaluate female fertility) Serology (rubella, toxoplasmosis, syphilis, CMV, HBV, HCV)
HIV-specific assessments	HIV-associated and accompanying symptoms Blood glucose, GOT, GPT, GGT, complete blood count Ultra-sensitive HIV-PCR, CD4+/CD8+ T-cell counts HIV antibody test of the partner
Male examination	Spermiogram, semen culture Serology (HBV, HCV)

## Male HIV infection

Following the decision to conceive with reproductive assistance, the couple should undergo a thorough sexual health and infection screen, including information about the male partner's HIV status. The possibility of HIV infection in the female partner

also has to be excluded. In some cases, it might be necessary to treat genital infections before starting reproductive treatment.

Table 1 shows the investigations as provided in the *German recommendations for assisted reproduction in HIV-discordant couples* (Weigel 2001). There are small differences between the European centers. For the UK recommendations see Gilling-Smith et al. 2003.

After sperm washing and testing for HIV, spermatozoa can be utilized in three different reproductive techniques depending on whether the couples have any additional fertility issues: intra-uterine insemination (IUI), extracorporeal fertilization by conventional in-vitro fertilization (IVF) and intracytoplasmic sperm injection followed by embryonic transfer. According to the German recommendations, the choice of method depends on the results of gynecological and andrological investigations and the couple's preference. The success rate using IUI has been shown to be reduced if the sperm is washed and then cryopreserved before use. This is necessary in some centers where PCR testing of the washed sample for HIV cannot be done on the day of insemination. This, together with the fact that semen quality can be impaired in some HIV-infected men (Dulioust 2002, Müller 2003, Pena 2003, Nicopoullos 2004), results in a number of couples being advised to have IVF or ICSI.

Couples should be informed about three further important aspects:

- Sperm-washing and testing can greatly reduce the risk of infection, but cannot exclude it completely. Following recent study results, this risk seems to be only theoretical and cannot be expressed in percentages.
- During treatment, consistent condom use is of utmost importance. HIV infection of the woman in the early stages of pregnancy can increase the risk of transmission to the child. Sauer (2006) reported a case of seroconversion in a woman already enrolled in a reproductive treatment program, prior to the first treatment, presumably due to condom breakage.
- Most couples attending European centers have to pay for treatment costs themselves. These are dependent on the type of technique applied, and range from about 500 to 5,000 Euro per cycle. An exception is France, where couples have cost-free access to treatment. In Germany, health insurances sometimes cover a part of the costs, but they are not obliged to.

Even the most sophisticated techniques cannot guarantee successful treatment.

Following successful treatment, couples are usually monitored for HIV status for 6-12 months after childbirth, depending on the center.

## Female HIV infection

HIV-positive women with unimpaired fertility can conceive by self-insemination. Similar to cases in which the male partner is infected, the German guidelines recommend a fertility screen and further investigations, as listed in Table 1. In some cases, ovarian stimulation may be advisable. Ovarian stimulation, however, requires highly qualified supervision to avoid multiple gestations.

It is important to time ovulation accurately (i.e., by use of computer-based ovulation kits or urine sticks). A simple inexpensive way of determining whether the cycles are ovulatory, which can be helpful in women who have regular cycles, is a basal temperature chart beginning about three months before the first self-insemination.

At the time of ovulation, couples can either have protected intercourse with a spermicide-free condom and introduce the ejaculate into the vaginal cavity afterwards, or the ejaculate can be vaginally injected using a syringe or applied with a portio cap after masturbation. Thus, the conception remains in the private sphere of the couple.

More than two inseminations per cycle are not advisable, as the fraction of motile sperm in the ejaculate can decrease with any additional tries. Furthermore, the couple might experience psychological strain through extensive planning.

After 6–12 months of unsuccessful self-insemination, the couple should have further fertility investigations with a view to assisted conception.

## **Fertility disorders**

Fertility disorders in HIV-positive women seem to have a higher prevalence than in an age-matched HIV-negative population (Ohl 2005), but data still show some conflicting results. The reasons discussed include an increased rate of upper genital tract infections (Sobel 2000), menstrual disorders, and cervical infertility (Gilles 2005). Coll (2006) assumes the possibility of subclinical hypogonadism, potentially due to mitochondrial dysfunction. In some cases, women will only be able to conceive by assisted reproduction. Dependent on the fertility status of both partners, IVF and ICSI can be considered as methods of choice.

Recent data reported from the Strasbourg program indicated infertility problems in most HIV-positive women. IVF and ICSI were far more effective than IUI (Ohl 2005). In the Barcelona program, Coll (2006) observed a decreased pregnancy rate in HIV-positive women after IVF compared to age-matched HIV-negative controls and HIV-positive women who received donated oocytes. Results indicated a decreased ovarian response to hyperstimulation in HIV-positive women. A slightly impaired ovarian response to stimulation during 66 ICSI cycles in 29 HIV-positive women was also described by Terriou (2005). Martinet (2006) found no difference in ovarian response between HIV-positive and HIV-negative women in Brussels.

Although many centers throughout Europe offer assisted reproduction if the male partner is infected, access to treatment for HIV-positive women is currently only possible in Belgium, France, Germany, Great Britain, and Spain. Outside of Europe, some US centers offer reproductive assistance to seropositive women.

## **HIV infection of both partners**

A growing number of HIV-concordant couples now seek reproductive counseling. In some centers, these couples are also accepted for reproductive treatment. One option for couples without fertility disorders might also be timed unprotected intercourse. The discussion pertaining to the transmission of mutated drug-resistant virus between partners, is still ongoing. Up until now, only a very small number of

“super infections” have been published, and they only occurred in individuals who were not on a HAART regimen.

Couples should be offered the same range of fertility counseling and screening as HIV-discordant couples. The current health of each partner should be carefully evaluated with a full report from their HIV physician.

## Psychosocial aspects

- Experiences, from more than a decade of counseling, show the importance of offering professional psychosocial support to couples before, as well as during, and after reproductive treatment.
- Up to one third of the couples decide against the realization of their wish for parenthood after in-depth counseling (Vernazza 2006). Accepting the desire to become parents and dealing with the underlying motives as well as the psychosocial situation in an empathic way enables couples to see obstacles as well as to develop alternative perspectives if this wish cannot be realized for various reasons.
- Frustration and disappointment may accompany failures or strains during treatment (i.e., unsuccessful treatment cycles, premature termination of pregnancy). Left alone with these strains, couples sometimes decide to conceive using unprotected intercourse, to avoid further stress. Depending on the risk perception of the partners, this decision may sometimes be well planned, but other times be born out of despair. These couples might be at risk of infection: in 56 HIV-discordant couples participating in the Milan program who attempted spontaneous conception after failing to conceive with artificial insemination, at least one infection occurred (Semprini 2005).
- Psychiatric co-morbidities in one or both partners (i.e., substance abuse, psychoses) can be reasons to at least postpone treatment. Professional diagnosis and support will be necessary in these cases.
- Often, the central importance of the wish for parenthood of many migrant couples is overlooked in parts of the medical and psychosocial counseling system. Language or communication difficulties on both sides, ignorance of different cultural backgrounds and lack of acceptance of “strange” life-styles can lead to feelings of discrimination, isolation, helplessness or despair in couples.
- Issues concerning the welfare of the child should be openly discussed during reproductive counseling (Frodsham 2004). Many couples are concerned about a potential negative effect of antiretroviral drugs on their offspring. Severe impairment of the health of the prospective parents might lead to concerns for the future well-being of the child.

## The future

Following the improvements in morbidity and mortality of men and women living with HIV/AIDS, healthcare professionals encounter a growing number of couples or individuals who are contemplating parenthood. Having a child is the expression of a fulfilled partnership and an important perspective of life. This is no less true in

couples afflicted with HIV/AIDS. In the medical and psychosocial care of patients, it is important to create an environment where reproductive aspects and parenting can be discussed on an open and non-judgmental basis.

Future priorities include continued reporting of data pertaining to the applied methodologies as well as to the outcomes, reporting of adverse results and the follow-up of couples (Giles 2005). The first steps towards optimizing semen processing procedures, namely quality control of virus detection in processed sperm and laboratory safety, have already been taken (Politch 2004, Pasquier 2006, Gilling-Smith 2005).

Meikle (2006) criticizes the current state of “fragmented knowledge” regarding infertility service practices for HIV-positive patients. Long-term outcomes in couples that received reproductive assistance, health outcomes among children, both in medical as well as in psychosocial terms, and consensus regarding best practices or surveillance of care provided by clinics have received little notice until now.

A great number of couples cannot afford to pay for the high costs of treatment, or travel long distances, sometimes even to other countries, to reach specialized units. There is an urgent need to develop strategies for the counseling and support of these couples. A new, still controversially discussed approach is the use of PREP (pre-exposure prophylaxis) to limit the susceptibility of the uninfected woman during timed intercourse. In 2005, a small study was initiated in Switzerland (Vernazza 2006). Couples are advised to have unprotected intercourse only at the time of ovulation. Two hours before intercourse, the woman takes one tablet of tenofovir orally. In addition, it is suggested to apply estriol gel vaginally during the first 5 days of the menstrual cycle. Ideally, VL of the HIV-positive partner should be reduced to < 1,000 by adequate HAART to further lower the risk of infection.

The use of donated oocytes in reproductive services for HIV-positive women (Coll 2006) is limited in several countries due to legal and ethical considerations. It even enables treatment of women who have reached an age where reproductive assistance is not usually offered anymore due to the high risk of miscarriages and malformation and the low success rate of assisted reproduction techniques.

Medical and technical progress open a wider range of options for couples, but aside from comparing higher or lower success rates, there is an urgent need to discuss psychological and psychosocial issues pertaining to the welfare of parents and child.

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## References

1. Al-Khan A, Colon J, Palta V et al. Assisted reproductive technology for men and women infected with human immunodeficiency virus type 1. *Clin Infect Dis* 2003; 36: 195-200. [http://www.natap.org/2003/feb/020103\\_7.htm](http://www.natap.org/2003/feb/020103_7.htm)
2. Anderson DJ. Insemination with semen from HIV+ men: Technical considerations. Annual WHIN Meeting and Symposium, June 2005, San Juan, Puerto Rico. [http://depts.washington.edu/cfas/WHIN2005\\_sanjuan/anderson](http://depts.washington.edu/cfas/WHIN2005_sanjuan/anderson)
3. Barreiro P, Soriano S, Nunez M et al. Benefit of antiretroviral therapy for serodiscordant couples willing to be parents. *Int Cong Drug Therapy HIV 2004*, Glasgow: Abstract No. PL 13.3
4. Coll O, Suy A, Figueras F, et al. Decreased pregnancy rate after in-vitro fertilization in HIV-infected women receiving HAART. *AIDS* 2006; 20:121-3.
5. Chu MC, Pena JE, Nakhuda GS et al. Assessing the reproductive performance of men co-infected with HIV-1 and hepatitis C undergoing assisted reproduction. *Arch Gynecol Obstet* 2006, 274: 155-9.
6. Duloust E, Du AL, Costagliola D et al. Semen alterations in HIV-1 infected men. *Hum Reprod* 2002; 17: 2112-8. <http://amedeo.com/lit.php?id=12151446>
7. Frodsham LCG, Smith JR, Gilling-Smith C. Assessment of welfare of the child in HIV positive couples. *Hum Reprod* 2004; 19: 2420-3.
8. Giles M, Mijch A, Garland S. Assisted reproduction for HIV-infected couples. *Sexual Health* 2005, 2, 223-7.
9. Gilles C, Manigart Y, Konopnicki D. Management and outcome of cervical intraepithelial neoplasia lesions: a study of matched cases according to HIV status. *Gynec Oncol* 2005, 96, 122-8.
10. Gilling-Smith C, Almeida P. HIV, hepatitis B & hepatitis C and infertility: reducing risk. *Human Fertility* 2003; 6: 106-12. <http://amedeo.com/lit.php?id=12960441>
11. Gilling-Smith C, Emiliani S, Almeida P et al. Laboratory safety during assisted reproduction in patients with blood-borne viruses. *Hum Reprod* 2005; 20: 1433-8.
12. Kato S, Hanabusa H, Kaneko S et al. Complete removal of HIV-1 RNA and proviral DNA from semen by the swim-up method: assisted reproduction technique using spermatozoa free from HIV-1. *AIDS* 2006, 20: 967-973.
13. Mandelbrot L, Heard I, Henrion-Geant E, Henrion R. Natural conception in HIV-negative women with HIV-infected partners. *Lancet* 1997; 349: 850-1.
14. Martinet V, Manigart Y, Rozenberg S. Ovarian response to stimulation of HIV-positive patients during IVF treatment: a matched, controlled study. *Hum Reprod* 2006; 21: 1212-7.
15. Meikle S, Orleans M. Safeguarding the quality and safety of reproductive services for human immunodeficiency virus-positive adults. *Fert Ster* 2006; 2, 293-4.
16. Mencaglia L, Falcone P, Lentini GM et al. ICSI for treatment of human immunodeficiency virus and hepatitis C virus-serodiscordant couples with infected male partner. *Hum Reprod* 2005; 20: 2242-6.
17. Minkoff H, Santoro N. Ethical considerations in the treatment of infertility in women with HIV infection. *N Engl J Med* 2000; 342: 1748-50. <http://amedeo.com/lit.php?id=10841881>
18. Nakhuda GS, Pena JE, Sauer MV. Deaths of HIV-positive men in the context of assisted reproduction. *AIDS Patient Care STDS* 2005, 19:712-8.
19. Müller D, Gentili M, Beichert M, Melchert F, Weigel M. Sind HIV-Infizierte subfertil? – Und warum? *Reproduktionsmedizin* 2003; 19: 240
20. Nicopoulos JD, Almeida PA, Ramsay JW, Gilling-Smith C. The effect of HIV on sperm parameters and the outcome of IUI following sperm washing. *Hum Reprod* 2004; 19: 2289-97. <http://amedeo.com/lit.php?id=15242991>
21. Ohl J, Partisani M, Wittemer C, et al. Encouraging results despite complexity of multidisciplinary care of HIV-infected women with assisted reproduction. *Hum Reprod* 2005; 20: 3134-6. <http://amedeo.com/lit.php?id=16006462>

22. Pasquier C, Anderson D, Andreotti-Zaugg C, et al. Multicenter quality control of the detection of HIV-Genome in semen before medically assisted procreation. *J Med Vir* 2006; 78: 877-882
23. Pena JE, Thornton MH, Sauer MV. Assessing the clinical utility of in vitro fertilization with intracytoplasmic sperm injection in HIV type 1 serodiscordant couples: report of 113 consecutive cycles. *Fertil Steril* 2003; 80: 356-62. <http://amedeo.com/lit.php?id=12909499>
24. Pena JE, Thornton MH, Sauer MV. Reversible azospermia: anabolic steroids may profoundly affect HIV seropositive men undergoing assisted reproduction. *Obstetrics and Gynecology* 2003, 101: 1073-1075.
25. Pena JE, Thornton MH, Sauer MV. Complications of in vitro fertilization with intracytoplasmic sperm injection in HIV serodiscordant couples. *Arch Gynec Obstet* 2003; 268:198-201
26. Politch JA, Xu c, Tucker L, Anderson DJ. Separation of HIV type 1 from motile sperm by the double tube gradient method versus other methods. *Fertil Steril* 2004, 81: 440-7.
27. Sauer MV. Sperm washing techniques address the fertility needs of HIV-seropositive men: a clinical review. *Reproductive BioMedicine Online*; 2005, 10: 135-140. [www.rbmonline.com/Article/1541](http://www.rbmonline.com/Article/1541)
28. Sauer MV. HIV seroconversion in a woman preparing for assisted reproduction: an inherent risk in caring for HIV-serodiscordant couples. *Reproductive BioMedicine Online*; 2006, 12: 375-277. [www.rbmonline.com/Article/2108](http://www.rbmonline.com/Article/2108)
29. Semprini AE. European clinical experience with assisted reproductive technology in HIV-discordant couples. Annual WHIN Meeting & Symposium 2005, San Juan, Puerto Rico. [http://depts.washington.edu/cfas/WHIN2005\\_sanjuan/semprini](http://depts.washington.edu/cfas/WHIN2005_sanjuan/semprini)
30. Sobel JD. Gynecologic infections in HIV-infected women. *Clin Infect Dis* 2000, 31:1225-33. <http://amedeo.com/lit.php?id=11073756>
31. Terriou P, Auquier P, Chabert-Orsini V et al. Outcome of ICSI in HIV-1-infected women. *Hum Reprod* 2005 Oct; 20 (10): 2838-43.
32. Thornton AC, Romanelli F, Collins JD. Reproduction decision making for couples affected by HIV: a review of the literature. *Topics HIV Med* 2004; 12: 61-6. <http://www.iasusa.org/pub/topics/2004/issue2/61.pdf>
33. Waver MJ, Gray RH, Sewankambo NK et al. Rates of HIV-1 transmission per coital act, by stage of HIV-1 infection, in Rakai, Uganda. *J Infect Dis* 2005, 191: 1403-9. <http://amedeo.com/lit.php?id=15809897>
34. Weigel MM, Gentili M, Beichert M, Friese K, Sonnenberg-Schwan U. Reproductive assistance to HIV-discordant couples – the German approach. *Eur J Med Res* 2001; 6: 259-62. <http://amedeo.com/lit.php?id=11432794>
35. Weigel MM, Kremer H, Sonnenberg-Schwan U, Gözl J et al. Diagnostics and treatment of HIV-discordant couples who wish to have children. *Eur J Med Res* 2001; 6: 317-21. <http://amedeo.com/lit.php?id=11496900>
36. Vernazza PL, Hollander L, Semprini AE et al. HIV-discordant couples and parenthood: how are we dealing with the risk of transmission? *AIDS* 2006, 20: 635-6. <http://amedeo.com/lit.php?id=16470136>





## 31. Post-Exposure Prophylaxis (PEP)

Thore Lorenzen and Katrin Graefe

### Transmission

According to the current state of knowledge, there is a risk of HIV transmission if an HIV-negative person comes into contact with the blood, semen or vaginal fluids of an HIV-positive source person. In the opinion of leading experts, exposure of intact skin to HIV-contaminated body fluids (e.g. blood) is not sufficient to transfer the virus.

Transmission is possible if HIV-containing material enters the body by:

- accidental needlestick injury or incision by surgical instruments
- exposure of damaged skin or mucosal membranes
- unprotected sexual intercourse with an HIV-infected person
- IDU sharing needle or equipment
- transfusion of HIV-contaminated blood or blood products

### Transmission risk

HIV is not a very contagious pathogen. The transmission rate after a high-risk contact is about 1:1000 to 1:100. Compared with HIV, the transmission rate for hepatitis C virus is 10 times higher, and 100 times higher for hepatitis B virus. Factors for the probability of transmission are the amount of incorporated virus and the exposure time. Contact with body fluids of a patient with a high viral load probably holds a higher risk of contagion than a similar contact with body fluids of a patient under HAART with a suppressed viral load. Additionally, quick removal of infectious material e.g. from damaged skin or mucosal membrane by washing or disinfection supposedly decreases the risk of an HIV infection. For percutaneous contact with HIV-containing blood, experts assume an infectiousness of 0.3 % in total. According to retrospective data, calculations have been established to assess the transmission risks of accidental exposure more precisely (see Table 1).

Table 1: Calculations to assess estimated individual transmission risk after HIV exposure \*

Type of Exposure	Relative Risk
Deep needlestick injury or cut	16 : 1
Fresh blood on the penetrating instrument	5 : 1
Penetrating needle previously placed in blood vessel	5 : 1
Source person with high viral load (acute HIV infection, AIDS without ART)	6 : 1
Exposition of mucosal membrane	1 : 10
Exposition of inflammatory damaged skin	1 : 10

\* Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2004

Table 2 provides information about the assumed transmission risk of other types of exposure to HIV, for example unsafe sexual contact. Since only few data exist, these risk estimates vary enormously and should be judged with caution.

Table 2: HIV transmission risk for unprotected sexual contacts \*

Type of contact	Transmission risk per contact
Unprotected receptive anal sex with HIV-infected person	0.82 % (0.24 – 2.76)
Unprotected receptive anal sex with person of unknown HIV status	0.27 % (0.06 – 0.49)
Unprotected insertive anal sex with person of unknown HIV status	0.06 % (0.02 – 0.19)
Unprotected receptive vaginal sex	0.05 – 0.15 %
Unprotected insertive vaginal sex	0.03 – 5.6 %
Oral sex	Probability not known, single cases have been reported, particularly with incorporation of semen in the mouth.

\* Source: German-Austrian PEP recommendations 2004

Evaluation of primary HIV infection indicates that the establishment of the virus in various tissue reservoirs does not occur immediately after incorporation of the virus. Within a small time frame the establishment of the virus might be prevented by post-expositional intervention.

Simian models show that in mucosal membranes HIV primarily infects the local immunocompetent cells such as Langerhans' cells. These cells or their siblings migrate to regional lymph nodes: detection of HIV in the blood occurs days later. The process of local infection and migration of the cells to the lymph nodes takes approximately 24 to 48 hours. Theoretically, treatment with appropriate substances may avert a systemic infection.

## Effectiveness and limitations of PEP

Early reports on the use of AZT after occupational needlestick injuries date from 1989. An analysis of retrospective case-control studies shows that even prophylaxis with a single substance after exposure reduces the probability of an infection by approximately 80 %. The combination of multiple drugs is supposedly even more potent. Unfortunately there have been transmissions despite the use of PEP. Transmission of HIV infection cannot always be prevented. Many of the described cases of PEP failure following accidental exposure were treated with AZT monotherapy. But there are also reports about failures of antiretroviral combination therapies.

With increasing prevalence of resistance under antiretroviral therapy future problems might arise with transmission of resistant virus strains. International surveillance studies report increasing transmission rates of mutant viruses. But, what to do is still unclear: resistance testing takes days (or perhaps weeks). So results would be too late to avoid spread of resistant viruses using appropriate antiretrovirals.

## When is PEP indicated?

The risk of possible HIV transmission should be considered by a physician experienced in HIV treatment. It is important to establish whether the source person has a supposed or confirmed HIV infection. Unclear HIV status should be clarified: the source person should be asked for consent to perform HIV testing. Denial of consent has to be respected as per actual jurisdiction. If the source person agrees to be tested, this should be performed immediately. For source persons with confirmed HIV infection, the actual HIV viral load, stage of disease, former and current HAART have to be taken into consideration. Optimally, a resistance analysis would also be available. The affected person should be asked about the first aid procedures that have already been performed.

After clarification of these queries, the exposed person has to be informed about possible adverse effects and risks of pharmaceutical PEP. It should be emphasized that none of the administered substances is approved for use in this special setting. This is also important with regard to the coverage of cost, especially for sexual exposure. The medication cannot be prescribed at the expense of the health insurance. PEP for occupational exposure is usually covered by statutory accident insurance (in Germany).

Table 3 gives an overview of situations in which PEP is recommended according to current guidelines. This serves as an orientation, although deviations may be necessary in individual cases.

## Potential risks of PEP

The risks of PEP mainly concern the adverse effects of the antiretroviral substances. Most frequently, this refers to gastrointestinal symptoms such as nausea, vomiting or diarrhea. Changes of hematology, transaminases or creatinine are also possible. Additionally, there have been reports of elevated triglycerides and cholesterol levels, and insulin resistance even in short term use of protease inhibitors.

It is unknown whether the temporary use of antiretroviral substances may lead to long term side effects, but this seems secondary since the main emphasis is to prevent a chronic and potentially life-threatening disease. For pregnant women particular caution is required since data concerning teratogenicity are lacking.

## 700 Post-Exposure Prophylaxis (PEP)

Table 3: Overview of recommendations for usage of PEP

<b>Occupational Exposure</b>	
<ul style="list-style-type: none"> <li>• Percutaneous needlestick injury with hollow needle (body fluids with high viral load: blood, liquor, material from biopsies, cultured virus)</li> </ul>	Recommended
Deep injury (e.g. cuts), apparently blood stained	Recommended
Needle used before for intravenous injection	Recommended
<ul style="list-style-type: none"> <li>• Superficial injury (e.g. with surgical needle)</li> </ul>	Considered
Where required, exemption, if source person has AIDS or high viral load	Recommended
<ul style="list-style-type: none"> <li>• Contact of mucosal membrane or damaged skin with fluids with high viral load</li> </ul>	Considered
<ul style="list-style-type: none"> <li>• Percutaneous contact with body fluids other than blood (e.g. urine, saliva)</li> </ul>	Not Recommended
<ul style="list-style-type: none"> <li>• Contact of intact skin with blood (including high viral load)</li> </ul>	Not Recommended
<ul style="list-style-type: none"> <li>• Contact of skin or mucosal membranes with body fluids such as urine or saliva</li> </ul>	Not Recommended
<b>Non-occupational Exposure</b>	
<ul style="list-style-type: none"> <li>• Transfusion of HIV containing blood products (or if HIV contamination is highly probable)</li> </ul>	Recommended
<ul style="list-style-type: none"> <li>• Unprotected receptive sex with an HIV-infected person</li> </ul>	Recommended
<ul style="list-style-type: none"> <li>• IDU sharing contaminated needle or equipment</li> </ul>	Recommended
<ul style="list-style-type: none"> <li>• Unprotected receptive oral sex with ejaculation with an HIV-infected person</li> </ul>	Considered
<ul style="list-style-type: none"> <li>• Kissing and other sexual contacts without semen-/blood-mucosal membrane contact</li> </ul>	Not Recommended
<ul style="list-style-type: none"> <li>• Accidental needlestick injury</li> </ul>	Not Recommended

Source: German-Austrian PEP recommendations against HIV infection 2004

### Initial interventions

According to actual guidelines, depending on the type of exposure, different procedures are recommended following HIV-exposure. Following needlestick or cut injuries with HIV-contaminated instruments, fluid should be expressed by squeezing the tissue surrounding the wound and striking out proximal blood vessels towards the wound. Too intense massage or contusions have to be avoided. The wound should be flushed with an alcoholic, virucidal antiseptic for a minimum of 10 minutes. For skin that has been in contact with blood or body fluids removal of the infectious material and subsequent extensive disinfection with a skin antiseptic appears sufficient. After contamination of an eye, immediate flush with PVP iodine solution 2.5 % is recommended. If such a solution is not available the eye should be washed with water. The oral cavity should be washed several times (about 10-

15 seconds each) with an aqueous solution or preferably 80 % alcohol after contact with potentially infectious material.

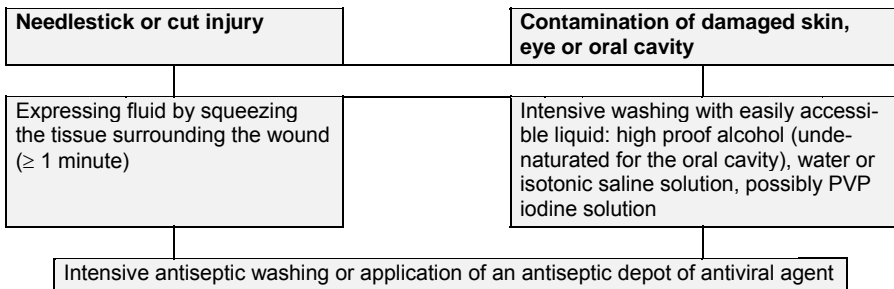


Figure 1: Recommended initial interventions after HIV exposure (Source: German-Austrian recommendations for Post-Exposure Prophylaxis against HIV infection 2004)

Persons, who, through sexual exposure, have contact of anal or genital mucosae to infectious material, should wash the penis with soap and water; genital mucosae should be flushed with water after urination, which might wash contaminated material from the urethra. Intense washing of the vagina or intestines is not recommended due to an elevated risk of injuries.

After implementation of the initial interventions, an expert in HIV treatment and antiretroviral therapy should be consulted for the decision whether pharmaceutical PEP needs to be started.

Accurate evaluation and documentation of the course of the accident is very important, especially for occupational exposure. The process of informing the patient about the risks of PEP needs to be documented carefully and the patient should sign an informed consent.

## Initiation of PEP

Time is the most important factor for initiation of PEP. The best chance to prevent transmission is within the first 24 hours of exposure. After that time period, the risk of systemic spread of the virus increases. Initiating PEP after more than 72 hours following exposure does not seem reasonable.

PEP should be initiated as soon as possible, preferably within 2 hours of exposure.

If, in this short time frame, consultation with a physician experienced in HIV treatment is not possible, it might be advantageous to just initiate PEP. Interrupting a regimen that isn't indicated is always an option.

Actual recommendations prefer a regimen with a combination of antiretroviral substances given over 4 weeks, preferably consisting of two NRTIs and one PI (see Table 5). NNRTIs, especially nevirapine, should not be used for PEP because of the risk of severe adverse effects (hepatotoxicity). For efavirenz such severe adverse effects have not been reported but the impact on the CNS, particularly in the first weeks of intake, limits its use for PEP.

## 702 Post-Exposure Prophylaxis (PEP)

As far as possible, known resistance against antiretroviral substances of the source person should be taken into account; in many cases, this information will not be available. Therefore use of standard regimens for PEP has proven practical. Recommended combinations are shown in Table 5.

Tenofovir is not listed in the table of standard prophylaxis. This substance needs one phosphorylation step less for activation compared to the other NRTIs, which might be beneficial concerning time. Until now, no evidence exists confirming this hypothesis, but current trials are ongoing. The new recommendations for nonoccupational exposure to HIV in the United States mention tenofovir equally to the other NRTIs.

In addition, since 2003, the fusion inhibitor T-20 (Fuzeon™) has been approved for HIV therapy. Other substances, such as attachment inhibitors or coreceptor antagonists are under investigation. These new substances with their mechanism to inhibit viral cell entry might also be interesting with regard to increasing efficiency of PEP. Focusing on enfuvirtide, the subcutaneous route of application and high costs currently prevent its routine use.

Furthermore, difficulties in monitoring a possible seroconversion might occur as development of antibodies against enfuvirtide may lead to cross reaction with gp41 and a positive result in the HIV-ELISA test.

During pregnancy, PEP should only be used after careful consideration of the benefits since there are only limited data on teratogenic effects. In any case, advice of a physician experienced in HIV treatment and pregnancies should be obtained.

After contact with potentially infectious material, not only HIV, but also other diseases might be transmitted. Apart from HIV, testing should be performed for hepatitis B and C. Persons exposed to HBV should receive hepatitis B immunoglobulin and a vaccine series simultaneously if they have no sufficient vaccination status.

Table 4: Recommended antiretroviral combinations for HIV Post-exposure Prophylaxis \*

NRTI	PI / NNRTI
AZT + 3TC	Nelfinavir (Viracept™, 2 x 1,250 mg)
1. Combivir™ (2 x 300/150 mg)	or
or	Lopinavir/r (Kaletra™, 2 x 400/100 mg)
2. Retrovir™ (2 x 250 mg) plus	plus or
Epivir™ (2 x 150 mg or 1 x 300 mg)	Indinavir (Crixivan™, 3 x 800 mg)
	or
	Efavirenz (Sustiva™, 1 x 600 mg)

\* Source: German-Austrian PEP recommendations. Comment: routine use of efavirenz is not recommended by the editors of HIV medicine due to high incidence of CNS events.

After unprotected sexual contacts, transmissions of other STDs such as syphilis or gonorrhoea should be taken into consideration. Testing is recommended at 2 and 4 weeks after exposure.

## Management of PEP

After initiation of PEP, the patient should not be discharged without a follow-up consultation. The consecutive intake of antiretrovirals demands a high amount of discipline and potential adverse effects should be diagnosed early. Persons exposed to HIV are under high psychological pressure. It is important not to dramatize the situation but emphasize the generally low risk of transmission.

Adverse effects generally include gastrointestinal symptoms. Less frequent are changes in hematology, liver enzymes or creatinine. These should be tested after 14 days and again after 4 weeks - at the end of the PEP. Despite close monitoring, different studies report discontinuation rates of 40-50 %. At the end of a completed course or discontinued PEP, HIV testing should be performed after 6 weeks, 3 and 6 months. An HIV PCR only needs to be performed if there is reasonable suspicion of a primary HIV infection.

In any case, the patient has to be advised to practice safer sex until a reliable negative test result is achieved.

## References

1. Bassett IV, Freedberg KA, Walensky RP. Two drugs or three? Balancing efficacy, toxicity, and resistance in postexposure prophylaxis for occupational exposure to HIV. *Clin Infect Dis* 2004, 39:395-401. <http://amedeo.com/lit.php?id=15307008>
2. Centers for Disease Control. Guidelines for prevention of transmission of HIV and hepatitis B virus to health-care and public-safety workers. *MMWR* 1989; 3-37. <http://hiv.net/link.php?id=42>
3. Centers for Disease Control. Serious adverse events attributed to nevirapine regimens for postexposure prophylaxis after HIV exposures-worldwide, 1997-2000. *MMWR* 2001, 49:1153-6. <http://hiv.net/link.php?id=43>
4. Centers for Disease Control. Updated U.S. Public Health Service guidelines for the management of occupational exposures to HBV, HCV, and HIV and recommendations for postexposure prophylaxis. *MMWR* 2001, 50: 1-41. <http://hiv.net/link.php?id=44>
5. Daar ES, Moudgil T, Meyer RD, Ho DD. Transient high levels of viremia in patients with primary HIV type 1 infection. *N Engl J Med* 1991, 324: 961-4. <http://amedeo.com/lit.php?id=1823118>
6. Deutsch-Österreichische Empfehlungen zur Postexpositionellen Prophylaxe der HIV-Infektion. Aktualisierung September 2004 [http://www.daignet.de/media/PEP\\_0904.pdf](http://www.daignet.de/media/PEP_0904.pdf)
7. Gerberding JL. Incidence and prevalence of HIV, hepatitis B virus, hepatitis C virus, and cytomegalovirus among health care personnel at risk for blood exposure: final report from a longitudinal study. *J Infect Dis* 1994, 170:1410-1417. <http://amedeo.com/lit.php?id=7995979>
8. Gounden YP, Moodley J: Exposure to HIV among healthcare workers in South Africa. *Int J Gynaecol Obstet* 2000, 69:265-70. <http://amedeo.com/lit.php?id=12156187>
9. Ippolito G, Puro V, De Carli G, Italian Study Group On Occupational Risk Of HIV Infection. The risk of occupational HIV in health care workers. *Arch Int Med* 1993, 153:1451-8. <http://amedeo.com/lit.php?id=8512436>
10. Katz MH, Gerberding JL. Postexposure treatment of people exposed to the HIV through sexual contact or injection-drug use. *N Engl J Med* 1997, 336: 1097-1100. <http://amedeo.com/lit.php?id=9091810>
11. Limb S, Kawsar M, Forster GE. HIV post-exposure prophylaxis after sexual assault: the experience of a sexual assault service in London. *Int J STD AIDS* 2002, 13:602-5. <http://amedeo.com/lit.php?id=12230923>
12. Martin LN, Murphey-Corb M, Soike KF, Davison-Fairburn B, Baskin GB. Effects of initiation of 3'-azido,3'-deoxythymidine (zidovudine) treatment at different times after infection of rhesus monkeys with simian immunodeficiency virus. *J Infect Dis* 1993, 168:825-35. <http://amedeo.com/lit.php?id=7690823>
13. Merchant RC, Mayer KH. Perspectives on new recommendations for nonoccupational HIV postexposure prophylaxis. *JAMA* 2005, 293:2407-9. <http://amedeo.com/lit.php?id=15900012>
14. Noor MA, Lo JC, Mulligan K, et al. Metabolic effects of indinavir in healthy HIV-seronegative men. *AIDS* 2001, 15: F11-F18. <http://amedeo.com/lit.php?id=11399973>

## 704 Post-Exposure Prophylaxis (PEP)

15. Otten RA, Smith DK, Adams DR, et al. Efficacy of postexposure prophylaxis after intravaginal exposure of pig-tailed macaques to a human-derived retrovirus (HIV type 2). *J Virol* 2000, 74:9771-5. <http://amedeo.com/lit.php?id=11000253>
16. Panel on Clinical Practices for Treatment of HIV Infection. Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. <http://hiv.net/link.php?id=48>
17. Parkin JM, Murphy M, Anderson J, El-Gadi S, Forster G, Pinching AJ. Tolerability and side-effects of post-exposure prophylaxis for HIV infection. *Lancet* 2000, 355:722-3. <http://amedeo.com/lit.php?id=10703807>
18. Puro V. Genotypic resistance tests for the management of postexposure prophylaxis. *Scand J Infect Dis Suppl.* 2003; 35 Suppl 106: 93-8. <http://amedeo.com/lit.php?id=15000596>
19. Puro V, Cicalini S, De Carli G et al. Towards a standard HIV post exposure prophylaxis for healthcare workers in Europe. *Euro Surveill* 2004; 9. <http://www.eurosurveillance.org/em/v09n06/0906-222.asp>
20. Smith DK, Grohskopf LA, Black RJ, et al. Antiretroviral postexposure prophylaxis after sexual, injection-drug use, or other nonoccupational exposure to HIV in the United States: recommendations from the U.S. Department of Health and Human Services. *MMWR Recomm Rep* 2005;54:1-20. <http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5402a1.htm>
21. Spira AI, Marx PA, Patterson BK, et al. Cellular targets of infection and route of viral dissemination after an intravaginal inoculation of simian immunodeficiency virus into rhesus macaques. *J Exp Med* 1996, 183:215-25. <http://amedeo.com/lit.php?id=8551225>
22. Tokars JI, Marcus R, Culver DH, et al. Surveillance of HIV infection and zidovudine use among health care workers after occupational exposure to HIV-infected blood. *Ann Intern Med* 1993, 118:913-9. <http://amedeo.com/lit.php?id=8387737>
23. Weinberg GA, Luque AE, Brown ST, et al. Nonoccupational HIV postexposure prophylaxis. *JAMA.* 2005 Oct 5;294(13):1615; author reply 1615-6. <http://amedeo.com/lit.php?id=16204657>
24. Weiss SH, Goedert JJ, Gartner S, et al. Risk of HIV-1 infection among laboratory workers. *Science* 1988, 239: 68-71. <http://amedeo.com/lit.php?id=3336776>
25. Robert Koch-Institut : RKI Ratgeber Infektionskrankheiten. Merkblätter für Ärzte. Hepatitis B, aktualisierte Fassung vom August 2002. <http://hiv.net/link.php?id=141>
26. Robert Koch-Institut : Empfehlungen der Ständigen Impfkommission (STIKO) am Robert Koch-Institut. *Epidemiologisches Bulletin* 2002, 28: 227-42. <http://hiv.net/link.php?id=142>



## Part 5

# Drugs

## 32. Drug Profiles

Bernd Sebastian Kamps, Christian Hoffmann

### 3TC – Lamivudine

3TC is a well-tolerated cytidine analog. Resistance develops rapidly: only a single point mutation (M184V) is required. However, this mutation can increase the sensitivity of AZT-resistant viruses and reduce viral fitness. 3TC is also effective against hepatitis B virus.

**Trade name:** Epivir™; component of Combivir™, Trizivir™, and Kivexa™.

Epivir™ tablets: 150 mg or 300 mg 3TC; oral solution 10 mg/ml

Combivir™ tablets: 150 mg 3TC + 300 mg AZT

Trizivir™ tablets: 150 mg 3TC + 300 mg AZT + 300 mg abacavir

Kivexa™ tablets: 300 mg 3TC + 600 mg abacavir

Zeffix™ tablets: 100 mg 3TC. Only for HBV, **never** for HIV!!! (dose is too low!).

**Class:** Nucleoside Reverse Transcriptase Inhibitor (NRTI)

**Manufacturer:** GlaxoSmithKline

**Indication:** HIV infection (also chronic hepatitis B)

**Oral dose Epivir™:** 300 mg qd or 150 mg bid. Dose adjustment is required with reduced creatinine clearance:

CrCl (ml/min)	Dose
30–49	150 mg qd
15–29	150 mg first dose, then 100 mg qd
5–14	150 mg first dose, then 50 mg qd
<5	50 mg first dose, then 25 mg qd

Children receive 4 mg/kg, with a maximum of 150 mg bid.

**Oral dose Combivir™:** 1 tablet bid, containing 150 mg 3TC and 300 mg AZT.

**Oral dose Trizivir™:** 1 tablet bid, containing 150 mg 3TC and 300 mg AZT and 300 mg abacavir.

Patients with a creatinine clearance below 50 ml/min or with impaired liver function should not receive Combivir™ or Trizivir™, but rather the individual formulations of AZT and 3TC.

**Side effects:** rare when using the individual drug. Fatigue, nausea, vomiting, diarrhea, headache, insomnia, myalgia and arthralgia may occur, but are usually due to other drugs in the combination (see AZT and abacavir). Peripheral polyneuropathy, pancreatitis and lactic acidosis are rare.

**Comments/Warnings:** 3TC requires dose adjustment based on renal function.

**Internet sources:**

USA: Epivir™: <http://hiv.net/link.php?id=49>

Combivir™: <http://hiv.net/link.php?id=50>

Trizivir™: <http://hiv.net/link.php?id=51>

**References:**

1. Anderson PL, Kakuda TN, Kawle S, Fletcher CV. Antiviral dynamics and sex differences of zidovudine and lamivudine triphosphate concentrations in HIV-infected individuals. *AIDS* 2003; 17: 2159-68. <http://amedeo.com/lit.php?id=14523272>
2. Bani-Sadr F, Palmer P, Scieux C, Molina JM. Ninety-six-week efficacy of combination therapy with lamivudine and tenofovir in patients coinfecting with HIV-1 and wild-type hepatitis B virus. *Clin Infect Dis* 2004; 39: 1062-4. <http://amedeo.com/lit.php?id=15472862>
3. DeJesus E, McCarty D, Farthing CF, et al. Once-daily versus twice-daily lamivudine, in combination with zidovudine and efavirenz, for the treatment of antiretroviral-naïve adults with HIV infection: a randomized equivalence trial. *Clin Infect Dis* 2004; 39: 411-8. <http://amedeo.com/lit.php?id=15307010>
4. Kanwal F, Gralnek IM, Martin P, Dulai GS, Farid M, Spiegel BM. Treatment alternatives for chronic hepatitis B virus infection: a cost-effectiveness analysis. *Ann Intern Med* 2005; 142: 821-31. Abstract: <http://amedeo.com/lit.php?id=15897532>
5. Miller V, Stark T, Loeliger AE, Lange JM. The impact of the M184V substitution in HIV-1 reverse transcriptase on treatment response. *HIV Med* 2002, 3:135-45. <http://amedeo.com/lit.php?id=12010361>
6. Sension MG, Bellos NC, Johnson J, et al. Lamivudine 300 mg QD versus continued lamivudine 150 mg BID with stavudine and a protease inhibitor in suppressed patients. *HIV Clin Trials* 2002; 3:361-70. <http://amedeo.com/lit.php?id=12407485>
7. Winters MA, Bosch RJ, Albrecht MA, Katzenstein DA. Clinical impact of the M184V mutation on switching to didanosine or maintaining lamivudine treatment in NRTI-experienced patients. *J Infect Dis* 2003; 188: 537-40. <http://amedeo.com/lit.php?id=12898440>

## Abacavir (ABC)

Abacavir is a guanosine analog with good CNS penetration. Abacavir is licensed for once-daily dosing, both as the individual drug and as a component of the fixed-dose combination Kivexa™. The main problem with abacavir is the hypersensitivity reaction (HSR): abacavir should be prescribed only by HIV-experienced clinicians! The drug is otherwise well tolerated, and probably has little mitochondrial toxicity. Cross-resistance occurs with numerous other NRTIs. Resistance develops rapidly with triple nuke regimens containing 3TC and tenofovir.

**Trade name:** Ziagen™; component of Kivexa™/ Epzicom™ and Trizivir™

Ziagen™ tablets: 300 mg abacavir; oral solution 20 mg/ml in 240 ml bottles

Kivexa/Epzicom™ tablets: 600 mg abacavir + 300 mg 3TC

Trizivir™ tablets: 300 mg abacavir + 150 mg 3TC + 300 mg AZT

**Drug class:** NRTI

**Manufacturer:** GlaxoSmithKline

**Indications:** HIV infection

**Oral dose:** 300 mg bid or 600 mg qd. Abacavir can be taken with or without food.

**Side effects:** abacavir causes a hypersensitivity syndrome (HSR) in about 2 to 8 % of patients. This usually occurs within the first six weeks after initiation of treatment. Pruritus and rash are common, but may also be absent. The HSR may present as just fever and slowly developing malaise. Gastrointestinal complaints (nausea,

diarrhea, abdominal pain) and fatigue are also possible, but not necessarily linked to the HSR. Elevated liver function tests, insomnia and dizziness are rare. There is probably a genetic predisposition for the HSR.

**Comments/Warnings:** abacavir is contraindicated in cases with previously diagnosed abacavir hypersensitivity and after interruption of therapy, if a prior HSR cannot be definitively ruled out in retrospect. Patients should be well advised about the HSR, but not frightened. With only mild symptoms (see below), abacavir should not be stopped too quickly, as an intercurrent infection may simulate the HSR. Therapy may be continued for one or two days under close observation.

Rechallenge after suspected HSR is contraindicated (may be fatal).

Patients should be told to consult a doctor **immediately** if at least two of the following symptoms occur:

- fever
- shortness of breath, sore throat or cough
- rash (erythema and/or pruritus)
- nausea or vomiting or diarrhea or abdominal pain
- extreme fatigue or diffuse pain or general malaise

Abacavir should not be used in a triple nuke combination with 3TC and tenofovir due to rapid development of resistance.

**Interactions:** 0.7 g/kg ethanol (e.g. 0.5 l wine) increases the AUC of abacavir by 41 % and increases half-life by 26 %.

#### Internet sources:

USA: <http://hiv.net/link.php?id=53>

#### References:

1. Carr A, Workman C, Smith DE, et al. Abacavir substitution for nucleoside analogs in patients with hiv lipotrophy: a randomized trial. *JAMA* 2002, 288: 207-15. <http://amedeo.com/lit.php?id=12095385>
2. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis* 2004; 39: 1038-46. Epub 2004 Sep 10. <http://amedeo.com/lit.php?id=15472858>
3. Hewitt RG. Abacavir hypersensitivity reaction. *Clin Infect Dis* 2002, 34: 1137-42. <http://amedeo.com/lit.php?id=11915004>
4. Ibbotson T, Perry C. Lamivudine/Zidovudine/Abacavir: triple combination tablet. *Drugs* 2003; 63: 1089-98. <http://amedeo.com/lit.php?id=12749741>
5. Mallal S, Nolan D, Witt C, et al. Association between presence of HLA-B\*5701, HLA-DR7, and HLA-DQ3 and hypersensitivity to HIV-1 reverse-transcriptase inhibitor abacavir. *Lancet* 2002, 359: 727-32. <http://amedeo.com/lit.php?id=11888582>
6. Martin A, Smith DE, Carr A, Ringland C, Amin J, Emery S et al. Reversibility of lipotrophy in HIV-infected patients 2 years after switching from a thymidine analogue to abacavir: the MITOX Extension Study. *AIDS* 2004; 18: 1029-36. <http://amedeo.com/lit.php?id=15096806>
7. Martinez E, Arnaiz JA, Podzamczar D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with HIV infection. *N Engl J Med* 2003; 349: 1036-46. <http://amedeo.com/lit.php?id=12968087>
8. Moyle GJ, DeJesus E, Cahn P, et al. Abacavir once or twice daily combined with once-daily lamivudine and efavirenz for the treatment of antiretroviral-naive HIV-infected adults. *J AIDS* 2005; 38: 417-25. Abstract: <http://amedeo.com/lit.php?id=15764958>
9. Sankatsing SU, Prins JM. Agranulocytosis and fever seven weeks after starting abacavir. *AIDS* 2001, 15: 2464-5.
10. Toerner JG, Cvetkovich T. Kawasaki-like syndrome: abacavir hypersensitivity? *Clin Infect Dis* 2002; 34: 131-3.

## Acyclovir

**Trade name:** Zovirax™ (among many others)

**Drug class:** virostatic

**Manufacturer:** acyclovir is manufactured by several companies. Generics are usually cheaper than the originally introduced formulation (Zovirax™).

**Indications:** treatment and prophylaxis of HSV and VZV infections.

**Dose:** for genital HSV infection: 400 mg po 5x/day for 7 days. In severe cases (ulcerating genital herpes) intravenous treatment with 5-10 mg/kg iv tid. For HSV encephalitis or HSV esophagitis 10 mg/kg iv tid.

For dermatomal herpes zoster 800 mg po 5x/day for 7 days. In cases of disseminated or complicated herpes zoster 10 mg/kg iv tid.

**Side effects:** rare. Headache, nausea and elevation of creatinine may occur. Phlebitis can occur with intravenous dosing.

**Comments/Warnings:** Initiation of treatment for HSV infections should be within the first 24 hours after appearance of symptoms if possible, for VZV infection within the first 4 days. Adequate fluid intake is important.

**Internet sources:**

USA: <http://hiv.net/link.php?id=55>

**References:**

1. Conant MA, Schacker TW, Murphy RL, et al. Valaciclovir versus aciclovir for herpes simplex virus infection in HIV-infected individuals: two randomized trials. *Int J STD AIDS* 2002, 13:12-21. <http://amedeo.com/lit.php?id=11802924>
2. Gnann JW Jr, Whitley RJ. Clinical practice. Herpes zoster. *N Engl J Med* 2002, 347:340-6.
3. Ioannidis JP, Collier AC, Cooper DA, et al. Clinical efficacy of high-dose acyclovir in patients with HIV infection: a meta-analysis of randomized individual patient data. *J Infect Dis* 1998, 178:349-59. <http://amedeo.com/lit.php?id=9697714>
4. Wagstaff AJ, Faulds D, Goa KL. Aciclovir. A reappraisal of its antiviral activity, pharmacokinetic properties and therapeutic efficacy. *Drugs* 1994; 47:153-205. <http://amedeo.com/lit.php?id=7510619>

**Agenerase™** see Amprenavir

**Ambisome™** see Amphotericin B

## Amphotericin B

**Trade names:** Amphotericin B™, Ambisome™

Amphotericin B™: 50 mg amphotericin B powder/bottle

Liposomal amphotericin B: 50 mg vials of Ambisome™

**Drug class:** antimycotic

**Manufacturer:** Amphotericin B™: Bristol-Myers Squibb; Ambisome™: Gilead

**Indications:** Fungal infections, including aspergillosis, cryptococcosis, treatment-resistant candidiasis, histoplasmosis, coccidioidomycosis.

**Indications for Ambisome™:** life-threatening situations with the mycoses listed above. Mainly in cases of pre-existing impaired renal function, elevations in creatinine on amphotericin B (creatinine > 2.0 mg/dl) or poor tolerability of amphotericin B infusions.

Ambisome™ is very expensive!

**Dose (per day) of amphotericin B™:**

Aspergillosis: 1.0 to 1.5 mg/kg

Candidiasis: 0.2 to 0.8 mg/kg

Coccidioidomycosis: 0.5 to 1.0 mg/kg

Cryptococcosis: 0.7 to 1.0 mg/kg

Histoplasmosis: 0.5 to 1.0 mg/kg

**Dose of Ambisome™:** initial daily dose of 1 mg/kg, if necessary this may be gradually increased to 3 mg/kg.

**Side effects:** nephrotoxicity! Hypokalemia! Gastrointestinal complaints. Frequent: fever, chills, and hypotension approx. 10-20 min after starting infusion. Thrombophlebitis. Side effects are generally less severe with Ambisome™.

**Comments/Warnings:** daily monitoring of electrolytes (for non-liposomal amphotericin B a central venous line is always necessary due to thrombophlebitis, hypokalemia and the usually required potassium substitution! Sodium should be kept at normal levels), creatinine, BUN, ALT, blood count. If possible, do not combine with other nephrotoxic drugs.

Always prehydrate with 1000 ml 0.9 % NaCl. First test dose always with 5 mg in 250 ml 5 % glucose over 30–60 min under monitoring of blood pressure and pulse for the first hour. If the test dose is tolerated, half of the planned maintenance dose may subsequently be given on the same day. In cases of fever/chills (can be very impressive!): 50 mg pethidine iv plus 1 ampule clemastine (Tavegil™), may be repeated after 30 min; steroids if complaints persist (prednisolone 1 mg/kg).

If side effects are severe, switch to Ambisome™, which is probably not more effective (apyrexia, survival) than conventional amphotericin B, but significantly better tolerated and less nephrotoxic (no test dose, no prehydration, no central line necessary). Never mix amphotericin infusions, and always protect from light. Infuse slowly! The longer the infusion time (>3 hours), the better the tolerability! Always use 5 % glucose as a diluent!

**Internet sources:**

USA: Ambisome™: <http://hiv.net/link.php?id=58>

**References:**

1. Arathoon EG, Gotuzzo E, Noriega LM, et al. Randomized, double-blind, multicenter study of caspofungin versus amphotericin B for treatment of oropharyngeal and esophageal candidiases. *Antimicrob Agents Chemother* 2002, 46: 451-7. <http://amedeo.com/lit.php?id=11796357>
2. Baddour LM, Perfect JR, Ostrosky-Zeichner L. Successful use of amphotericin B lipid complex in the treatment of cryptococcosis. *Clin Infect Dis* 2005; 40: Suppl 6: Abstract: <http://amedeo.com/lit.php?id=15809927>
3. Coukell AJ, Brogden RN. Liposomal amphotericin B. Therapeutic use in the management of fungal infections and visceral leishmaniasis. *Drugs* 1998, 55:585-612. <http://amedeo.com/lit.php?id=9561346>

4. Johnson PC, Wheat LJ, Cloud GA, et al. Safety and efficacy of liposomal amphotericin B compared with conventional amphotericin B for induction therapy of histoplasmosis in patients with AIDS. *Ann Intern Med* 2002, 137:105-9. <http://amedeo.com/lit.php?id=12118965>
5. Larsen RA, Bauer M, Thomas AM, Graybill JR. Amphotericin B and fluconazole, a potent combination therapy for cryptococcal meningitis. *Antimicrob Agents Chemother* 2004; 48: 985-91. <http://amedeo.com/lit.php?id=14982793>
6. Wheat LJ, Cloud G, Johnson PC, et al. Clearance of fungal burden during treatment of disseminated histoplasmosis with liposomal amphotericin B versus itraconazole. *Antimicrob Agents Chemother* 2001, 45:2354-7. <http://amedeo.com/lit.php?id=11451696>

## Amprenavir

Due to the high pill burden, unboosted dosing of amprenavir (8 pills bid) is hardly acceptable today. When boosted with ritonavir, the drug undoubtedly has better efficacy, but was nevertheless inferior to efavirenz in one study. In the USA, the improved formulation, fosamprenavir, has been licensed since 2003 (see corresponding chapter). It is possible that all Agenerase™ formulations will be withdrawn from the market. Currently available remain pediatric capsules and solution.

**Trade name:** Agenerase™

50 mg capsule. Solution: 240 ml with 15 mg pro ml.

**Drug class:** protease inhibitor

**Manufacturer:** GlaxoSmithKline

**Indications:** Pediatric HIV patients with previous PI-treatment.

**Oral dose:** According to body weight: 2 x 20 mg/kg (capsules). 2 x 22.5 mg/kg (solution) – the bioavailability of amprenavir oral solution is about 14 % less.

**Side effects:** mostly gastrointestinal with nausea, vomiting, diarrhea, flatulence, tenesmus, perioral paresthesia. Occasional headache, fatigue, and rash in 5-10 %. See fosamprenavir.

**Comments/Warnings:** amprenavir solution contains 50 % propylene glycol. It is therefore contraindicated for concurrent administration with metronidazole.

**Internet sources:**

USA: Capsules: <http://hiv.net/link.php?id=61>

Solution: <http://hiv.net/link.php?id=62>

Combination with ritonavir: <http://hiv.net/link.php?id=63>

**References:**

1. Chapman TM, Plosker GL, Perry CM. Fosamprenavir: a review of its use in the management of antiretroviral therapy-naïve patients with HIV infection. *Drugs* 2004; 64: 2101-24. <http://amedeo.com/lit.php?id=15341507>
2. Mauss S, Schmutz G, Kuschak D. Unfavourable interaction of amprenavir and lopinavir in combination with ritonavir? *AIDS* 2002; 16: 296-7.
3. Yogev R, Kovacs A, Chadwick EG, Homans JD, Lou Y, Symonds WT. Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother* 2005; 49: 336-41. Abstract: <http://amedeo.com/lit.php?id=15616313>
4. Zachary KC, Hanna GJ, D'Aquila RT. HIV type 1 hypersusceptibility to amprenavir in vitro can be associated with virus load response to treatment in vivo. *Clin Infect Dis* 2001, 33: 2075-7. <http://amedeo.com/lit.php?id=11700580>

## Atazanavir

Atazanavir, in comparison to other PIs, has a favorable lipid profile. Whether this will have implications for lipodystrophy remains to be seen. Another advantage is once daily dosing. The most important side effects of atazanavir are elevated bilirubin levels, which may even be associated with jaundice. In some countries, Atazanavir is not licensed for primary therapy. Where possible, it should always be boosted with ritonavir.

**Trade name:** Reyataz™; abbr. AZV.

100, 150 and 200 mg capsules

**Drug class:** protease inhibitor (PI)

**Manufacturer:** Bristol-Myers Squibb

**Indications:** treatment-experienced adults experiencing therapy failure.

**Oral dose:** treatment-experienced adults: 300 mg atazanavir once daily combined with 100 mg ritonavir once daily, and taken with a meal. Also possible: 400 mg once daily together with a meal.

**Side effects:** hepatotoxicity, hyperbilirubinemia (up to 50 %), elevated transaminases; jaundice is not unusual. Diarrhea in approx. 30 %. In addition: nausea, vomiting, headache, insomnia, abdominal pain, rash, and asthenia. In contrast to other PIs: No dyslipidemia. The effect on lipodystrophy remains unknown. QT prolongation.

**Comments/Warnings:** capsules should be swallowed without chewing.

The following are contraindicated: cisapride, pimozide, midazolam, triazolam, simvastatin, lovastatin, ergotamines, calcium antagonists and proton pump inhibitors. Life-threatening interactions may occur with concomitant administration of amiodarone, lidocaine (systemic dosing), tricyclic anti-depressants and quinidine (measure plasma levels!).

It should not be given with rifampin (reduces plasma levels of atazanavir by 90 %), St. John's wort, and antacids; caution with sildenafil, vardenafil.

When combined with efavirenz, it may be necessary to increase atazanavir dosage (dose adjustment not established, TDM helpful)

Do not combine with indinavir.

Atazanavir should not be taken simultaneously with ddI. Combination of these drugs is only possible if ddI is taken at least two hours after atazanavir/ritonavir and food. The reason: the buffer in ddI chewable tablets prevents absorption of atazanavir.

Rifabutin: reduce rifabutin dose by 75 % (instead of 300 mg daily, give only 150 mg every other day or three times per week).

Clarithromycin: do not combine boosted atazanavir with clarithromycin.

Caution with impaired liver function. Atazanavir is contraindicated in patients with Child Pugh B and C.

Contraception: an alternative to the pill is recommended.

**Internet sources:**

USA: <http://hiv.net/link.php?id=224>



**References:**

1. Barreiro P, Rendon A, Rodriguez-Novoa S, Soriano V. Atazanavir: the advent of a new generation of more convenient protease inhibitors. *HIV Clin Trials* 2005; 6: 50-61. Abstract: <http://amedeo.com/lit.php?id=15765311>
2. Colonna R, Rose R, McLaren C, Thiry A, Parkin N, Friborg J. Identification of I50L as the signature atazanavir (ATV)-resistance mutation in treatment-naive HIV-1-infected patients receiving ATV-containing regimens. *J Infect Dis* 2004; 189: 1802-10. <http://amedeo.com/lit.php?id=15122516>
3. Friedland G, Andrews L, Schreiber T, et al. Lack of an effect of atazanavir on steady-state pharmacokinetics of methadone in patients chronically treated for opiate addiction. *AIDS* 2005; 19: 1635-41. Abstract: <http://amedeo.com/lit.php?id=16184033>
4. Goldsmith D, Perry C. Atazanavir. *Drugs* 2003; 63: 1679-93. <http://amedeo.com/lit.php?id=12904086>
5. Guffanti M, De Pascalis CR, Seminari E, et al. Pharmacokinetics of amprenavir given once or twice a day when combined with atazanavir in heavily pre-treated HIV-positive patients. *AIDS* 2003; 17: 2669-71. <http://amedeo.com/lit.php?id=14685066>
6. Havlir DV, O'Marro SD. Atazanavir: new option for treatment of HIV infection. *Clin Infect Dis* 2004; 38: 1599-604. <http://amedeo.com/lit.php?id=15156449>
7. Mobius U, Lubach-Ruitman M, Castro-Frenzel B, et al. Switching to atazanavir improves metabolic disorders in antiretroviral-experienced patients with severe hyperlipidemia. *J Acquir Immune Defic Syndr* 2005; 39: 174-80. Abstract: <http://amedeo.com/lit.php?id=15905733>
8. Murphy RL, Sanne I, Cahn P, Phanuphak P, Percival L, Kelleher T et al. Dose-ranging, randomized, clinical trial of atazanavir with lamivudine and stavudine in antiretroviral-naive subjects: 48-week results. *AIDS* 2003; 17: 2603-14. <http://amedeo.com/lit.php?id=14685054>
9. Petersen K, Riddle MS, Jones LE, et al. Use of bilirubin as a marker of adherence to atazanavir-based antiretroviral therapy. *AIDS* 2005; 19: 1700-2. Abstract: <http://amedeo.com/lit.php?id=16184044>
10. Schnell T, Schmidt B, Moschik G, et al. Distinct cross-resistance profiles of the new protease inhibitors amprenavir, lopinavir, and atazanavir in a panel of clinical samples. *AIDS* 2003; 17: 1258-61. <http://amedeo.com/lit.php?id=12819531>
11. Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated HIV-infected patients. *Antimicrob Agents Chemother* 2004; 48: 2091-6. <http://amedeo.com/lit.php?id=15155205>
12. Wood R, Phanuphak P, Cahn P, et al. Long-term efficacy and safety of atazanavir with stavudine and lamivudine in patients previously treated with nelfinavir or atazanavir. *J Acquir Immune Defic Syndr* 2004; 36: 684-692. <http://amedeo.com/lit.php?id=15167287>

## Atovaquone

**Trade names:** Wellvone™, Mepron™

Suspension with 750 mg/5 ml

**Drug class:** antibiotic

**Manufacturer:** GlaxoSmithKline

**Indications:** PCP prophylaxis in cases of hypersensitivity to cotrimoxazole; also reserve drug for treatment of mild to moderate PCP and for cerebral toxoplasmosis.

**Dose:** for treatment 750-1500 mg bid (i.e. 1-2 measuring spoons of 5 ml bid) for 21 days. For prophylaxis 750 mg bid (i.e. 1 measuring spoon of 5 ml bid) or 1,500 mg qd.

**Side effects:** gastrointestinal complaints such as nausea, vomiting and diarrhea are frequent (often mild), as are rashes, which occur in approx. 20 %. More rarely headache, insomnia. Elevated liver enzymes, elevated amylase. Anemia, leukopenia.

**Comments/Warnings:** atovaquone should be taken with meals, ideally with fatty dishes, as this improves absorption. In most countries, atovaquone is considerably more expensive than other drugs for PCP prophylaxis.

Rifampin and possibly also rifabutin lower plasma levels of atovaquone by approx. 50 %. The combination with these two drugs is therefore not recommended. Fluconazole probably increases levels.

Lopinavir seems to lower the plasma concentration of atovaquone. Dose adjustment may be necessary.

**Internet sources:**

UK: <http://hiv.net/link.php?id=174>

**References:**

1. Chan C, Montaner J, Lefebvre EA, et al. Atovaquone suspension compared with aero-solized pentamidine for prevention of *Pneumocystis carinii* pneumonia in HIV-infected subjects intolerant of trimethoprim or sulfonamides. *J Infect Dis* 1999, 180:369-76. <http://amedeo.com/lit.php?id=10395851>
2. Chirgwin K, Hafner R, Leport C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with AIDS: ACTG 237/ANRS 039 Study. *Clin Infect Dis* 2002, 34:1243-50. <http://amedeo.com/lit.php?id=11941551>
3. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998, 339:1889-95. <http://amedeo.com/lit.php?id=9862944>
4. Hughes WT, Dankner WM, Yogev R, et al. Comparison of atovaquone and azithromycin with trimethoprim-sulfamethoxazole for the prevention of serious bacterial infections in children with HIV infection. *Clin Infect Dis* 2005; 40: 136-45. Abstract: <http://amedeo.com/lit.php?id=15614703>
5. Rosenberg DM, McCarthy W, Slavinsky J, et al. Atovaquone suspension for treatment of *Pneumocystis carinii* pneumonia in HIV-infected patients. *AIDS* 2001, 15:211-4. <http://amedeo.com/lit.php?id=11216929>

## Azithromycin

**Trade names:** Ultreon™, Zithromax™

Ultreon™ tablets with 600 mg

Zithromax™ tablets with 250 mg

Zithromax™ powder for suspension with 200 mg per 5 ml

**Drug class:** macrolide antibiotic

**Manufacturer:** Pfizer, Mack-Ilert

**Indications:** treatment and prophylaxis of MAC infection. Infections of the upper and lower respiratory tract, otitis media. Uncomplicated gonorrhoea, uncomplicated genital infections with *Chlamydia trachomatis*, chancroid.

**Dose:** primary prophylaxis of disseminated MAC infection: 1200 mg azithromycin weekly (2 tablets Ultreon™ 600 mg per week). MAC treatment: 1 tablet Ultreon™ 600 mg qd, only in combination with ethambutol and rifabutin.

Uncomplicated gonorrhoea: 1000 mg azithromycin as a single dose.

Uncomplicated genital infections with *Chlamydia trachomatis*: if an alternative to doxycycline is needed, 1000 mg azithromycin may be given as a single dose.

Chancroid: 1000 mg azithromycin as a single dose.

**Side effects:** mainly gastrointestinal with stomach cramps, loss of appetite, nausea, vomiting, diarrhea. Rarely, elevations of transaminases, cholestatic jaundice. Reversible ototoxicity with high doses. Rarely taste disturbances.

**Comments/Warnings:** caution in cases of known macrolide allergy! Reduced absorption of azithromycin with concurrent dosing of Mg- and Al-containing antacids. These drugs should be taken one hour before or two hours after azithromycin.

**Internet sources:**

USA: <http://hiv.net/link.php?id=176>

**References:**

1. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with HIV. *Clin Infect Dis* 2000; 31:1245-52. <http://amedeo.com/lit.php?id=11073759>
2. Havlir DV, Dube MP, Sattler FR, et al. Prophylaxis against disseminated *Mycobacterium avium* complex with weekly azithromycin, daily rifabutin, or both. *N Engl J Med* 1996, 335:392-8. <http://amedeo.com/lit.php?id=8676932>
3. Oldfield EC 3rd, Fessel WJ, Dunne MW, et al. Once weekly azithromycin therapy for prevention of *Mycobacterium avium* complex infection in patients with AIDS: a randomized, double-blind, placebo-controlled multicenter trial. *Clin Infect Dis* 1998, 26:611-9. <http://amedeo.com/lit.php?id=9524832>
4. Phillips P, Chan K, Hogg R, et al. Azithromycin prophylaxis for *Mycobacterium avium* complex during the era of HAART: evaluation of a provincial program. *Clin Infect Dis* 2002, 34: 371-8. <http://amedeo.com/lit.php?id=11774085>
5. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for *Mycobacterium avium* complex bacteremia in patients with HIV infection. *Clin Infect Dis* 1998, 27:1278-85. <http://amedeo.com/lit.php?id=9827282>

## AZT – Zidovudine

AZT, a thymidine analog and the oldest HIV drug, continues to be a component of many HAART regimens and transmission prophylaxis. Extensive data, good CNS penetration. The most important side effect is myelotoxicity which may cause severe anemia. Unfortunately, once daily dosing is not possible.

**Trade name:** Retrovir™; component of Combivir™ and Trizivir™

Retrovir™ capsules: 100 mg or 250 mg, tablets: 300 mg; 200 ml bottles for infusion (10 mg/ml), 10 mg/ml syrup

Combivir™ tablets: 300 mg AZT + 150 mg 3TC

Trizivir™ tablets: 300 mg AZT + 150 mg 3TC + 300 mg abacavir

**Manufacturer:** GlaxoSmithKline

**Indications:** HIV infection. Prevention of maternal-fetal HIV transmission.

**Dose:** 250 mg bid. In Combivir™ and Trizivir™ 300 mg bid.

Creatinine clearance below 20 ml/min: 300 to 400 mg daily.

Hemodialysis: 300 mg daily. Hepatic failure: 100 mg tid.

**Side effects:** nausea, vomiting, abdominal discomfort, headache, myalgia, and dizziness. Macrocytic anemia (MCV almost always elevated), rarely neutropenia. Elevations in LDH, CPK and transaminases may occur. Episodes of lactic acidosis are rare.

**Comments/Warnings:** do not combine with d4T! There is increased myelotoxicity if used with other myelosuppressive drugs, especially ganciclovir, but also co-trimoxazole, dapson, pyrimethamine, interferon, sulfadiazine, amphotericin B, ribavirin and various other chemotherapeutic agents. Anemia can develop even after months on AZT.

As ribavirin antagonizes the antiviral activity of AZT in vitro, Concurrent use of AZT and ribavirin should be avoided.

Initially monthly monitoring of blood count, transaminases, CPK and bilirubin. Gastrointestinal complaints can be treated symptomatically and usually subside after a few weeks.

AZT should always be a component of transmission prophylaxis!

**Internet sources:**

USA: Retrovir™ tablets: <http://hiv.net/link.php?id=66>

Retrovir™ IV infusion: <http://hiv.net/link.php?id=67>

Combivir™: <http://hiv.net/link.php?id=68>

Trizivir™: <http://hiv.net/link.php?id=69>

**References:**

1. Antoniou T, Gough K, Yoong D, Arbess G. Severe anemia secondary to a probable drug interaction between zidovudine and valproic acid. *Clin Infect Dis* 2004; 38: e38-40. Epub 2004 Feb 11. <http://amedeo.com/lit.php?id=14986271>
2. Burger DM, Meenhorst PL, Koks CHW, Beijnen JH. Drug interactions with zidovudine. *AIDS* 1993, 7:445-60.
3. Dabis F, Elenga N, Meda N, et al. 18-Month mortality and perinatal exposure to zidovudine in West Africa. *AIDS* 2001, 15: 771-779. <http://amedeo.com/lit.php?id=11371692>
4. Dunn D. Short-term risk of disease progression in HIV-1-infected children receiving no antiretroviral therapy or zidovudine monotherapy: a meta-analysis. *Lancet* 2003; 362: 1605-11. <http://amedeo.com/lit.php?id=14630440>
5. Fischl MA: The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial. *N Engl J Med* 1987, 317:185 -91. <http://amedeo.com/lit.php?id=3299089>
6. Leroy V, Karon JM, Alioum A, et al. Twenty-four month efficacy of a maternal short-course zidovudine regimen to prevent mother-to-child transmission of HIV-1 in West Africa. *AIDS* 2002, 16: 631-41. <http://amedeo.com/lit.php?id=11873008>
7. Ruane PJ, Richmond GJ, DeJesus E, et al. Pharmacodynamic effects of zidovudine 600 mg once/day versus 300 mg twice/day in therapy-naive patients infected with human immunodeficiency virus. *Pharmacotherapy* 2004; 24: 307-12. <http://amedeo.com/lit.php?id=15040643>

**Caelyx™** see Doxorubicin, liposomal

## Cidofovir

**Trade name:** Vistide™

Vials with 375 mg in 5 ml

**Drug class:** virostatic

**Manufacturer:** Gilead

**Indications:** CMV retinitis in HIV-infected patients without renal dysfunction, mainly in cases of resistance/contraindications to ganciclovir or foscavir. As an adjunctive treatment to HAART for PML patients, although efficacy is uncertain.

**Dose:** induction dose 5 mg/kg iv weekly, by day 21 maintenance therapy with 5 mg/kg iv every two weeks. A precise treatment plan (comedication, hydration, etc.) is necessary!

**Side effects:** renal failure is dose limiting! Proteinuria, elevated creatinine. Cases of acute renal failure have been reported after 1 or 2 doses of cidofovir. Less frequent: neutropenia, dyspnea, alopecia, decreased intraocular pressure, iritis, uveitis.

Fever, chills, headache, rash, nausea and vomiting are usually caused by probenecid and should subside within 12 hours. Complaints may be lessened with food intake, antipyretics, or anti-emetics.

**Comments/Warnings:** with normal renal function, cidofovir should be given according to the following scheme (draw up protocol):

-3 h	2 g probenecid (4 tbl. of 500 mg)
-3 to -1 h	1000-2000 ml 0.9 % NaCl
0 to + 2 h	Cidofovir in 500 ml 0.9 % NaCl over 1-2 h. 1000 ml 0.9 % NaCl in parallel.
+4 h	1 g probenecid (2 tbl. of 500 mg)
+10 h	1 g probenecid (2 tbl. of 500 mg)

If serum creatinine increases by more than 0.3 mg/dl: reduce dose to 3 mg/kg. If serum creatinine increases by more than 0.5 mg/dl above levels prior to treatment: **discontinue** cidofovir. Cidofovir is always contraindicated at serum creatinine levels > 1.5 mg/dl or creatinine clearance below 55 ml/min or proteinuria > 100 mg/dl.

Potentially, nephrotoxic drugs such as aminoglycosides, amphotericin B, foscarnet, iv pentamidine or vancomycin must be avoided or discontinued at least 7 days prior to treatment with cidofovir.

Always ensure sufficient hydration! Probenecid is always necessary to reduce nephrotoxicity! Cidofovir should only be used if other drugs are unsuitable.

Renal function (serum creatinine, electrolytes, proteinuria) and blood count should be checked before **each** dose of cidofovir.

Probenecid has drug interactions with acetaminophen, acyclovir, angiotensin converting enzyme inhibitors, aminosalicic acid, barbiturates, benzodiazepines, bumetanide, clofibrate, methotrexate, famotidine, furosemide, non-steroidal anti-inflammatory drugs and theophylline.

**Internet sources:**

USA: <http://hiv.net/link.php?id=71>

**References:**

1. Berenguer J, Mallolas J, and the Spanish Cidofovir Study Group. Intravenous cidofovir for compassionate use in AIDS Patients with cytomegalovirus retinitis. *Clin Inf Dis* 2000, 30: 182-84. <http://amedeo.com/lit.php?id=10619750>
2. Cundy KC, Petty BG, Flaherty J, et al. Clinical pharmacokinetics of cidofovir in HIV-infected patients. *Antimicrob Agents Chemother* 1995, 39:1247-52. <http://amedeo.com/lit.php?id=7574510>
3. Jacobson MA, Wilson S, Stanley H, et al. Phase I study of combination therapy with intravenous cidofovir and oral ganciclovir for CMV retinitis in patients with AIDS. *Clin Infect Dis* 1999, 28:528-33. <http://amedeo.com/lit.php?id=10194072>
4. Marra CM, Rajcic N, Barker DE, et al. A pilot study of cidofovir for progressive multifocal leukoencephalopathy in AIDS. *AIDS* 2002, 16:1791-1797. <http://amedeo.com/lit.php?id=12218391>
5. Plosker GL, Noble S. Cidofovir: a review of its use in cytomegalovirus retinitis in patients with AIDS. *Drugs* 1999, 58:325-45. <http://amedeo.com/lit.php?id=10473024>

## Clarithromycin

**Trade names:** Klacid™, Mavid™, Biaxin™

Mavid™ tablets with 500 mg

Klacid™ tablets with 250 mg

**Drug class:** antibiotic**Manufacturer:** Abbott**Indications:** prophylaxis and treatment of MAC disease. Other bacterial infections of respiratory tract, including pneumonia.**Dose:** 500 mg bid, both for primary MAC prophylaxis and for maintenance therapy. 50 % dose reduction and good hydration if creatinine clearance is below 30 ml/min.**Side effects:** mainly gastrointestinal complaints such as nausea, vomiting, abdominal discomfort (rarely tenesmus), and diarrhea. In addition, allergic skin reactions, headache, elevated transaminases, alkaline phosphatase and bilirubin.**Comments/Warnings:** no concurrent treatment with rifampin, carbamazepine, cisapride, terfenadine, pimozone and other macrolide antibiotics such as erythromycin or azithromycin.

Lopinavir and ritonavir increase clarithromycin levels. Clarithromycin and AZT should be taken 1-2 hours apart.

**Internet sources:**USA: <http://hiv.net/link.php?id=73> (trade name: Biaxin)**References:**

1. Cohn DL, Fisher EJ, Peng GT, et al. A prospective randomized trial of four three-drug regimens in the treatment of disseminated *Mycobacterium avium* complex disease in AIDS patients: excess mortality associated with high-dose clarithromycin. *Clin Infect Dis* 1999, 29:125-33. <http://amedeo.com/lit.php?id=10433575>
2. Dunne M, Fessel J, Kumar P, et al. A randomized, double-blind trial comparing azithromycin and clarithromycin in the treatment of disseminated *Mycobacterium avium* infection in patients with HIV. *Clin Infect Dis* 2000, 31:1245-52. <http://amedeo.com/lit.php?id=11073759>
3. Pierce M, Crampton S, Henry D, et al. A randomized trial of clarithromycin as prophylaxis against disseminated *Mycobacterium avium* complex infection in patients with advanced AIDS. *N Engl J Med* 1996, 335:384-91. <http://amedeo.com/lit.php?id=8663871>
4. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of MAC bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *NEJM* 1996, 335:377-83. <http://amedeo.com/lit.php?id=8676931>

## Clindamycin

**Drug class:** antibiotic

**Manufacturer:** Clindamycin is manufactured by several different companies.

**Indications:** for HIV patients: mainly toxoplasmic encephalitis (TE)

**Dose:** 600 mg iv every 6 h or 600 mg po every 6 h for acute TE. Half dose for (oral) maintenance therapy. In renal failure, reduce dose to a quarter or a third. For TE treatment, clindamycin should be combined with pyrimethamine.

**Side effects:** diarrhea in 10-30 % of patients. Allergies are also frequent and often require discontinuation.

In cases of infection with *Clostridium difficile* "Pseudomembranous colitis": the clinical spectrum ranges from mild watery to severe diarrhea with blood and mucous, leukocytosis, fever and severe abdominal cramps, which may progress to peritonitis, shock and toxic megacolon. For every occurrence of diarrhea on clindamycin: discontinue and give vancomycin.

**Comments/Warnings:** clindamycin is contraindicated in inflammatory bowel disease and antibiotic-induced colitis. Caution with reduced hepatic or renal function and in asthma. No concurrent administration of antiperistaltics!

**Internet sources:**

USA: <http://hiv.net/link.php?id=76> (trade name Cleocin™).

**References:**

1. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992, 116:33-43. <http://amedeo.com/lit.php?id=1727093>
2. Katlama C, De Wit S, O'Doherty E, Van Glabeke M, Clumeck N. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996, 22:268-75. <http://amedeo.com/lit.php?id=8838183>

## Combivir™

Tablets containing 150 mg 3TC + 300 mg AZT

**Drug class:** NRTI

**Manufacturer:** GlaxoSmithKline

**Indications:** HIV infection

**Oral dose:** 1 tablet bid

In cases of reduced renal function (creatinine clearance below 50 ml/min) and anemia, Combivir™ should be replaced with the individual drugs to allow for adjustment of 3TC and AZT doses.

**Warnings and side effects:** see chapters on 3TC and AZT.

**Internet sources:**

USA: <http://hiv.net/link.php?id=68>

## Co-trimoxazole

**Drug class:** antibiotic. Co-trimoxazole is a fixed combination of trimethoprim and sulfamethoxazole (TMP/SMX)

**Manufacturer:** co-trimoxazole is manufactured by several companies.

**Indications:** prophylaxis and treatment of *Pneumocystis pneumonia* (PCP). Prophylaxis and treatment (reserve drug) of cerebral toxoplasmosis.

**Dose:** PCP *prophylaxis*: 80/400 mg qd or 160/800 mg TMP/SMX 3 x/week. PCP *therapy*: 5 mg/kg (based on trimethoprim) po or iv every 8 h for 21 days, therefore usually 4 to 5 ampules à 80/400 mg every 8 h. Toxoplasmosis prophylaxis: 1 tablet (160/800 mg) qd.

Reduced renal function: halve dose with creatinine clearance of 15 to 50 ml/min. Co-trimoxazole is contraindicated below 15 ml/min.

**Side effects:** allergies, in high doses up to 50 %. In cases of mild allergy, treatment can often be continued. In other cases desensitization is usually possible. High intravenous doses also cause myelotoxicity (anemia, neutropenia!), nausea, vomiting, headache, raised transaminases.

**Comments/Warnings:** caution with sulfonamide allergy! Co-trimoxazole oral suspension for children can be used for desensitization: increase the dose slowly over six days from 12.5, 25, 37.5, 50 and 75 to 100 % of the 480 mg tablet dose (for details see Leoung 2001, see below).

Co-trimoxazole can increase levels of anticoagulants and phenytoin and reduce the efficacy of oral contraceptives.

### References:

1. Bozzette SA, Finkelstein DM, Spector SA, et al. A randomized trial of three antipneumocystis agents in patients with advanced HIV. *N Engl J Med* 1995, 332:693-9. <http://amedeo.com/lit.php?id=7854375>
2. DiRienzo AG, van Der Horst C, Finkelstein DM, et al. Efficacy of trimethoprim-sulfamethoxazole for the prevention of bacterial infections in a randomized prophylaxis trial of patients with advanced HIV infection. *AIDS Res Hum Retroviruses* 2002, 18:89-94. <http://amedeo.com/lit.php?id=11839141>
3. Duval X, Pajot O, Le Moing V, et al. Maintenance therapy with cotrimoxazole for toxoplasmic encephalitis in the era of highly active antiretroviral therapy. *AIDS* 2004; 18: 1342-4. <http://amedeo.com/lit.php?id=15362670>
4. El-Sadr WM, Luskin-Hawk R, Yurik TM, et al. A randomized trial of daily and thrice-weekly trimethoprim-sulfamethoxazole for the prevention of *Pneumocystis carinii* pneumonia in HIV-infected persons. *Clin Infect Dis* 1999, 29:775-783. <http://amedeo.com/lit.php?id=10589887>
5. Leoung GS, Stanford JF, Giordano MF, et al. Trimethoprim-sulfamethoxazole (TMP-SMZ) dose escalation versus direct rechallenge for pneumocystis carinii pneumonia prophylaxis in HIV-infected patients with previous adverse reaction to TMP-SMZ. *J Infect Dis* 2001, 184:992-7. <http://amedeo.com/lit.php?id=11574913>
6. Martin JN, Rose DA, Hadley WK, et al. Emergence of trimethoprim-sulfamethoxazole resistance in the AIDS Era. *J Infect Dis* 1999, 180:1809-18. <http://amedeo.com/lit.php?id=10558935>
7. Para MF, Finkelstein D, Becker S, et al. Reduced toxicity with gradual initiation of trimethoprim-sulfamethoxazole as primary prophylaxis for *Pneumocystis carinii* pneumonia. ACTG 268. *J Acquir Immune Defic Syndr* 2000, 24:337-43. <http://amedeo.com/lit.php?id=11015150>
8. Toma E, Thorne A, Singer J, et al. Clindamycin with primaquine vs. Trimethoprim-sulfamethoxazole therapy for mild and moderately severe *Pneumocystis carinii* pneumonia in patients with AIDS: a multicenter, double-blind, randomized trial (CTN 004). *Clin Infect Dis* 1998, 27:524-30. <http://amedeo.com/lit.php?id=9770152>

**Crixivan**<sup>TM</sup> see Indinavir



## d4T – Stavudine

Stavudine is a thymidine analog similar to AZT. Subjective tolerability is good; the drug was long considered an important alternative to AZT. Due to the mitochondrial toxicity (lipoatrophy, lactic acidosis, peripheral neuropathy), particularly in combination with ddI, the (long-term) use of d4T is no longer recommended.

**Trade name:** Zerit™

Capsules: 15 mg, 20 mg, 30 mg, 40 mg. Solution 1 mg/ml.

**Drug class:** NRTI

**Manufacturer:** Bristol-Myers Squibb

**Indications:** HIV infection

**Oral dose:** 40 mg bid for body weight > 60 kg, but 30 mg bid for body weight < 60 kg.

In renal failure:

Weight	CrCl 26-50 ml/min	CrCl below 26 ml/min (incl. dialysis patients)*
<60 kg	15 mg bid	15 mg qd
>60 kg	20 mg bid	20 mg qd

\*Hemodialysis: patients should take d4T after dialysis, and at the same time on non-dialysis days.

**Side effects:** peripheral neuropathy, especially in combination with ddI (up to 24 %). d4T has been linked to lipoatrophy more than other NRTIs. However, the following are less frequent than with AZT: diarrhea, nausea, vomiting, headache. Rare, but potentially fatal: lactic acidosis, which occurs mostly in combination with ddI (especially in pregnancy!). Further side effects: hepatic steatosis, pancreatitis.

**Comments/Warnings:** d4T should not be combined with AZT.

Contraindicated in patients with existing peripheral neuropathy.

If possible, no concurrent treatment with other neurotoxic drugs (ddC, ethambutol, cisplatin, INH, vincristine, etc.)

d4T can be taken on an empty stomach or with a light meal. If symptoms of peripheral neuropathy occur, treatment with d4T should be discontinued.

### References:

- Domingo P, Labarga P, Palacios R, Guerra MF, Terron JA, Elias MJ et al. Improvement of dyslipidemia in patients switching from stavudine to tenofovir: preliminary results. *AIDS* 2004; 18: 1475-8. <http://amedeo.com/lit.php?id=15199328>
- Joly V, Flandre P, Meiffredy V, et al. Efficacy of zidovudine compared to stavudine, both in combination with lamivudine and indinavir, in HIV-infected nucleoside-experienced patients with no prior exposure to lamivudine. *Antimicrob Agents Chemother* 2002; 46: 1906-13. <http://amedeo.com/lit.php?id=12019107>
- McComsey GA, Paulsen DM, Lonergan JT, et al. Improvements in lipoatrophy, mitochondrial DNA levels and fat apoptosis after replacing stavudine with abacavir or zidovudine. *AIDS* 2005; 19: 15-23. Abstract: <http://amedeo.com/lit.php?id=15627029>
- Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. *JAMA* 2004; 292: 180-9. <http://amedeo.com/lit.php?id=15249567>
- Shah SS, Rodriguez T, McGowan JP. Miller Fisher variant of Guillain-Barre syndrome associated with lactic acidosis and stavudine therapy. *Clin Infect Dis* 2003; 36: e131-3. <http://amedeo.com/lit.php?id=12746793>

6. Shlay JC, Visnegarwala F, Bartsch G, et al. Body composition and metabolic changes in antiretroviral-naive patients randomized to didanosine and stavudine vs. abacavir and lamivudine. *J AIDS* 2005; 38: 147-55. <http://amedeo.com/lit.php?id=15671799>
7. van der Valk M, Casula M, Weverlingz GJ, et al. Prevalence of lipoatrophy and mitochondrial DNA content of blood and subcutaneous fat in HIV-1-infected patients randomly allocated to zidovudine- or stavudine-based therapy. *Antivir Ther* 2004; 9: 385-93. <http://amedeo.com/lit.php?id=15259901>
8. Yogev R, Lee S, Wiznia A, et al. Stavudine, nevirapine and ritonavir in stable antiretroviral therapy-experienced children with HIV infection. *Pediatr Infect Dis J* 2002; 21: 119-125. <http://amedeo.com/lit.php?id=11840078>

## Dapsone

Tablets with 50 mg.

**Drug class:** antibiotic

**Manufacturer:** FatoL and some other companies.

**Indications:** For HIV-patients, dapsone is a reserve drug for prophylaxis of *Pneumocystis pneumonia* and cerebral toxoplasmosis.

**Dose:** 100 mg daily. Alternative: 50 mg qd **plus** pyrimethamine 50 mg bid/week **plus** folic acid 30 mg/week.

**Side effects:** allergies (pruritus, rash), fever. Frequently hemolytic anemia (with almost obligatory elevation of LDH!), hepatitis.

**Comments/Warnings:** dapsone is contraindicated in severe anemia and must be used with caution in G-6-PD deficiency. It is contraindicated in Mediterranean G-6-PD deficiency. Not to be taken simultaneously with ddI, antacids and H<sub>2</sub> blockers (to be taken at least two hours apart). Development of LDH on dapsone is usually not useful for diagnostic purposes. Rifabutin and rifampin lower dapsone levels.

### References:

1. El-Sadr WM, Murphy RL, Yurik TM, et al. Atovaquone compared with dapsone for the prevention of *Pneumocystis carinii* pneumonia in patients with HIV infection who cannot tolerate trimethoprim, sulfonamides, or both. *N Engl J Med* 1998; 339:1889-95. <http://amedeo.com/lit.php?id=9862944>
2. Girard PM, Landman R, Gaudebout C, et al. Dapsone-pyrimethamine compared with aerosolized pentamidine as primary prophylaxis against *Pneumocystis carinii* pneumonia and toxoplasmosis in HIV infection. *N Engl J Med* 1993; 328:1514-20. <http://amedeo.com/lit.php?id=8479488>
3. Torres RA, Barr M, Thorn M, et al. Randomized trial of dapsone and aerosolized pentamidine for the prophylaxis of *pneumocystis carinii* pneumonia and toxoplasmic encephalitis. *Am J Med* 1993; 95:573-83. <http://amedeo.com/lit.php?id=8018144>

**Daraprim™** see pyrimethamine

## Darunavir (TMC-114)

Darunavir (TMC-114) is a new protease inhibitor that has considerable activity against PI-resistant viruses. Important salvage drug. In Europe, darunavir is currently (beginning of 2006) available through an expanded access program (EAP), but will most probably be licensed later in 2006. Well tolerated, but must be boosted.

**Trade name:** Prezista™ (approved in the US). In Europe, currently in the EAP as 300 mg capsules.

**Drug class:** Protease inhibitor

**Manufacturer:** Tibotec/Janssen-Cilag

**Indications:** HIV infection, limited to intensively pre-treated patients.

**Dose:** 600 mg bid (2 capsules each time) plus 100 mg ritonavir bid in pre-treated patients. Lower doses and once-daily doses are currently being investigated in treatment-naïve patients.

**Side effects:** the usual PI side effects, with (although moderate) gastrointestinal complaints and dyslipidemia. However, the dyslipidemia is not as pronounced as with other PIs.

**Comments/warnings:** combination with lopinavir appears to be unfavorable, but because of the robust resistance profile of darunavir, the administration of a second PI is not always necessary. Interactions with atorvastatin.

#### References:

1. Katlama C, Carvalho MI, Cooper D, et al. TMC 114/r out performs investigator selected PI(s) in three class-experienced patients: week 24 primary analysis of POWER 1 (TMC 114-C213). Abstract WeOaLB0102, 3rd IAS 2005, Rio de Janeiro.
2. Katlama C, Berger D, Bellos N, et al. Efficacy of TMC114/r in 3-class experienced patients with limited treatment options: 24-week planned interim analysis of 2 96-week multinational dose-finding trials. Abstract 164LB, 3rd IAS 2005, Rio de Janeiro.
3. King NM, Prabu-Jeyabalan M, Nalivaika EA, et al. Structural and thermodynamic basis for the binding of TMC114, a next-generation human immunodeficiency virus type 1 protease inhibitor. *J Virol* 2004, 78:12012-21. <http://amedeo.com/lit.php?id=15479840>
4. De Meyer S, Hill A, De Baere I, et al. Effect of baseline susceptibility and on-treatment mutation on TMC-114 and control PI efficacy: preliminary analysis of data from PI-experienced patients from POWER 1 and POWER 2. Abstract 157, 13th CROI 2006, Denver.

## Daunorubicin, liposomal

**Trade name:** DaunoXome™

50 mg vials of liposomal daunorubicin

**Drug class:** cytostatic

**Manufacturer:** Gilead

**Indications:** Kaposi's sarcoma in patients with CD4+ T-cells < 200/μl and in cases of severe mucocutaneous or visceral KS.

**Dose:** 40 mg/m<sup>2</sup> q 2 wks. Duration according to response.

DaunoXome is administered intravenously over 30-60 minutes.

**Side effects:** during infusion: back pain, flushing. Symptoms usually resolve when the infusion is slowed or stopped. Fatigue, headaches, chills. Pancytopenia, elevated transaminases and alkaline phosphatase.

In myelosuppression (neutrophils < 1,000/μl): delay the next dose and treat with G-CSF if necessary.

Cardiac failure can occur suddenly and even weeks after discontinuation of therapy.

**Comments/Warnings:** contraindicated if there is hypersensitivity to anthracyclines; moreover, in patients who can be effectively treated with local therapy. Caution with pre-existing cardiovascular disease, previous treatment with anthracyclines.

LVEF should be evaluated before initiation of treatment, and monitored when the cumulative dose is 240 mg/m<sup>2</sup> (watch out for development of cardiomyopathy!).

Regular ECG monitoring. Temporary changes such as T-wave flattening, ST-segment depression and mild arrhythmia do not necessarily require discontinuation of DaunoXome™ treatment.

**Internet sources:**

USA: <http://hiv.net/link.php?id=82> (2.3 MB)

**References:**

1. Gill PS, Wernz J, Scadden DT, et al. Randomized phase III trial of liposomal daunorubicin versus doxorubicin, bleomycin, and vincristine in AIDS-related Kaposi's sarcoma. *J Clin Oncol* 1996; 14: 2353-64. <http://amedeo.com/lit.php?id=8708728>
2. Fumagalli L, Zucchetti M, Parisi I, et al. The pharmacokinetics of liposomal encapsulated daunorubicin are not modified by HAART in patients with HIV-associated Kaposi's sarcoma. *Cancer Chemother Pharmacol* 2000, 45: 495-501. <http://amedeo.com/lit.php?id=10854138>
3. Hjortsberg C, Persson U, Lidbrink E, Bennett C. Cost-effectiveness analysis of pegylated-liposomal doxorubicin and liposomal daunorubicin treatments in patients with Kaposi's sarcoma. *Acta Oncol* 1999, 38:1063-7. <http://amedeo.com/lit.php?id=10665764>
4. Rosenthal E, Poizot-Martin I, Saint-Marc T, Spano JP, Cacoub P. Phase IV study of liposomal daunorubicin (DaunoXome) in AIDS-related Kaposi sarcoma. *Am J Clin Oncol* 2002, 25:57-9. <http://amedeo.com/lit.php?id=11823698>

**DaunoXome™** see Daunorubicin, liposomal

## ddC – Zalcitabine

ddC was one of the first NRTIs. Due to the complicated dosing, moderate efficacy, risk of polyneuropathy and cross-resistance distribution was ceased in 2006 – a novelty in HIV medicine. ddC should be replaced by other drugs.

**Trade name:** Hivid™ 0.375 mg tablets, 0.75 mg tablets

**Drug class:** NRTI

**Manufacturer:** Hoffmann-La Roche

**Indications:** HIV infection

**Oral dose:** 0.75 mg tid

**Side effects:** peripheral neuropathy (up to 30 %), stomatitis with oral ulcers (up to 4 %), pancreatitis (<1 %). Rarely: rash, lactic acidosis, hepatic steatosis.

## ddl – Didanosine

ddl was one of the first NRTIs. In addition to gastrointestinal complaints, a presumably dose-dependent pancreatitis may occur in up to 10 % of patients. ddl has a long intracellular half-life and once-daily dosing is possible. However, the advantage is usually cancelled out by the disadvantage that the drug must be taken on an empty stomach.

Combination with tenofovir and d4T is problematic. Patent protection for ddl expires in August 2006 in the USA (<http://hiv.net/link.php?id=243>).

**Trade name:** Videx™

Enteric coated capsules: 125 mg, 200 mg, 250 mg, 400 mg. Powder: 4 g per bottle.

**Drug class:** NRTI

**Manufacturer:** Bristol-Myers Squibb

**Indications:** HIV infection

**Oral dose:** 400 mg qd (body weight > 60 kg) or 250 mg qd (body weight < 60 kg). ddl must be taken on an empty stomach, at least 2 hours after or at the latest 1 hour before meals.

**Side effects:** diarrhea, nausea, headache, rash. Pancreatitis, even after longer periods on treatment! Peripheral polyneuropathy. Rarely: episodes of lactic acidosis, especially in combination with d4T and ribavirin.

**Comments/Warnings:** acute and chronic pancreatitis are contraindications – caution in patients with alcoholism! If possible, concurrent treatment with drugs that can cause pancreatitis (e.g. intravenous pentamidine) should be avoided. The following drugs should be used with caution: ethambutol, cisplatin, disulfiram, ethionamide, INH, vincristine, etc. (peripheral neuropathy).

Concurrent dosing with tenofovir increases the  $C_{max}$  and AUC of ddl by 28 % and 44 %, respectively. The ddl dose should therefore be reduced to 250 mg. Tenofovir must be taken two hours before or one hour after ddl.

Treatment with indinavir, dapsone, keto/itraconazole, or tetracyclines should be given 2 hours before or after ddl. If possible, these combinations should be avoided (see HAART chapter). Ribavirin is contraindicated.

Initially, monthly monitoring of amylase, blood count, transaminases and bilirubin. Patients should be informed about the risk and signs of pancreatitis. ddl should be discontinued if there is clinical suspicion for pancreatitis, with no rechallenge.

**Internet sources:**

USA: <http://hiv.net/link.php?id=86>

**References:**

1. Butt AA. Fatal lactic acidosis and pancreatitis associated with ribavirin and didanosine therapy. *AIDS Read* 2003; 13: 344-8. <http://amedeo.com/lit.php?id=12889452>
2. Guo Y, Fung HB. Fatal lactic acidosis associated with coadministration of didanosine and tenofovir disoproxil fumarate. *Pharmacotherapy* 2004; 24: 1089-94. <http://amedeo.com/lit.php?id=15338857>

3. Hammer SM, Katzenstein DA, Hughes MD, et al. A trial comparing nucleoside monotherapy with combination therapy in HIV-infected adults with CD4 cell counts from 200 to 500/uI. *N Engl J Med* 1996; 335:1081-90. <http://amedeo.com/lit.php?id=8813038>
4. Leon A, Mallolas J, Martinez E, et al. High rate of virological failure in maintenance antiretroviral therapy with didanosine and tenofovir. *AIDS* 2005; 19: 1695-7. <http://amedeo.com/lit.php?id=16184042>
5. Maitland D, Moyle G, Hand J, et al. Early virologic failure in HIV-1 infected subjects on didanosine/tenofovir/efavirenz: 12-week results from a randomized trial. *AIDS* 2005; 19: 1183-8. <http://amedeo.com/lit.php?id=15990571>
6. Martinez E, Milinkovic A, de Lazzari E, et al. Pancreatic toxic effects associated with co-administration of didanosine and tenofovir in HIV-infected adults. *Lancet* 2004; 364: 65-7. <http://amedeo.com/lit.php?id=15234858>
7. Moreno A, Quereda C, Moreno L, et al. High rate of didanosine-related mitochondrial toxicity in HIV/HCV-coinfected patients receiving ribavirin. *Antivir Ther* 2004; 9: 133-8. <http://amedeo.com/lit.php?id=15040545>
8. Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing Didanosine. *Clin Infect Dis* 2003; 36: 1082-5. <http://amedeo.com/lit.php?id=12684925>
9. Negredo E, Bonjoch A, Paredes R, et al. Compromised immunologic recovery in treatment-experienced patients with HIV infection receiving both tenofovir disoproxil fumarate and didanosine in the TORO studies. *CID* 2005; 41: 901-5. <http://amedeo.com/lit.php?id=16107993>

**Diflucan™** see Fluconazole

## Delavirdine

Delavirdine is rarely used, due to impractical dosing and drug interactions. Other disadvantages: the usual NNRTI cross-resistances, and high pill burden.

**Trade name:** Rescriptor™

100 mg and 200 mg tablets

**Drug class:** NNRTI

**Manufacturer:** Pfizer

**Indications:** HIV infection

**Oral dose:** 400 mg tid

**Side effects:** rash, usually occurring within the first six weeks of treatment. In uncomplicated cases, give symptomatic antihistamines. Discontinue if systemic effects such as fever, conjunctivitis, myalgia and arthralgia occur. Nausea, elevated transaminases.

**Comments/Warnings:** delavirdine is contraindicated for concurrent treatment with rifabutin, rifampin, carbamazepine, phenytoin, alprazolam, astemizole, phenobarbital, cisapride, midazolam, terfenadine and triazolam.

There is little data on combination with nelfinavir, lopinavir and ritonavir.

Delavirdine interacts with numerous drugs via reduction of CYP3A-activity. It increases the AUC of sildenafil, dapson, clarithromycin, quinidine and warfarin. Delavirdine levels are lowered by ddI, H<sub>2</sub> blockers, carbamazepine, phenytoin and antacids.

**Patients should know** that they may also dissolve delavirdine in water: stir tablets in a glass for a few minutes and drink. Rinse the glass with a small amount of water and drink the rest.

**Internet sources:**

USA: <http://hiv.net/link.php?id=178>

**References:**

1. Conway B. Initial therapy with protease inhibitor-sparing regimens: evaluation of nevirapine and delavirdine. *Clin Infect Dis* 2000, Suppl 2:S130-4. <http://amedeo.com/lit.php?id=10860897>
2. Engelhorn C, Hoffmann F, Kurowski M, et al. Long-term pharmacokinetics of amprenavir in combination with delavirdine in HIV-infected children. *AIDS* 2004; 18: 1473-5. <http://amedeo.com/lit.php?id=15199327>
3. Harris M, Alexander C, O'Shaughnessy M, Montaner JS. Delavirdine increases drug exposure of ritonavir-boosted protease inhibitors. *AIDS* 2002; 16: 798-9.
4. Shelton MJ, Hewitt RG, Adams J, Della-Coletta A, Cox S, Morse GD. Pharmacokinetics of Ritonavir and Delavirdine in HIV-Infected Patients. *Antimicrob Agents Chemother* 2003; 47: 1694-1699. <http://amedeo.com/lit.php?id=12709342>
5. Smith D, Hales G, Roth N, et al. A randomized trial of nelfinavir, ritonavir, or delavirdine in combination with saquinavir-SGC and stavudine in treatment-experienced HIV-1-infected patients. *HIV Clin Trials* 2001, 2:97-107. <http://amedeo.com/lit.php?id=11590517>

## Doxorubicin (liposomal)

**Trade name:** Caelyx™, Doxil™

10 ml (20 mg) and 25 ml (50 mg) vials

**Drug class:** anthracycline

**Manufacturer:** Schering-Plough, Ortho Biotech (USA)

**Indications:** Kaposi's sarcoma in AIDS patients with < 200 CD4- T-cells/μl and severe mucocutaneous or visceral KS. Patients not tolerating chemotherapy with other drugs or with progressive disease despite other treatments.

**Dose:** in adults 20 mg/m<sup>2</sup> in 250 ml 5 % glucose solution intravenously over 30 minutes. Repeat after 3 weeks.

**Side effects:** myelosuppression (only 10-15 % neutropenia grade III-IV), cardiomyopathy, stomatitis (rarely severe), palmar-plantar erythrodysesthesia (PPE or hand-foot syndrome - erythematous rash which may be very painful. Treatment: cool affected areas). Rare: nausea (mild), diarrhea, alopecia.

**Comments/Warnings:** liposomal doxorubicin is contraindicated in decompensated cardiomyopathy, severe myelosuppression (neutrophils < 1,000/μl, platelets < 50,000/μl) and in patients who have previously received maximum cumulative doses of anthracyclines.

Cardiological examination is important (ECG, echocardiography: left ventricular ejection fraction, LVEF) before initiation of treatment and at periodic intervals during treatment. If the cumulative dose of 450 mg/m<sup>2</sup> is exceeded, echocardiography is necessary before each further cycle.

It is important to inform patients of PPE (may be induced by sweating, pressure, friction – therefore no tight gloves, no sun, no long warm showers, cool drinks).

Do not administer intramuscularly or subcutaneously. This drug is expensive: in Germany, two 20 mg vials cost approximately 1,343 Euro!

### References:

1. Martin-Carbonero L, Barrios A, Saballs P, et al. Pegylated liposomal doxorubicin plus highly active antiretroviral therapy versus highly active antiretroviral therapy alone in HIV patients with Kaposi's sarcoma. *AIDS* 2004; 18: 1737-40. <http://amedeo.com/lit.php?id=15280789>
2. Newell M, Milliken S, Goldstein D, et al. A phase II study of liposomal doxorubicin in the treatment of HIV-related Kaposi's sarcoma. *Aust N Z J Med* 1998; 28: 777-83. <http://amedeo.com/lit.php?id=9972406>
3. Nunez M, Saballs P, Valencia ME, et al. Response to liposomal doxorubicin and clinical outcome of HIV-1-infected patients with Kaposi's sarcoma receiving HAART. *HIV Clin Trials* 2001; 2: 429-37. <http://amedeo.com/lit.php?id=11673818>
4. Nunez M, Machuca A, Soriano V, Podzamczar D, Gonzalez-Lahoz J. Clearance of human herpesvirus type 8 viraemia in HIV-1-positive patients with Kaposi's sarcoma treated with liposomal doxorubicin. *AIDS* 2000; 14: 913-9. <http://amedeo.com/lit.php?id=10853972>

## Efavirenz

Efavirenz is a frequently used NNRTI with a simple dosing schedule, good tolerability. However, it has some CNS side effects (disturbances of sleep architecture, morning dizziness, somnolence). Further disadvantages include drug interactions and cross-resistance, as with the other members of this drug class.

**Trade name:** Sustiva™, Stocrin™

Capsules: 50 mg, 100 mg, 200 mg, 600 mg

**Drug class:** NNRTI

**Manufacturer:** Bristol-Myers Squibb, MSD

**Indications:** HIV infection

**Oral dose:** 600 mg daily (1 capsule of 600 mg qd or 3 capsules of 200 mg qd), preferably before going to bed.

**Side effects:** CNS symptoms occur frequently! Nightmares, confusion, dizziness, somnolence, abnormal thinking, impaired concentration, insomnia, and depersonalization. These symptoms usually resolve after a few weeks. A rash (15 %) may also occur in the first weeks, but severe cases of blistering, desquamation and ulceration are rare. Gynecomastia.

Elevation of liver function tests and biliary enzymes, especially  $\gamma$ GT. Dyslipidemia.

**Comments/Warnings:** contraindicated in pregnancy!

Contraindicated for concurrent administration with ergotamines, astemizole, cisapride, midazolam, terfenadine and triazolam. Should not be combined with contraceptive pills.

Should not be given in combination with saquinavir or amprenavir without ritonavir boost (insufficient plasma levels of saquinavir and amprenavir).

Dose adjustments in combination with:

- Lopinavir: increase lopinavir dose to 4 capsules bid.
- Atazanavir: increase to 400 mg (ATV/RTV: 400/100); take with meals
- Indinavir: increase indinavir dose to 1,000 mg tid.



- Rifabutin: increase rifabutin dose to 450 mg/day.
- Methadone: possibly increase methadone dose by 20 to 40 %.

When switching therapy from a PI to efavirenz, overlapping therapy is recommended for one week.

Efavirenz can be taken with fatty meals, as this increases absorption.

### Internet sources:

USA: <http://hiv.net/link.php?id=88>

### References:

1. Ananworanich J, Moor Z, Siangphoe U, et al. Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs. *AIDS* 2005; 19: 185-92. Abstract: <http://amedeo.com/lit.php?id=15668544>
2. Boffito M, Rossati A, Reynolds HE, et al. Undefined duration of opiate withdrawal induced by efavirenz in drug users with hiv infection and undergoing chronic methadone treatment. *AIDS Res Hum Retroviruses* 2002; 18: 341-2.
3. Brennan-Benson P, Lyus R, Harrison T, Pakianathan M, Macallan D. Pharmacokinetic interactions between efavirenz and rifampicin in the treatment of HIV and tuberculosis: one size does not fit all. *AIDS* 2005; 19: 1541-3. Abstract: <http://amedeo.com/lit.php?id=16135909>
4. Clifford DB, Evans S, Yang Y, et al. Impact of efavirenz on neuropsychological performance and symptoms in HIV-infected individuals. *Ann Intern Med* 2005; 143: 714-21. Abstract: <http://amedeo.com/lit.php?id=16287792>
5. Fumaz CR, Munoz-Moreno JA, Molto J, et al. Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychological issues, and adherence. *J Acquir Immune Defic Syndr* 2005; 38: 560-5. Abstract: <http://amedeo.com/lit.php?id=15793366>
6. Fundaro C, Genovese O, Rendelli C, Tamburrini E, Salvaggio E. Myelomeningocele in a child with intrauterine exposure to efavirenz. *AIDS* 2002, 16: 299-300.
7. Gallego L, Barreiro P, del Rio R, et al. Analyzing sleep abnormalities in HIV-infected patients treated with Efavirenz. *Clin Infect Dis* 2004; 38: 430-2. <http://amedeo.com/lit.php?id=14727217>
8. Gulick RM, Ribaudo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med* 2004; 350: 1850-61. <http://amedeo.com/lit.php?id=15115831>
9. McComsey G, Bhumbra N, Ma JF, Rathore M, Alvarez A. Impact of protease inhibitor substitution with efavirenz in HIV-infected children: results of the First Pediatric Switch Study. *Pediatrics* 2003; 111: e275-81. <http://amedeo.com/lit.php?id=12612284>
10. Mira JA, Lozano F, Santos J, et al. Gynaecomastia in HIV-infected men on highly active antiretroviral therapy: association with efavirenz and didanosine treatment. *Antivir Ther* 2004; 9: 511-7. <http://amedeo.com/lit.php?id=15456082>
11. Staszewski S, Morales-Ramirez J, Tashima KT, et al. Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team. *N Engl J Med* 1999, 341:1865-73. <http://amedeo.com/lit.php?id=10601505>
12. van Leth F, Huisamen CB, Badaro R, et al. Plasma HIV-1 RNA decline within the first two weeks of treatment is comparable for nevirapine, efavirenz, or both drugs combined and is not predictive of long-term virologic efficacy: A 2NN substudy. *J Acquir Immune Defic Syndr* 2005; 38: 296-300. Abstract: <http://amedeo.com/lit.php?id=15735447>
13. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; 363: 1253-63. <http://amedeo.com/lit.php?id=15094269>
14. Weiner M, Benator D, Peloquin CA, et al. Evaluation of the drug interaction between rifabutin and efavirenz in patients with HIV infection and tuberculosis. *Clin Infect Dis* 2005; 41: 1343-9. Epub 2005 Sep 29. Abstract: <http://amedeo.com/lit.php?id=16206114>
15. Winston A, Pozniak A, Smith N, et al. Dose escalation or immediate full dose when switching from efavirenz to nevirapine-based highly active antiretroviral therapy in HIV-1-infected individuals? *AIDS* 2004; 18: 572-4. <http://amedeo.com/lit.php?id=15090815>

## Emtricitabine (FTC)

Emtricitabine is a well-tolerated cytidine analog, comparable to 3TC both biochemically and in its resistance profile, but has a significantly longer half-life. It can be taken once a day.

**Trade name:** Emtriva™. Also in Truvada™ in combination with tenofovir.

Hard capsules with 200 mg; solution: 170 ml with 10 mg/ml.

**Drug class:** NRTI

**Manufacturer:** Gilead

**Indications:** HIV infection

**Dose:** 200 mg qd (solution: 240 mg = 24 ml). Dose adjustment is required with reduced creatinine clearance:

CrCl (ml/min)	Dose
30–49	200 mg every 2 days
15–29	200 mg every 3 days
Below 14 or dialysis	200 mg every 4 days

**Side effects:** probably rare. Most commonly headache, nausea, diarrhea, rash. Possibly hyperpigmentation.

**Internet sources:**

USA: <http://hiv.net/link.php?id=223>

**References:**

1. Bang LM, Scott LJ. Emtricitabine: An antiretroviral agent for HIV infection. *Drugs* 2003; 63: 2413-24. <http://amedeo.com/lit.php?id=14609348>
2. Rousseau FS, Wakeford C, Mommeja-Marin H, et al. Prospective randomized trial of emtricitabine versus Lamivudine short-term monotherapy in HIV-infected patients. *J Infect Dis* 2003; 188: 1652-8. <http://amedeo.com/lit.php?id=14639535>
3. Saag MS, Cahn P, Raffi F, et al. Efficacy and safety of emtricitabine vs stavudine in combination therapy in antiretroviral-naïve patients: a randomized trial. *JAMA* 2004; 292: 180-9. <http://amedeo.com/lit.php?id=15249567>
4. Saag MS. Emtricitabine, a new antiretroviral agent with activity against HIV and Hepatitis B Virus. *Clin Infect Dis* 2006; 42: 126-31. <http://amedeo.com/lit.php?id=16323102>
5. Wang LH, Wiznia AA, Rathore MH, et al. Pharmacokinetics and safety of single oral doses of emtricitabine in HIV-infected children. *Antimicrob Agents Chemother* 2004; 48: 183-91. <http://amedeo.com/lit.php?id=14693538>

**Emtriva™** see Emtricitabine

**Enfuvirtide** see T-20

**Epivir™** see 3TC (at the beginning of this chapter)

**Epzicom™** see Kivexa

**Erypo™** see Erythropoetin

## Erythropoietin

**Trade name:** Erypo™

Vials with 2,000, 4,000 or 10,000 I.U./ml

**Drug class:** anti-anemic

**Manufacturer:** Janssen-Cilag among other companies

**Indications:** anemia in renal failure, induced by drugs such as AZT, ribavirin or chemotherapy (symptomatic anemia; asymptomatic anemia when hemoglobin values are at least below 10-11 g/dl, if endogenous erythropoietin levels are below 500 mU/ml). Note: Always exclude more other causes of anemia (iron deficiency?!)

**Dose:** 100 I.U./kg body weight once weekly subcutaneously until a hematocrit of 30 to 35 % is reached. If there is no response after 6 weeks of treatment, increase dose to 200 I.U./kg/week. If there is no response after a further 6 weeks: discontinue. If response is achieved, a weekly maintenance dose of 100-200 I.U./kg body weight is usually sufficient. At hematocrit values > 40 % or hemoglobin > 13 g/dl: discontinue.

**Side effects:** flu-like symptoms especially at the start of treatment, such as headache, arthralgia, asthenia, dizziness and fatigue.

**Comments/Warnings:** erythropoietin is contraindicated with uncontrolled hypertension. It is expensive and should be used sparingly. Before initiating treatment, other causes of anemia should be excluded. These include:

- Vitamin B12 or folic acid deficiency, iron deficiency, occult blood loss, hematological disorders such as thalassemia and myelodysplasia.
- AIDS-defining illnesses with bone marrow involvement such as MAC infection, tuberculosis, CMV infection, lymphoma, Kaposi's sarcoma.

Strict monitoring of blood pressure initially!

Subcutaneous administration of Erypo™ is **contraindicated** in patients with chronic renal insufficiency or terminal renal failure due to the risk of antibody-induced erythroblastopenia (PRCA, Pure Red Cell Aplasia).

Erypo™ must be stored at 2° to 8° Celsius in the original package. Do not freeze!

**Drug interactions:** erythropoietin can diminish the efficacy of concurrently administered antihypertensives. Concurrent treatment with anticonvulsive drugs may increase seizure susceptibility.

As cyclosporine A binds to erythrocytes, blood concentrations of cyclosporine A should be monitored if administered together with erythropoietin.

## Ethambutol

**Drug class:** tuberculostatic

**Manufacturer:** Ethambutol is manufactured by several different companies.

**Indications:** tuberculosis, MAC infection

**Dose:** 15 to 25 mg/kg (maximum 2 g) daily, usually 3 tablets à 400 mg qd. Ethambutol should only be given as combination therapy.

Dose reduction in renal failure:

CrCl	Dose
Above 75 ml/min	25 mg/kg
40-75 ml/min	15 mg/kg
30-40 ml/min	15 mg/kg every second day
<30 ml/min	Measurement of serum levels required *

\*Serum levels should be within the range of the minimal inhibitory concentration 2-5 µg/ml after 2-4 hours.

**Side effects:** ethambutol can lead to optical neuritis with impaired vision (decreased acuity, restricted fields, loss of red-green color discrimination). It is usually reversible if ethambutol is discontinued immediately.

Other side effects: nausea, vomiting, abdominal pain, headache, dizziness, pruritus, arthralgia, elevated serum uric acid (acute gout attacks possible!), abnormal liver function tests.

**Comments/Warnings:** ethambutol is contraindicated with pre-existing optical nerve damage.

Ophthalmologic examination before initiation of treatment and subsequently at 4-week intervals (color discrimination, field of vision, acuity). Immediate discontinuation to prevent optical atrophy if drug-related impairment of vision occurs.

Patients should be informed that impairment of vision may occur and to immediately report this to the treating physician.

Aluminum hydroxide reduces absorption of ethambutol; ethambutol should therefore be taken at least one hour before antacids.

Monitor liver values and uric acid levels at monthly intervals.

#### References:

1. Shafran SD, Singer J, Zarowny DP, et al. A comparison of two regimens for the treatment of Mycobacterium avium complex bacteremia in AIDS: rifabutin, ethambutol, and clarithromycin versus rifampin, ethambutol, clofazimine, and ciprofloxacin. *N Engl J Med* 1996, 335:377-83. <http://amedeo.com/lit.php?id=8676931>
2. Ward TT, Rimland D, Kauffman C, Huycke M, Evans TG, Heifets L. Randomized, open-label trial of azithromycin plus ethambutol vs. clarithromycin plus ethambutol as therapy for Mycobacterium avium complex bacteremia in patients with HIV infection. *Clin Infect Dis* 1998, 27:1278-85. <http://amedeo.com/lit.php?id=9827282>

**Filgrastim** see G-CSF

## Fluconazole

Fluconazole is an antifungal azole and the drug of choice for treatment of candidiasis in HIV infection and for secondary prophylaxis of cryptococcosis. It is also a component of acute therapy for cryptococcosis.

**Trade name:** Diflucan™, several generics

50 mg, 100 mg and 200 mg capsules

Oral solution with 50 mg per 10 ml. Powder for suspension with 50 mg per 5 ml

Bottles for infusion with 100 mg, 200 mg and 400 mg

Diflucan Derm: 50 mg capsules; oral solution with 50 mg in 10 ml

**Drug class:** antimycotic

**Manufacturer:** Pfizer and several other companies

**Indications:** Candidiasis, cryptococcal meningitis. Also certain rare mycoses.

**Dose:** for oral candidiasis: 100 mg qd po; for *Candida* esophagitis 200 mg qd for 7-10 days. Double the dose on the first day. An attempt may be made with a higher dose if there is persistent candidiasis after 10 days (up to 800 mg daily).

Cryptococcal meningitis: Initially, 400 mg daily (up to 800 mg possible), combined with flucytosine and amphotericin B if possible. After completion of acute therapy – usually after 6 weeks – maintenance therapy with 200 mg fluconazole daily.

Renal insufficiency: halve dose with creatinine clearance of 50 to 10 ml/min; reduce to 25 % below 10 ml/min.

**Side effects:** overall good tolerability, rarely gastrointestinal complaints and elevated transaminases. Reversible alopecia in approximately 10 % of cases with more than 400 mg daily.

**Comments/warnings:** long-term treatment may lead to development of resistant strains. Not effective against *C. krusei* or *Aspergillus*. In cases of *C. glabrata* infection, higher doses are required (sensitivity dose-dependent). Levels are reduced by rifabutin or rifampin. Fluconazole increases the serum concentrations of rifabutin, atovaquone, clarithromycin, theophylline, opiates, coumarins, benzodiazepines, phenytoin and anti-convulsive drugs as well as AZT.

The tablets have good absorption, and infusions (2-3 times more expensive) are only required in cases of non-adherence, mucositis or problems with absorption.

### Internet sources:

USA: <http://hiv.net/link.php?id=94>

### References:

1. Friese G, Discher T, Fussle R, Schmalreck A, Lohmeyer J. Development of azole resistance during fluconazole maintenance therapy for AIDS-associated cryptococcal disease. *AIDS* 2001, 15:2344-5.
2. Perea S, Lopez-Ribot JL, Kirkpatrick WR, et al. Prevalence of molecular mechanisms of resistance to azole antifungal agents in *Candida albicans* strains displaying high-level fluconazole resistance isolated from HIV-infected patients. *Antimicrob Agents Chemother* 2001, 45: 2676-84. <http://amedeo.com/lit.php?id=11557454>
3. de Wet N, Llanos-Cuentas A, Suleiman J, et al. A randomized, double-blind, parallel-group, dose-response study of micafungin compared with fluconazole for the treatment of esophageal candidiasis in HIV-positive patients. *Clin Infect Dis* 2004; 39: 842-9. <http://amedeo.com/lit.php?id=15472817>
4. Wheat LJ, Connolly P, Haddad N, et al. Antigen clearance during treatment of disseminated histoplasmosis with itraconazole versus fluconazole in patients with AIDS. *Antimicrob Agents Chemother* 2002, 46: 248-50. <http://amedeo.com/lit.php?id=11751146>

## Fosamprenavir

Fosamprenavir is a calcium phosphate ester of amprenavir, which is more soluble and is better absorbed than amprenavir. This significantly reduces the number of pills compared to amprenavir. Overall tolerability is fairly good. Fosamprenavir has an interesting resistance profile and a variety of possibilities for dosing (see below).

**Trade name:** USA: Lexiva™, Europe: Telzir™

Film-coated tablets with 700 mg (60 = N3). Suspension 50 mg/ml (225 ml = N1)

**Drug class:** protease inhibitor

**Manufacturer:** GlaxoSmithKline

**Indications:** HIV infection, both treatment-naïve and -experienced patients

**Dose:** the recommended daily doses for **treatment-naïve** patients vary:

- 1,400 mg bid (2 pills bid; without ritonavir - not licensed in Europe!).
- 1,400 mg qd + 200 mg ritonavir qd (4 pills qd, not in Europe).
- 700 mg bid + 100 mg ritonavir bid (2 pills bid).

The once-daily version is not recommended for PI-experienced patients. **PI-experienced** patients should therefore only receive the following dose:

- 700 mg bid + 100 mg ritonavir bid (2 pills bid).

There are no restrictions with respect to fasting conditions – fosamprenavir may be taken with or without food.

**Side effects:** diarrhea, nausea, vomiting, headache, rash (up to 20 %). Rarely Stevens-Johnson syndrome (< 1 %).

**Comments/warnings:** contraindicated: cisapride, pimozide, midazolam, triazolam, ergotamines. Flecainide and propafenone are also contraindicated when fosamprenavir is boosted with ritonavir. There may be life-threatening interactions upon concurrent administration of amiodarone, lidocaine (systemic), tricyclic antidepressants and quinidine (measure levels!).

Do not use together with rifampin (this reduces amprenavir plasma levels by 90 %), delavirdine or St. John's wort; use cautiously with simvastatin, lovastatin, sildenafil, vardenafil. Carbamazepine, phenobarbital, phenytoin and dexamethasone can lower plasma levels of amprenavir.

Efavirenz seems to lower plasma levels significantly (probably to an extent that is clinically relevant). However, this is not the case if fosamprenavir is boosted with ritonavir. But: if fosamprenavir + ritonavir are administered once-daily, the ritonavir dose should be increased by 100 mg: efavirenz + 1,400 mg fosamprenavir qd + **300** mg ritonavir qd. Twice-daily dosing does not require a dose adjustment of ritonavir.

Rifabutin: dose reduction of rifabutin by at least 50 %. If fosamprenavir is boosted with ritonavir, a 75% reduction of the rifabutin dose is required (instead of 300 mg daily, only 150 mg every other day, or 150 mg three times per week).

Ketoconazole, itraconazole: if dosed > 400 mg daily, possibly dose reduction of ketoconazole/itraconazole. If fosamprenavir is boosted with ritonavir, ketoconazole and itraconazole doses above 200 mg daily are not recommended.

Caution in patients with sulfonamide allergy.

Caution with reduced liver function (possibly dose reduction). There is no data on the combination with ritonavir for such cases.

Methadone: an increased methadone dose might be required.

Contraception: an alternative to the pill is recommended.

Caution in combination with lopinavir – plasma levels of both drugs are reduced!

### Internet sources:

USA: <http://hiv.net/link.php?id=222>

### References:

1. Chapman TM, Plosker GL, Perry CM. Fosamprenavir: a review of its use in the management of antiretroviral therapy-naïve patients with HIV infection. *Drugs* 2004; 64: 2101-24. <http://amedeo.com/lit.php?id=15341507>
2. Ford SL, Wire MB, Lou Y, Baker KL, Stein DS. Effect of antacids and ranitidine on the single-dose pharmacokinetics of fosamprenavir. *Antimicrob Agents Chemother* 2005; 49: 467-9. Abstract: <http://amedeo.com/lit.php?id=15616339>
3. Gathe JC Jr, Iye P, Wood R, et al. SOLO: 48-week efficacy and safety comparison of once-daily fosamprenavir/ritonavir versus twice-daily nelfinavir in naïve HIV-1-infected patients. *AIDS* 2004; 18: 1529-37. <http://amedeo.com/lit.php?id=15238771>
4. Kashuba AD, Tierney C, Downey GF, et al. Combining fosamprenavir with lopinavir/ritonavir substantially reduces amprenavir and lopinavir exposure: ACTG protocol A5143 results. *AIDS* 2005; 19: 145-52. Abstract: <http://amedeo.com/lit.php?id=15668539>
5. Quercia R, Garnier E, Ferre V, et al. Salvage therapy with ritonavir-boosted amprenavir/fosamprenavir: virological and immunological response in two years follow-up. *HIV Clin Trials* 2005; 6: 73-80. Abstract: <http://amedeo.com/lit.php?id=15983891>
6. Yogev R, Kovacs A, Chadwick EG, Homans JD, Lou Y, Symonds WT. Single-dose safety and pharmacokinetics of amprenavir (141W94), a human immunodeficiency virus type 1 (HIV-1) protease inhibitor, in HIV-infected children. *Antimicrob Agents Chemother* 2005; 49: 336-41. Abstract: <http://amedeo.com/lit.php?id=15616313>

## Foscarnet

**Trade name:** Foscavir™

250 ml and 500 ml bottles with 24 mg/ml

**Drug class:** virostatic

**Manufacturer:** AstraZeneca

**Indications:** reserve drug for induction and maintenance therapy of CMV retinitis. Severe acyclovir-resistant herpes or varicella zoster infections.

**Dose:** 90 mg/kg iv over at least 2 hours twice daily for induction therapy (2-3 weeks) of CMV retinitis. 90-120 mg/kg over 2 hours once daily for maintenance therapy. HSV and VZV infections: 60 mg/kg iv bid for 2 weeks.

**Side effects:** nephrotoxicity! Usually reversible after discontinuation of foscarnet. Electrolyte changes (hypocalcemia, hypokalemia) are also common. More rarely: anemia, neutropenia, fever, rash, headache, nausea, vomiting, diarrhea. Often painful penile ulcerations (wash after every urination!).

**Comments/Warnings:** good hydration! At least 2.5 l fluids daily! To prevent hypocalcemia give one ampule of 10 % calcium solution in 100 ml 5 % glucose immediately prior to infusion of foscarnet. Give 500-1,000 ml 5 % glucose before or after foscarnet dose. Do not mix infusions.

Initial monitoring of Na, K, Ca, creatinine, blood count at least 3x/week.

No concurrent treatment with other nephrotoxic drugs.

Adjust dose in renal insufficiency. See prescribing information.

**References:**

1. Breton G, Fillet AM, Katlama C, Bricaire F, Caumes E. Acyclovir-resistant herpes zoster in HIV-infected patients: results of foscarnet therapy. *Clin Infect Dis* 1998; 27: 1525-7. <http://amedeo.com/lit.php?id=9868672>
2. Cheung TW, Jayaweera DT, Pearce D, et al. Safety of oral versus intravenous hydration during induction therapy with intravenous foscarnet in AIDS patients with cytomegalovirus infections. *Int J STD AIDS* 2000; 11: 640-7. <http://amedeo.com/lit.php?id=11057934>
3. Salmon-Ceron D, Fillet AM, Aboulker JP, et al. Effect of a 14-day course of foscarnet on cytomegalovirus (CMV) blood markers in a randomized study of HIV-infected patients with persistent CMV viremia. *Clin Infect Dis* 1999; 28: 901-5. <http://amedeo.com/lit.php?id=10825058>
4. Weinberg A, Jabs DA, Chou S, et al. mutations conferring foscarnet resistance in a cohort of patients with acquired immunodeficiency syndrome and cytomegalovirus retinitis. *J Infect Dis* 2003; 187: 777-784. <http://amedeo.com/lit.php?id=12599051>
5. Zanetta G, Maurice-Esteva L, Mousson C, et al. Foscarnet-induced crystalline glomerulonephritis with nephrotic syndrome and acute renal failure after kidney transplantation. *Transplantation* 1999; 67: 1376-8. <http://amedeo.com/lit.php?id=10360595>

**Foscavir™** see Foscarnet

**Fuzeon™** see T-20

## Ganciclovir

**Trade name:** Cymeven™

Bottles for injection with 500 mg. Orally, valganciclovir should be used instead of ganciclovir (see Valganciclovir).

**Drug class:** virostatic

**Manufacturer:** Hoffmann-La Roche

**Indications:** CMV retinitis. Since the approval of valganciclovir: only for use in patients for whom oral treatment is not possible.

**Dose:** initial treatment with normal renal function: 5 mg/kg bid as an iv infusion over one hour, for at least 14-21 days. Maintenance: 6 mg/kg iv qd, 5 x/week.

**Side effects:** leukopenia, anemia and thrombocytopenia are dose limiting. Nausea, vomiting, diarrhea or CNS symptoms such as confusion or headache are rare.

**Comments/Warnings:** monitor blood count every two days. Reduce dose by 30 % to 50 % for neutrophil counts between 500 and 800/μl; discontinue drug when below 500/μl (G-CSF if necessary!). Contraindicated in neutropenia < 500/μl, thrombocytopenia < 25,000/μl and concurrent chemotherapy. Caution if administering with AZT and ddi (increased toxicity!).

Ganciclovir is a potential teratogen and carcinogen. Dose adjustment is necessary in renal insufficiency (see link below).

**Internet sources:**

USA: <http://hiv.net/link.php?id=97>



**References:**

1. Czock D, Scholle C, Rasche FM, Schaarschmidt D, Keller F. Pharmacokinetics of valganciclovir and ganciclovir in renal impairment. *Clin Pharmacol Ther* 2002, 72: 142-50. <http://amedeo.com/lit.php?id=12189361>
2. Imai Y, Shum C, Martin DF, Kuppermann BD, Drew WL, Margolis TP. Emergence of drug-resistant cytomegalovirus retinitis in the contralateral eyes of patients with AIDS treated with ganciclovir. *J Infect Dis* 2004; 189: 611-5. Epub 2004 Jan 28. <http://amedeo.com/lit.php?id=14767813>

**G-CSF**

**Trade names:** Neupogen™ (Filgrastim), Granocyte™ (Lenograstim)

Granocyte™: Vials with 13.4 mil I.U. and 33.6 mil I.U.

Neupogen™: prefilled syringes with 300 µg and 480 µg

Neupogen™: vials with 300 µg in 1 ml and 480 µg in 1.6 ml

**Drug class:** cytokine

**Manufacturer:** Amgen, Chugai Pharma

**Indications:** neutropenia, especially drug-induced (AZT, ganciclovir, interferon, myelosuppressive chemotherapy), rarely HIV-related.

**Dose:** according to protocol for chemotherapy, usually approx. 5 µg/kg Neupogen™ daily on fixed days. Outside of chemotherapy protocols, 1-5 µg/kg Neupogen™ 1-3x/week, titrate dose down. The goal is usually at least 1,000 neutrophil granulocytes/µl. For Granocyte™ doses see product information.

**Side effects:** bone, back or muscle pain in 10 to 20 % of patients, sometimes severe (requiring generous analgesia). Irritation at the injection site.

**Comments/Warnings:** G-CSF is expensive. Long-term treatment should be avoided (change the drug causing neutropenia if possible). Remainders of individual ampules should be kept refrigerated in a syringe.

**Monitoring:** blood count twice weekly.

**Internet sources:**

USA, Neupogen™: <http://hiv.net/link.php?id=100>

**References:**

1. Campbell TB, Rapaport E, Schooley RT, Kuritzkes DR. Increased replication of HIV-1 minor variants during hematopoietic stem-cell mobilization with filgrastim. *J Infect Dis* 2004; 190: 257-66. Epub 2004 Jun 22. <http://amedeo.com/lit.php?id=15216459>
2. Davidson M, Min YI, Holbrook JT, et al. Use of filgrastim as adjuvant therapy in patients with AIDS-related cytomegalovirus retinitis. *AIDS* 2002, 16:757-65. <http://amedeo.com/lit.php?id=11964532>
3. Davidson M, Min YI, Holbrook JT, et al. Influence of filgrastim (granulocyte colony-stimulating factor) on HIV type 1 RNA in patients with cytomegalovirus retinitis. *J Infect Dis* 2002, 186: 1013-8. <http://amedeo.com/lit.php?id=12232843>

**Hivid™** see ddC – no longer on the market.

## Indinavir

Indinavir was, in 1996, one of the first protease inhibitors. Today, however, its use is limited due to side effects. There is cross-resistance with other PIs. Indinavir requires three times daily dosing on an empty stomach in its unboosted form – an unacceptable form of administration today. Indinavir is therefore now used almost exclusively with ritonavir boosting.

**Trade name:** Crixivan™. Capsules of 100 mg, 200 mg, 333 mg and 400 mg

**Drug class:** protease inhibitor

**Manufacturer:** Merck/MSD

**Indications:** HIV infection

**Dose:** in combination with ritonavir: 800 mg bid (two 400 mg capsules bid) plus 100 mg ritonavir bid (one 100 mg capsule bid). Or, 400 mg bid (one 400 mg capsule bid) plus 400 mg ritonavir bid (four 100 mg capsules bid). Dose reduction is often possible on TDM.

Dose without ritonavir boost (uncommon): 800 mg tid (two 400 mg capsules tid) one hour before or two hours after meals.

Impaired liver function: 600 mg tid (three 200 mg capsules tid).

**Side effects:** nephrolithiasis (in up to 25 %). Less frequently: nephrotoxicity with elevated serum creatinine. Diarrhea, nausea, vomiting. A sicca syndrome occurs relatively frequently (dry skin, mouth, eyes); ingrown toenails and paronychia; rarely alopecia. Asymptomatic hyperbilirubinemia.

Lipodystrophy (“Crixbelly”), dyslipidemia, disorders of glucose metabolism.

**Comments/Warnings:** the concurrent use of rifampin, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, or St. John’s wort is contraindicated.

The following dose adjustments are necessary:

- Rifabutin: boosting with ritonavir: 150 mg rifabutin every 2 days or three times a week.
- Ketoconazole and itraconazole: 600 mg indinavir tid.
- Sildenafil: maximum 25 mg sildenafil/48h.

At least 1.5 l of fluid should be consumed daily to prevent nephrolithiasis. The occurrence of nephrolithiasis and probably skin problems too, correlates with plasma levels. No concurrent administration of dDI.

In combination with ritonavir, indinavir can be taken twice daily and with meals.

### Internet sources:

USA: <http://hiv.net/link.php?id=102>

### References:

1. Aarnoutse RE, Brinkman K, Benetucci J, Begovac J, Stek M Jr, Burger DM. Pharmacokinetics of indinavir/ritonavir (800/100 mg twice a day) combined with efavirenz in HIV-infected patients. *AIDS* 2004; 18: 565-7. <http://amedeo.com/lit.php?id=15090812>
2. Bergshoeff AS, Fraaij PL, van Rossum AM, et al. Pharmacokinetics of indinavir combined with low-dose ritonavir in human immunodeficiency virus type 1-infected children. *Antimicrob Agents Chemother* 2004; 48: 1904-7. <http://amedeo.com/lit.php?id=15105157>

3. Ghosn J, Lamotte C, Ait-Mohand H, et al. Efficacy of a twice-daily antiretroviral regimen containing 100 mg ritonavir/400 mg indinavir in HIV-infected patients. *AIDS* 2003; 17: 209-14. <http://amedeo.com/lit.php?id=12545081>
4. Gulick RM, Meibohm A, Havlir D, et al. Six-year follow-up of HIV-1-infected adults in a clinical trial of antiretroviral therapy with indinavir, zidovudine, and lamivudine. *AIDS* 2003; 17: 2345-2349. <http://amedeo.com/lit.php?id=14571186>
5. Hammer SM, Squires KE, Hughes MD, et al. A controlled trial of two nucleoside analogues plus indinavir in persons with HIV infection and CD4 cell counts of 200 per cubic millimeter or less. *N Engl J Med* 1997; 337:725-33. <http://amedeo.com/lit.php?id=9287227>
6. Wasmuth JC, la Porte CJ, Schneider K, Burger DM, Rockstroh JK. Comparison of two reduced-dose regimens of indinavir (600 mg vs 400 mg twice daily) and ritonavir (100 mg twice daily) in healthy volunteers (COREDIR). *Antivir Ther* 2004; 9: 213-20. <http://amedeo.com/lit.php?id=15134183>

## Interferon alfa 2a/2b

**Trade names:** 2a: Roferon™, pegylated: Pegasys™; 2b: Intron A™, pegylated: PegIntron™

Pegasys™ (pegylated interferon alfa-2a): vials with 135 and 180 µg

PegIntron™ (pegylated interferon alfa-2b): vials with 50, 80, 100, 120 and 150 µg

Roferon-A™: prefilled syringes with 3, 4.5, 6 or 9 mil I.U. Alternatively, vials with 3 or 18 mil I.U. or cartridges with 18 mil I.U.

Intron A™ (Interferon alfa-2b): either in pen devices with 18, 30 or 60 mil I.U. or in vials with corresponding syringes and cannulas with 18 or 25 mil I.U.

**Drug class:** cytokine

**Manufacturer:** Hoffmann-La Roche (Roferon™, Pegasys™); Schering-Plough (Intron A™, PEG-Intron™)

**Indications:** severe Kaposi's sarcoma in patients with good immune status (> 300 CD4+ T-cells/µl); in such cases also always try HAART first. Chronic hepatitis C, possibly also for hepatitis B.

**Dose:** Pegasys™: 180 µg 1 x/week

PEG-Intron™: 1.5 µg/kg body weight 1 x/week

Standard interferons: 6 mil I.U. 3 x/week

Duration is dependent on success of treatment of KS, on HCV genotype and success of treatment for hepatitis C. Interferon is injected subcutaneously.

**Side effects:** Frequent! Influenza-like symptoms such as fever, chills, headaches and myalgia. Depression (even suicidality), irritability, fatigue, sleeping disorders, personality changes. Anemia, thrombocytopenia and leukopenia. Autoimmune thyroiditis. Reversible hair loss. Possibly also impaired vision.

**Comments/Warnings:** influenza-like symptoms usually occur a few hours after dosing and can be reduced with paracetamol. Administration of interferon is recommended in the evenings before going to bed, and one to two 500 mg tablets paracetamol may be taken one hour earlier.

All side effects are usually reversible.

Contraindications are severe liver or renal dysfunction (decompensated liver cirrhosis), severe heart disease, bone marrow disorders, CNS disorders (e.g. epilepsy, severe depression), uncompensated thyroid disorders.

Monitor blood count every two weeks initially, later monthly with standard laboratory tests. TSH every three months.

Interferons must be kept refrigerated.

### References:

1. Bani-Sadr F, Carrat F, Rosenthal E, et al. Spontaneous hepatic decompensation in patients coinfecting with HIV and hepatitis C virus during interferon-ribavirin combination treatment. *Clin Infect Dis* 2005; 41: 1806-9. <http://amedeo.com/lit.php?id=16288408>
2. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; 351: 451-9. <http://amedeo.com/lit.php?id=15282352>
3. Farel C, Suzman DL, McLaughlin M, et al. Serious ophthalmic pathology compromising vision in HCV/HIV co-infected patients treated with peginterferon alpha-2b and ribavirin. *AIDS* 2004; 18: 1805-9. <http://amedeo.com/lit.php?id=15316341>
4. Keating G, Curran M. Peginterferon-alpha-2a (40kD) plus Ribavirin: A review of its use in the management of chronic hepatitis C. *Drugs* 2003; 63: 701-730. <http://amedeo.com/lit.php?id=12656650>
5. Plosker GL, Keating GM. Peginterferon-alpha-2a (40kD) Plus Ribavirin : A Review of its Use in Hepatitis C Virus and HIV Co-infection. *Drugs* 2004; 64: 2823-43. <http://amedeo.com/lit.php?id=15563253>
6. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 351: 438-50. <http://amedeo.com/lit.php?id=15282351>

## Interleukin-2

Interleukin-2 is not licensed for HIV therapy; it may be justified in individual cases in the absence of CD4+ T-cell reconstitution – less than 100 CD4+ T-cells despite several months of complete viral suppression. It should otherwise only be used within clinical studies (ESPRIT, SILCAAT).

**Trade name:** Proleukin™ (Aldesleukin). Bottles for injection with  $18 \times 10^6$  I.E.

**Drug class:** cytokine

**Manufacturer:** Chiron

**Dose:** in cycles: 4.5-9 Mio I.E. sc bid for 5 days, every 6-8 weeks.

**Side effects:** almost obligatory fever, very often also chills. In addition fatigue, malaise, nausea/vomiting, myalgia, rarely hypotension (caution with antihypertensive drugs), dyspnea.

**Comments/warnings:** extensive counseling of patient! The clinician must have experience with this drug! Generous administration of paracetamol to reduce fever and influenza-like symptoms. Side effects usually subside 1-2 days after the last dose. IL-2 is contraindicated in individuals with severe coronary disease, severe infections or  $pO_2 < 60$  mm; it is also contraindicated in pregnancy.

Antihypertensive drugs may potentiate further any hypotension induced by IL-2.

IL-2 toxicity increases if hepatotoxic, nephrotoxic, myelotoxic or cardiotoxic drugs are administered at the same time.

### Internet sources:

USA: <http://hiv.net/link.php?id=112>

**References:**

1. Bonnet F, Saves M, Morlat PH, et al. Correlations of soluble interleukin-2 and tumor necrosis factor type II receptors with immunologic and virologic responses under HAART. *J Clin Immunol* 2002, 22: 75-82. <http://amedeo.com/lit.php?id=11998896>
2. Levy Y, Gahery-Segard H, Durier C, et al. Immunological and virological efficacy of a therapeutic immunization combined with interleukin-2 in chronically HIV-1 infected patients. *AIDS* 2005; 19: 279-86. Abstract: <http://amedeo.com/lit.php?id=15718838>
3. Martin BK, Wu AW, Gelman R, Mitsuyasu RT. quality of life in a clinical trial of highly active antiretroviral therapy alone or with intravenous or subcutaneous interleukin-2 administration. *J Acquir Immune Defic Syndr* 2005; 40: 428-433. Abstract: <http://amedeo.com/lit.php?id=16280697>
4. Stellbrink HJ, Van Lunzen J, Westby M, et al. Effects of interleukin-2 plus highly active antiretroviral therapy on HIV-1 replication and proviral DNA (COSMIC trial). *AIDS* 2002, 16: 1479-1487. <http://amedeo.com/lit.php?id=12131185>

**Intron A™** see Interferon

**Invirase™** see Saquinavir

## Isoniazid (INH)

**Drug class:** tuberculostatic

**Manufacturer:** isoniazid is offered by different manufacturers

**Indications:** combination therapy of tuberculosis.

Prophylactic treatment after tuberculin conversion.

**Dose:** 200 to 300 mg qd (4 to 5 mg/kg, maximum 300 mg) po, iv only in severe cases during the first two weeks of therapy. For prophylaxis of neuropathy, INH should always be combined with 100 mg pyridoxine po qd.

Pediatric dose: 6 (to 10) mg/kg qd, maximum 300 mg.

**Side effects:** toxic hepatitis, more frequent in older patients, with chronic liver disease and alcohol abuse. Peripheral neuropathy (PNP). Discontinue INH in severe cases and treat for several weeks with pyridoxine and vitamin B12. Psychosis, CNS symptoms. Fever, rash, nausea, vomiting, anemia, leukopenia, thrombocytopenia.

**Comments/Warnings:** contraindications are acute hepatitis and history of INH-associated hepatopathy or severe febrile reactions, peripheral neuropathy, macrohematuria.

Patients with epilepsy on treatment with carbamazepine or an hydantoin derivative might require dose adjustment of these drugs if given concurrently.

Interactions with barbiturates, cycloserine, theophylline, phenytoin and rifampin; doses of these drugs should be reduced due to CNS disorders.

Reduced absorption if taken concurrently with aluminum-based antacids.

No alcohol during treatment. Avoid ddl and d4T, if possible (high risk for PNP).

Initially, biweekly monitoring of blood count, transaminases, bilirubin, and renal function. Discontinue INH with elevated transaminases to more than 3-fold initial levels and symptoms; or with a 5-fold elevation even in the absence of symptoms.

### References:

1. Benator D, Bhattacharya M, Bozeman L, et al. Rifapentine and isoniazid once a week versus rifampicin and isoniazid twice a week for treatment of drug-susceptible pulmonary tuberculosis in HIV-negative patients: a randomised clinical trial. *Lancet* 2002, 360: 528. <http://amedeo.com/lit.php?id=12241657>
2. Sadaphal P, Astemborski J, Graham NM, et al. Isoniazid preventive therapy, hepatitis c virus infection, and hepatotoxicity among injection drug users infected with mycobacterium tuberculosis. *Clin Infect Dis* 2001, 33: 1687-91. <http://amedeo.com/lit.php?id=11641824>
3. Scholten JN, Driver CR, Munsiff SS, Kaye K, Rubino MA, Gourevitch MN et al. Effectiveness of isoniazid treatment for latent tuberculosis infection among human immunodeficiency virus (HIV)-infected and HIV-uninfected injection drug users in methadone programs. *Clin Infect Dis* 2003; 37: 1686-92. Epub 2003 Nov 17. <http://amedeo.com/lit.php?id=14689352>

## Itraconazole

**Trade name:** Sempera™

100 mg capsules

Oral solution (Sempera Liquid™) with 10 mg/ml (150 ml)

**Drug class:** antimycotic

**Manufacturer:** Janssen-Cilag / GlaxoSmithKline

**Indications:** histoplasmosis, aspergillosis, treatment-resistant *Candida* infections (second choice).

**Dose:** histoplasmosis, aspergillosis 200 mg bid.

Fluconazole-resistant *Candida* infections: 100 mg qd to 100 mg bid (up to 200 mg bid), ideally as itraconazole oral solution.

**Side effects:** nausea, vomiting, rash, dizziness. Toxic hepatitis.

**Comments/Warnings:** due to numerous interactions and unreliable plasma levels, oral dosing of itraconazole is problematic. However, in contrast to fluconazole, it is effective for many non-albicans strains, aspergillosis, and histoplasmosis.

No concurrent administration of itraconazole capsules with ddI, H2 blockers, omeprazole, antacids. No concurrent administration (of capsules or oral solution) with rifampin, rifabutin, carbamazepine, phenytoin, phenobarbital, simvastatin, lovastatin and isoniazid (these lower the bioavailability of itraconazole).

Itraconazole increases serum levels of cyclosporine, calcium antagonists, digoxin, lovastatin, simvastatin and indinavir. Dose adjustment of indinavir: 600 mg tid.

Itraconazole has a negative inotropic effect and should not be given to patients with heart failure.

To achieve maximum absorption:

- the capsules should be taken immediately after a full meal. Acidic drinks such as coke and orange juice may increase absorption;
- the oral solution should be taken between meals, and not together with grapefruit juice.

### Internet sources:

USA: <http://hiv.net/link.php?id=114>

**References:**

1. Caillot D, Bassaris H, McGeer A, et al. Intravenous itraconazole followed by oral itraconazole in the treatment of invasive pulmonary aspergillosis in patients with hematologic malignancies, chronic granulomatous disease, or AIDS. *Clin Infect Dis* 2001; 33: e83-90. <http://amedeo.com/lit.php?id=11550120>
2. Chariyalertsak S, Supparatpinyo K, Sirisanthana T, Nelson KE. A controlled trial of itraconazole as primary prophylaxis for systemic fungal infections in patients with advanced HIV infection in thailand. *Clin Infect Dis* 2002; 34: 277-284. <http://amedeo.com/lit.php?id=11740718>
3. Crommentuyn KM, Mulder JW, Sparidans RW, Huitema AD, Schellens JH, Beijnen JH. Drug-drug interaction between itraconazole and the antiretroviral drug lopinavir/ritonavir in an HIV-1-infected patient with disseminated histoplasmosis. *Clin Infect Dis* 2004; 38: e73-5. <http://amedeo.com/lit.php?id=15095234>
4. Wheat LJ, Connolly P, Haddad N, et al. Antigen clearance during treatment of disseminated histoplasmosis with itraconazole versus fluconazole in patients with AIDS. *Antimicrob Agents Chemother* 2002; 46: 248-50. <http://amedeo.com/lit.php?id=11751146>

**Kaletra™** see Lopinavir

## **Kivexa™ (USA: Epzicom™)**

Combination pill with 3TC (300 mg) and abacavir (600 mg).

As with Ziagen™, watch for hypersensitivity syndrome.

**Drug class:** nucleoside reverse transcriptase inhibitors (NRTI)

**Manufacturer:** GlaxoSmithKline

**Indications:** HIV infection

**Dose:** 1 tablet daily. Replace Kivexa™ with the individual drugs if kidney function is impaired (creatinine clearance below 50 ml/min), in order to adjust the 3TC dose.

**Side effects:** hypersensitivity syndrome with abacavir (see abacavir section!).

**Comments/Warnings:** abacavir hypersensitivity syndrome (2-6 %) can be life-threatening. For further information, see 3TC and abacavir.

**Internet sources:**

<http://hiv.net/link.php?id=240>

**Reference:**

1. DeJesus E, Herrera G, Teofilo E, et al. Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults. *Clin Infect Dis* 2004; 39 :1038-46. <http://amedeo.com/lit.php?id=15472858>

**Klacid™** see Clarithromycin

**Lamivudine** see 3TC (at the beginning of this chapter)

**Lexiva™** see Fosamprenavir

## Lopinavir

Lopinavir is an effective drug for salvage therapy, particularly in PI-experienced patients. It remains to be proven whether or not lopinavir is superior to other boosted PIs for first-line therapy. Disadvantages include gastrointestinal side effects (diarrhea) and the often significant dyslipidemia, which is probably more extreme than with some other PIs. As with all PIs, lipodystrophy and various drug interactions should be considered.

**Trade name:** Kaletra™

Tablets with 200 mg lopinavir + 50 mg ritonavir; bottles of 120 tablets.

Capsules with 133.3 mg lopinavir + 33.3 mg ritonavir; bottles of 180 capsules.

Solutions with 80 mg lopinavir + 20 mg ritonavir per ml; bottles of 160 ml.

Tablets will replace capsules

**Drug class:** protease inhibitor

**Manufacturer:** Abbott

**Indications:** HIV infection

**Oral dose:** The new formulation (approval in 2006): 2 tablets bid. 3 capsules bid or 5 ml solution bid with meals. In the USA: 6 capsules qd.

In combination with efavirenz or nevirapine, the lopinavir dose should be increased to 4 capsules bid or 6.5 ml solution bid. Measure plasma levels!

**Side effects:** mainly diarrhea, nausea, dyslipidemia, and lipodystrophy. Also: headaches, and elevated transaminases.

**Comments/Warnings:** drug interactions are numerous. All drugs metabolized by the CYP3A or CYP2D6 enzyme systems are contraindicated: flecainide, propafenone, astemizole, terfenadine, ergotamines, cisapride, pimozone, midazolam, triazolam. Rifampin and St. John's wort reduce the efficacy of lopinavir.

Caution with: lovastatin, simvastatin (myopathy, rhabdomyolysis), carbamazepine, phenobarbital, phenytoin or sildenafil (hypotension), amiodarone, warfarin, lidocaine, tricyclic antidepressants, quinidine, cyclosporine, tacrolimus. Measure plasma levels in patients with reduced liver function tests.

If lopinavir is combined with ddI, ddI must be taken one hour before or two hours after lopinavir. Lopinavir solution contains alcohol, therefore no comedication with disulfiram or metronidazole. Caution with the pill (contraception not safe).

When used with rifabutin, the rifabutin dose should be reduced by 75 %, i.e. to 150 mg qd every two days. Increasing the methadone dose may be necessary.

Capsules (not tablets) should be kept refrigerated for a maximum of 4-6 weeks at a maximum temperature of 25°C.

**Internet sources:**

USA: <http://hiv.net/link.php?id=116>

**References:**

1. Eron JJ, Feinberg J, Kessler HA, et al. Once-daily versus twice-daily lopinavir/ritonavir in antiretroviral-naive HIV-positive patients: a 48-week randomized clinical trial. *J Infect Dis* 2004; 189: 265-72. <http://amedeo.com/lit.php?id=14722892>
2. Eyer-Silva WA, Neves-Motta R, Pinto JF, et al. Inflammatory oedema associated with lopinavir-including HAART regimens in advanced HIV-1 infection: report of 3 cases. *AIDS* 2002, 16: 673-4.



3. Hicks C, King MS, Gulick RM, et al. Long-term safety and durable antiretroviral activity of lopinavir/ritonavir in treatment-naive patients: 4 year follow-up study. *AIDS* 2004; 18: 775-9. <http://amedeo.com/lit.php?id=15075512>
4. la Porte CJ, Schippers EF, van der Ende ME, et al. Pharmacokinetics of once-daily lopinavir/ritonavir and the influence of dose modifications. *AIDS* 2005; 19: 1105-7. Abstract: <http://amedeo.com/lit.php?id=15958844>
5. Martinez E, Domingo P, Galindo MJ, et al. Risk of metabolic abnormalities in patients infected with HIV receiving antiretroviral therapy that contains lopinavir-ritonavir. *Clin Infect Dis* 2004; 38: 1017-23. <http://amedeo.com/lit.php?id=15034836>
6. Raguin G, Chene G, Morand-Joubert L, et al. Salvage therapy with amprenavir, lopinavir and ritonavir 200 mg/d or 400 mg/d in HIV-infected patients in virological failure. *Antivir Ther* 2004; 9: 615-25. <http://amedeo.com/lit.php?id=15456093>
7. Schnell T, Schmidt B, Moschik G, et al. Distinct cross-resistance profiles of the new protease inhibitors amprenavir, lopinavir, and atazanavir in a panel of clinical samples. *AIDS* 2003; 17: 1258-61. <http://amedeo.com/lit.php?id=12819531>
8. Walsmley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med* 2002, 346: 2039-46. <http://amedeo.com/lit.php?id=12087139>

**Mavid™** see Clarithromycin

**Mycobutin™** see Rifabutin

## Nelfinavir

Nelfinavir is a well-tolerated PI, but is slightly less potent than boosted PIs. In comparison to NNRTIs, nelfinavir fares rather badly. The main problems include frequent diarrhea and the high pill burden.

**Trade name:** Viracept™, abbr. NFV

250 mg film-coated tablets (N2: 270); 50 mg/g oral powder (N1: 144 g). Film-coated tablets with 625 mg, in Europe not available.

**Drug class:** protease inhibitor

**Manufacturer:** Hoffmann-La Roche, Pfizer

**Indications:** HIV infection

**Oral dose:** 1250 mg bid or 750 mg tid with meals.

**Side effects:** diarrhea! Meteorism, and nausea also occur. Lipodystrophy, dyslipidemia, reduced glucose tolerance.

**Comments/Warnings:** contraindicated for comedication with rifampin, the pill, astemizole, terfenadine, cisapride, triazolam, ergotamines, simvastatin, lovastatin, and St. John's wort.

In combination with rifabutin: 150 mg rifabutin qd and increase nelfinavir dose to 1,250 mg bid or 1,000 mg tid.

Methadone: if withdrawal symptoms occur, dose may be increased.

Sildenafil: maximum 25 mg/48 h.

Nelfinavir should be taken with meals. Diarrhea can often be controlled with loperamide (maximum 16 mg/day).

Boosting with ritonavir is not advisable, as levels are not significantly changed.

**Internet sources:**

USA: <http://hiv.net/link.php?id=118>

**References:**

1. Dube MP, Parker RA, Tebas P, et al. Glucose metabolism, lipid, and body fat changes in antiretroviral-naive subjects randomized to nelfinavir or efavirenz plus dual nucleosides. *AIDS* 2005; 19: 1807-18. Abstract: <http://amedeo.com/lit.php?id=16227788>
2. Grossman Z, Paxinos EE, Averbuch D, et al. Mutation D30N is not preferentially selected by human immunodeficiency virus type 1 subtype C in the development of resistance to nelfinavir. *Antimicrob Agents Chemother* 2004; 48: 2159-65. <http://amedeo.com/lit.php?id=15155216>
3. Mirochnick M, Stek A, Acevedo M, et al. Safety and pharmacokinetics of nelfinavir coadministered with zidovudine and lamivudine in infants during the first 6 weeks of life. *J Acquir Immune Defic Syndr* 2005; 39: 189-94. Abstract: <http://amedeo.com/lit.php?id=15905735>
4. Timmermans S, Tempelman C, Godfried MH, et al. Nelfinavir and nevirapine side effects during pregnancy. *AIDS* 2005; 19: 795-9. Abstract: <http://amedeo.com/lit.php?id=15867493>
5. Walsmley S, Bernstein B, King M, et al. Lopinavir-ritonavir versus nelfinavir for the initial treatment of HIV infection. *N Engl J Med* 2002; 346: 2039-46. <http://amedeo.com/lit.php?id=12087139>

**Neupogen™** see G-CSF

## Nevirapine

Nevirapine is a frequently prescribed NNRTI, which is also used successfully for the prevention of mother-to-child transmission. As with all NNRTIs, a single point mutation is sufficient to develop high-level resistance. Nevirapine is very useful for simplification of successful HAART regimens. Lead-in dosing should always be performed. With very good long-term tolerability (favorable lipid profile!), the main problem is hepatotoxicity within the first months of treatment (see below).

**Trade name:** Viramune™, abbr. NVP

200 mg tablets (N1 = 60, N2 = 120 tablets). 50 mg/5 ml suspension

**Drug class:** NNRTI

**Manufacturer:** Boehringer Ingelheim

**Indications:** HIV infection

**Oral dose:** 1 tablet bid. Always start with lead-in dosing! The initial lead-in dose (1 tablet/day over two weeks) reduces the frequency of rash. For resumption of treatment after treatment interruption, lead-in dosing is generally not necessary if the drug was well tolerated. Due to its long half-life, nevirapine should be discontinued at least three days before other backbone drugs, in order to prevent resistance. Nevirapine may be taken on an empty stomach or with meals.

**Side effects:** mainly hepatotoxicity, rash. Less frequently: fever, nausea, drowsiness, headache, myalgia. These side effects may occur with or without hepatotoxicity and/or rash.  $\gamma$ GT elevation on nevirapine is almost the rule.

To detect **hepatotoxicity** (occurring in 15 %; defined as an increase in transaminases to at least three times the upper limit of normal), liver function tests should be monitored biweekly for the first two months. Thereafter, monthly tests are neces-

sary, as more than half of the hepatotoxic episodes occur after the first quarter of treatment. In such cases, treatment must be interrupted until liver function tests have returned to initial levels. Treatment is restarted with 200 mg qd. The dose may be increased to 200 mg bid only after a prolonged period of observation. If liver enzymes increase again, nevirapine should be permanently discontinued. The website of the EMEA provides detailed guidelines: <http://hiv.net/link.php?id=120>. The risk is greater with a good immune status (women > 250 CD4+ T-cells/ $\mu$ l: 12-fold ; men > 400 CD4+ T-cells/ $\mu$ l: 5-fold).

A **rash**, often pruritic and usually occurring within the first six weeks of treatment, can be treated with antihistamines if mucous membranes are not involved and if transaminases are normal. Topical formulations are effective against pruritus. Nevirapine must be discontinued if a severe rash occurs; in these cases, steroids may be used (e.g. prednisolone 1 mg/kg for 3-5 days). Nevirapine should also be discontinued if other systemic symptoms occur (fever, conjunctivitis, myalgia, arthralgia, malaise). If the rash occurs during the first two weeks of treatment, the dose should not be increased until the rash has resolved completely. Prophylactic treatment with steroids or antihistamines is not advised.

**Comments/Warnings:** cautious use in hepatic dysfunction (TDM).

Contraindicated for comedication with rifampin, ketoconazole, St. John's wort and the pill.

Azole derivatives: fluconazole should be used for antimycotic treatment.

Dose adjustment in combination with

- Lopinavir: possibly increase Kaletra™ (measure plasma levels!)
- Indinavir: increase indinavir dose to 1,000 mg tid.
- Methadone: if withdrawal symptoms occur, dose may need to be increased.

Nevirapine has a favorable long-term profile. In particular, lipid levels are usually positively influenced.  $\gamma$ GT is almost always increased during long-term treatment. Values of up to 150 U/l can be tolerated. Nevirapine should not be given for post-exposure prophylaxis.

**Internet sources:**

USA: <http://hiv.net/link.php?id=121>

**References:**

1. Back D, Gibbons S, Khoo S. Pharmacokinetic drug interactions with nevirapine. *J Acquir Immune Defic Syndr* 2003; 34 Suppl 1: S8-14. <http://amedeo.com/lit.php?id=14562853>
2. Chi BH, Wang L, Read JS, et al. Timing of maternal and neonatal dosing of nevirapine and the risk of mother-to-child transmission of HIV-1: HIVNET 024. *AIDS* 2005; 19: 1857-64. Abstract: <http://amedeo.com/lit.php?id=16227794>
3. Clarke SM, Mulcahy FM, Tjia J, et al. Pharmacokinetic interactions of nevirapine and methadone and guidelines for use of nevirapine to treat Injection drug users. *Clin Infect Dis* 2001, 33. <http://amedeo.com/lit.php?id=11568856>
4. De Maat MM, Ter Heine R, Van Gorp EC, et al. Case series of acute hepatitis in a non-selected group of HIV-infected patients on nevirapine-containing antiretroviral treatment. *AIDS* 2003; 17: 2209-14. <http://amedeo.com/lit.php?id=14523278>
5. Gil P, de Gorgolas M, Estrada V, et al. Long-term efficacy and safety of protease inhibitor switching to nevirapine in HIV-infected patients with undetectable virus load. *Clin Infect Dis* 2004; 39: 1024-9. <http://amedeo.com/lit.php?id=15472856>
6. Gonzalez de Requena D, Nunez M, Jimenez-Nacher I, Soriano V. Liver toxicity caused by nevirapine. *AIDS* 2002, 16: 290-1. <http://amedeo.com/lit.php?id=11807315>

## 748 Drug Profiles

7. Johnson JA, Li JF, Morris L, et al. Emergence of drug-resistant HIV-1 after intrapartum administration of single-dose nevirapine is substantially underestimated. *J Infect Dis* 2005; 192: 16-23. Epub 2005 Jun 1. Abstract: <http://amedeo.com/lit.php?id=15942889>
8. Lallemand M, Jourdain G, Le Coeur S, et al. Single-dose perinatal nevirapine plus standard zidovudine to prevent mother-to-child transmission of HIV-1 in Thailand. *N Engl J Med* 2004; 351: 217-28. <http://amedeo.com/lit.php?id=15247338>
9. Martinez E, Arnaiz JA, Podzamczar D, et al. Substitution of nevirapine, efavirenz, or abacavir for protease inhibitors in patients with HIV infection. *NEJM* 2003; 349: 1036-46. <http://amedeo.com/lit.php?id=12968087>
10. Martinez E, Blanco JL, Arnaiz JA, et al. Hepatotoxicity in HIV-1-infected patients receiving nevirapine-containing antiretroviral therapy. *AIDS* 2001, 15: 1261-1268. <http://amedeo.com/lit.php?id=11426070>
11. Negredo E, Molto J, Burger D, et al. Lopinavir/ritonavir plus nevirapine as a nucleoside-sparing approach in antiretroviral-experienced patients (NEKA study). *J Acquir Immune Defic Syndr* 2005; 38: 47-52. Abstract: <http://amedeo.com/lit.php?id=15608524>
12. Parienti JJ, Massari V, Descamps D, et al. Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy. *Clin Infect Dis* 2004; 38: 1311-6. <http://amedeo.com/lit.php?id=15127346>
13. Sanne I, Mommeja-Marin H, Hinkle J, et al. Severe hepatotoxicity associated with nevirapine use in HIV-infected subjects. *JID* 2005; 191: 825-9. Abstract: <http://amedeo.com/lit.php?id=15717255>
14. Timmermans S, Tempelman C, Godfried MH, et al. Nelfinavir and nevirapine side effects during pregnancy. *AIDS* 2005; 19: 795-9. Abstract: <http://amedeo.com/lit.php?id=15867493>
15. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004; 363: 1253-63. <http://amedeo.com/lit.php?id=15094269>

**Norvir™** see Ritonavir

**Pegasys™** see Interferon

**PegIntron™** see Interferon

**Pentacarinat™** see Pentamidine

## Pentamidine

**Trade name:** Pentacarinat™ 300 mg vials

**Drug class:** antibiotic

**Manufacturer:** Aventis, GlaxoSmithKline

**Indications:** treatment and secondary prophylaxis of *Pneumocystis pneumonia* if co-trimoxazole is contraindicated (hypersensitivity, resistance to treatment).

**Dose:** treatment: 200-300 mg Pentacarinat™ iv for five days (4 mg/kg), then halve the dose. In very mild cases, daily inhalations with 300 mg.

In renal failure and creatinine clearance of 50-10 ml/min: 4 mg/kg q 24-36 h; < 10 ml/min: 4 mg/kg q 48 h.

Prophylaxis: inhalation of 300 mg 1-2 x/month.

**Side effects:** frequent with intravenous dosing! Nausea, vomiting, metallic taste; nephrotoxicity (increased creatinine in the second week of treatment) up to renal

failure. Hypo- or hyperglycemia (possible even months after end of treatment), hypotension, arrhythmia, pancreatitis.

Leukopenia and thrombocytopenia. Inhalation may induce cough, rarely asthma attacks.

**Comments/Warnings:**

*Inhalation:* pentamidine as an aerosol is contraindicated in asthma and treatment with beta-blockers. Inhalation may be ineffective with pulmonary disease. Prior inhalation of a  $\beta$ -mimetic may be desirable.

*Infusions:* caution in liver or renal failure, hyper- or hypotension, hyperglycemia, cytopenia. Always ensure sufficient intake of electrolytes and fluids. No concurrent administration of other nephrotoxic drugs (e.g. aminoglycosides, amphotericin B, foscarnet). Patient should remain in supine position before, during and after infusions of pentamidine (caution: hypotension!). Pentamidine should be infused slowly over at least 2 hours! Daily monitoring of BUN, serum creatinine, blood count, fasting blood glucose, urinalysis and serum electrolytes, weekly monitoring of bilirubin, alkaline phosphatase, transaminases.

**References:**

1. Chan M, Lee-Pack LR, Favell K, Chan CK. Acute pulmonary effects of three nebulizers for administering aerosol pentamidine: comparison of Parineb to Fisonab and Respirgard II. *J Aerosol Med* 1996, 9: 521-6. <http://amedeo.com/lit.php?id=10163666>
2. Girgis I, Gualberti J, Langan L, et al. A prospective study of the effect of I.V. pentamidine therapy on ventricular arrhythmias and QTc prolongation in HIV-infected patients. *Chest* 1997, 112: 646-53. <http://amedeo.com/lit.php?id=9315796>
3. O'Brien JG, Dong BJ, Coleman RL, Gee L, Balano KB. A 5-year retrospective review of adverse drug reactions and their risk factors in HIV-infected patients who were receiving intravenous pentamidine therapy for *Pneumocystis carinii* pneumonia. *Clin Infect Dis* 1997, 24: 854-9. <http://amedeo.com/lit.php?id=9142782>
4. Warnock AC, Rimland D. Comparison of trimethoprim-sulfamethoxazole, dapsone, and pentamidine in the prophylaxis of *Pneumocystis carinii* pneumonia. *Pharmacotherapy* 1996, 16: 1030-8. <http://amedeo.com/lit.php?id=8947975>
5. Wei CC, Pack LL, Chan CK. Effects of long-term aerosol pentamidine for *Pneumocystis carinii* prophylaxis on pulmonary function. *Chest* 1998, 114: 742-7. <http://amedeo.com/lit.php?id=9743160>

**Prezista™** see Darunavir

**Proleukin™** see Interleukin-2

## Pyrimethamine

**Trade name:** Daraprim™

25 mg tablets

**Manufacturer:** GlaxoSmithKline

**Indications:** prophylaxis and treatment of cerebral toxoplasmosis. Prophylaxis of pneumocystis pneumonia.

**Dose:** treatment of toxoplasmosis: Daraprim™ 2 tbl. à 25 mg bid (for 3 days, then halve the dose) **plus** Leucovorin™ 1 tbl. à 15 mg every other day **plus either** sulfadiazine or clindamycin.

PCP prophylaxis in combination with dapsone: Daraprim™ 2 tbl. à 25 mg per week **plus** Dapsone™ 1 tbl. à 50 mg qd **plus** Leucovorin™ 2 tbl. à 15 mg per week.

**Side effects:** Myelosuppressive! Most important side effect is anemia. Thrombocytopenia and leukopenia. Nausea, colics, vomiting, diarrhea. Rarely seizures, tremor or ataxia.

**Comments/Warnings:** pyrimethamine is contraindicated in megaloblastic anemia resulting from folic acid deficiency. Caution in patients with seizures, renal failure, asthma or G6PD deficiency. All patients on pyrimethamine should receive folic acid to decrease myelosuppression. Initial weekly monitoring of blood counts.

**Product information UK:** <http://hiv.net/link.php?id=124>

### References:

1. Chene G, Morlat P, Lepout C, et al. Intention-to-treat vs. on-treatment analyses of clinical trial data: experience from a study of pyrimethamine in the primary prophylaxis of toxoplasmosis in HIV-infected patients. *Control Clin Trials* 1998, 19: 233-48. <http://amedeo.com/lit.php?id=9620807>
2. Jacobson JM, Hafner R, Remington J, et al. Dose-escalation, phase I/II study of azithromycin and pyrimethamine for the treatment of toxoplasmic encephalitis in AIDS. *AIDS* 2001, 15: 583-9. <http://amedeo.com/lit.php?id=11316995>
3. Podzamczar D, Miro JM, Ferrer E, et al. Thrice-weekly sulfadiazine-pyrimethamine for maintenance therapy of toxoplasmic encephalitis in HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2000, 19: 89-95. <http://amedeo.com/lit.php?id=10746493>
4. Schurmann D, Bergmann F, Albrecht H, et al. Effectiveness of twice-weekly pyrimethamine-sulfadoxine as primary prophylaxis of *Pneumocystis carinii* pneumonia and toxoplasmic encephalitis in patients with advanced HIV infection. *Eur J Clin Microbiol Infect Dis* 2002, 21: 353-61. <http://amedeo.com/lit.php?id=12072919>
5. Torre D, Casari S, Speranza F, et al. Randomized trial of trimethoprim-sulfamethoxazole versus pyrimethamine-sulfadiazine for therapy of toxoplasmic encephalitis in patients with AIDS. *Antimicrob Agents Chemother* 1998, 42: 1346-9. <http://amedeo.com/lit.php?id=9624473>

**Rebetol™** see Ribavirin

## Ribavirin

**Trade names:** Copegus™, 200 mg film-coated tablets (N1: 42; N2: 168). Rebetol™, 200 mg hard capsules (N1: 84; N2: 168) or solution (40 mg/ml)

**Drug class:** virostatic

**Manufacturer:** Roche (Copegus™), Schering Plough (Rebetol™)

**Indication:** chronic Hepatitis C, only in combination with interferon

**Dose:** daily dose 800 mg for body weight < 65 kg, 1,000 mg for 65-85 kg, 1,200 mg for > 85 kg. Daily dose should be divided into two daily applications. Ribavirin should be taken with meals. Treatment duration depends on genotype and other factors. Lower doses yield a lower treatment response (see below)!

**Side effects:** the most important side effect is reversible hemolytic anemia; gastrointestinal complaints, headache and fatigue may also occur. Rarely lactic acidosis, pancreatitis in combination with NRTIs.

**Comments/Warnings:** ribavirin is contraindicated in severe coronary disease, renal failure, decompensated liver cirrhosis, and hemoglobinopathy. It is also contra-

indicated in pregnancy and reliable contraception is required due to ribavirin's potential teratogenicity.

Dose reduction (600-800 mg/day) may be necessary in cases of severe anemia (hemoglobin < 10 g/dl). However, consider always erythropoietin before dose reduction as there is a linear correlation between mg/kg ribavirin dose and treatment success. Discontinuation of ribavirin may be necessary at hemoglobin values < 8.5 g/dl. Avoid concurrent treatment with other myelosuppressive medications. AZT should be replaced by other NRTIs.

Ribavirin can lead to lactic acidosis in combination with other NRTIs! Most importantly, ddI should be avoided but care should be taken with other NRTIs!

Efavirenz-induced depression may worsen on ribavirin.

Monitoring of blood count, AST, ALT, lipase initially at weekly intervals, later monthly. Lactate measurement if unspecific symptoms occur!

### Internet sources:

USA: Copegus™: <http://hiv.net/link.php?id=197>, Rebetol™:  
<http://hiv.net/link.php?id=126>

### References:

1. Bani-Sadr F, Carrat F, Rosenthal E, et al. Spontaneous hepatic decompensation in patients coinfecting with HIV and hepatitis C virus during interferon-ribavirin combination treatment. *Clin Infect Dis* 2005; 41: 1806-9. Abstract: <http://amedeo.com/lit.php?id=16288408>
2. Butt AA. Fatal lactic acidosis and pancreatitis associated with ribavirin and didanosine therapy. *AIDS Read* 2003; 13: 344-8. <http://amedeo.com/lit.php?id=12889452>
3. Chung RT, Andersen J, Volberding P, et al. Peginterferon Alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; 351: 451-9. <http://amedeo.com/lit.php?id=15282352>
4. Keating G, Curran M. Peginterferon-alpha-2a (40kD) plus ribavirin: a review of its use in the management of chronic hepatitis C. *Drugs* 2003; 63: 701-730. <http://amedeo.com/lit.php?id=12656650>
5. Moreno A, Quereda C, Moreno L, Perez-Elias MJ, Muriel A, Casado JL et al. High rate of didanosine-related mitochondrial toxicity in HIV/HCV-coinfected patients receiving ribavirin. *Antivir Ther* 2004; 9: 133-8. <http://amedeo.com/lit.php?id=15040545>
6. Rendon AL, Nunez M, Romero M, et al. Early monitoring of ribavirin plasma concentrations may predict anemia and early virologic response in HIV/hepatitis C virus-coinfected patients. *J Acquir Immune Defic Syndr* 2005; 39: 401-5. Abstract: <http://amedeo.com/lit.php?id=16010160>
7. Rodriguez-Torres M, Torriani FJ, Soriano V, et al. Effect of ribavirin on intracellular and plasma pharmacokinetics of NRTIs in patients with HIV-HCV coinfection: results of a randomized clinical study. *Antimicrob Agents Chemother* 2005; 49: 3997-4008. <http://amedeo.com/lit.php?id=16189072>
8. Soriano V, Nunez M, Camino N, et al. Hepatitis C virus-RNA clearance in HIV-coinfected patients with chronic hepatitis C treated with pegylated interferon plus ribavirin. *Antivir Ther* 2004; 9: 505-9. <http://amedeo.com/lit.php?id=15456081>
9. Torriani FJ, Rodriguez-Torres M, Rockstroh JK, et al. Peginterferon Alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; 351: 438-50. <http://amedeo.com/lit.php?id=15282351>

**Rescriptor™** see Delavirdine

**Retrovir™** see AZT

**Reyataz™** see Atazanavir

## Rifabutin

**Trade name:** Mycobutin™

150 mg capsules

**Drug class:** antibiotic, tuberculostatic

**Manufacturer:** Pharmacia and other companies

**Indications:** infections with Mycobacterium avium complex (MAC), always in combination with other drugs (usually ethambutol and azithromycin). Also for treatment of tuberculosis, when rifampicin is not possible.

**Dose:** 300 mg rifabutin daily (+ azithromycin + ethambutol).

Renal failure: dose reduction by 50 % for creatinine clearance < 30 ml/min.

Dose adjustments for concurrent dosing with antiretroviral drugs:

Drug	Recommendation
Atazanavir/r*	Rifabutin: 150 mg every other day or three times per week
Fosamprenavir/r	Rifabutin: 150 mg every other day or three times per week
Indinavir/r*	Rifabutin: 150 mg every other day or three times per week
Lopinavir/r*	Rifabutin: 150 mg every other day or three times per week
Saquinavir/r*	Rifabutin: 150 mg every other day or three times per week
Tipranavir/r*	Rifabutin: 150 mg every other day or three times per week.
Nelfinavir	Nelfinavir 1,250 mg bid + rifabutin: 150 mg qd
Delavirdine	Rifabutin is contraindicated
Efavirenz	Rifabutin: Increase to 450 qd or 600 mg three times weekly
Nevirapine	Standard dose

\* /r = boosted with ritonavir

**Side effects:** Nausea, vomiting, elevation of liver enzymes, jaundice. Uveitis usually only with daily doses > 300 mg and concurrent treatment with clarithromycin or fluconazole. Red discoloration of urine, skin and body secretions (patients should be informed about this!).

**Comments/Warnings:** Rifabutin is contraindicated in cases of known hypersensitivity to rifabutin and rifampin; also in thrombocytopenia and severe hepatic dysfunction.

Rifabutin can decrease the efficacy of the following drugs:

analgesics, anticoagulants, corticosteroids, cyclosporine, digitalis (except digoxin), dapsone, oral antidiabetics, oral contraceptives, narcotic analgesics, phenytoin and quinidine.

Erythromycin, ketoconazole, itraconazole, fluconazole and clarithromycin can increase plasma levels of rifabutin.

Antacids should be taken at least three hours after rifabutin.

Monitor blood count and liver enzymes initially biweekly, later monthly.

**Internet sources:**

USA: <http://hiv.net/link.php?id=129>



**References:**

- Centers for Disease Control. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR* 2000, 49: 185-9. <http://amedeo.com/lit.php?id=11795500>
- Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. *Arch Intern Med* 2002, 162: 985-92. <http://amedeo.com/lit.php?id=11996607>
- Gallicano K, Khaliq Y, Carignan G, Tseng A, Walmsley S, Cameron DW. A pharmacokinetic study of intermittent rifabutin dosing with a combination of ritonavir and saquinavir in patients infected with HIV. *Clin Pharmacol Ther* 2001, 70: 149-58. <http://amedeo.com/lit.php?id=11503009>
- Gatti G, Papa P, Torre D, et al. Population pharmacokinetics of rifabutin in HIV-infected patients. *Antimicrob Agents Chemother* 1998, 42: 2017-23. <http://amedeo.com/lit.php?id=9687400>
- Hafner R, Bethel J, Standiford HC, et al. Tolerance and pharmacokinetic interactions of rifabutin and azithromycin. *Antimicrob Agents Chemother* 2001, 45: 1572-7. <http://amedeo.com/lit.php?id=11302832>
- Narita M, Stambaugh JJ, Hollender ES, et al. Use of rifabutin with protease inhibitors for HIV-infected patients with tuberculosis. *Clin Infect Dis* 2000, 30: 779-83. <http://amedeo.com/lit.php?id=10816148>
- Weiner M, Benator D, Peloquin CA, et al. Evaluation of the drug interaction between rifabutin and efavirenz in patients with HIV infection and tuberculosis. *Clin Infect Dis* 2005; 41: 1343-9. Abstract: <http://amedeo.com/lit.php?id=16206114>

## Rifampin (or rifampicin)

**Drug class:** tuberculostatic

**Manufacturer:** rifampin is manufactured by several companies

**Indications:** tuberculosis.

**Dose:** 600 mg daily (body weight > 50 kg) or 450 mg (body weight < 50 kg). Ideally taken in the morning on an empty stomach!

**Side effects:** toxic hepatitis (up to 20 %), cholestatic changes. Red discoloration of urine and other body fluids (inform patients!). Soft contact lenses may permanently stain red. Allergies are frequent. Gastrointestinal complaints such as nausea, vomiting, diarrhea.

**Comments/Warnings:** caution in patients with liver disease. Discontinue rifampin if ALT > 100 U/l or with elevated bilirubin (careful re-exposure with gradually increasing doses is possible after normalization of values), and in patients with severe and persistent diarrhea (pseudomembranous colitis!).

Rifampin should be avoided if concurrent ART with NNRTIs or PIs is necessary.

Rifampin increases metabolism of numerous drugs, reducing their efficacy if administered concurrently. These drugs include atovaquone, warfarin, barbiturates, benzodiazepines, beta-blockers, clarithromycin, contraceptives, steroids, oral anti-diabetics, cyclosporine, dapsone, digitalis, doxycycline, erythromycin, haloperidol, ketoconazole, methadone, phenytoin, theophylline, trimethoprim, verapamil. Combination with ketoconazole or voriconazole is contraindicated.

Antacids, opiates and anticholinergics reduce the bioavailability of orally administered rifampin if given simultaneously. To avoid this interaction, rifampin should be given several hours before these drugs.

Not for use in pregnancy.

Blood count and liver values should be monitored fortnightly.

**References:**

1. Finch CK, Chrisman CR, Baciewicz AM, Self TH. Rifampin and rifabutin drug interactions: an update. *Arch Intern Med* 2002; 162:985-92. <http://amedeo.com/lit.php?id=11996607>
2. Gurumurthy P, Ramachandran G, Hemanth Kumar AK, et al. Decreased bioavailability of rifampin and other antituberculosis drugs in patients with advanced HIV disease. *Antimicrob Agents Chemother* 2004; 48: 4473-5. <http://amedeo.com/lit.php?id=15504887>
3. Havlir DV, Barnes PF. Tuberculosis in patients with HIV infection. *N Engl J Med* 1999; 340:367-73.
4. Justesen US, Andersen AB, Klitgaard NA, Broesen K, Gerstoft J, Pedersen C. Pharmacokinetic interaction between rifampin and the combination of indinavir and low-dose ritonavir in HIV-infected patients. *Clin Infect Dis* 2004; 38: 426-9. <http://amedeo.com/lit.php?id=14727216>
5. Li J, Munsiff SS, Driver CR, Sackoff J. Relapse and acquired rifampin resistance in HIV-infected patients with tuberculosis treated with rifampin- or rifabutin-based regimens in New York City, 1997-2000. *Clin Infect Dis* 2005; 41: 83-91. <http://amedeo.com/lit.php?id=15937767>
6. Ribera E, Pou L, Lopez RM, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *J Acquir Immune Defic Syndr* 2001; 28: 450-3. <http://amedeo.com/lit.php?id=11744833>

**Ritonavir**

Due to its gastrointestinal side effects, the therapeutic dose of ritonavir is hardly acceptable and rarely prescribed. However, ritonavir remains an important drug for boosting other protease inhibitors. In these combinations, when lower doses are used, side effects of ritonavir are tolerable. Numerous drug interactions must be considered.

**Trade name:** Norvir™, but also included in Kaletra™ (see lopinavir)

100 mg Norvir™ soft gel capsules

80 mg/ml Norvir™ oral solution

**Drug class:** protease inhibitor

**Manufacturer:** Abbott

**Indications:** HIV infection

**Oral dose:** in very rare cases, in which ritonavir is used as a single PI, the dose is 600 mg bid (increase dose over two weeks: 300 mg bid on day 1-2, 400 mg bid on day 3-5, 500 mg bid on day 6-13). In all other cases, ritonavir is for boosting of other PIs! Daily doses in combination with approved PIs:

- Saquinavir (1000 mg Invirase™ bid): 100 mg ritonavir bid
- Indinavir (800 mg Crixivan™ bid): 100 mg ritonavir bid or  
Indinavir (400 mg Crixivan™ bid): 400 mg ritonavir bid
- Lopinavir (Kaletra™): Fixed combination, see lopinavir.
- Atazanavir (300 mg Reyataz™ qd): 100 mg ritonavir qd
- Fosamprenavir (700 mg Telzir™ bid): 100 mg ritonavir bid or  
Fosamprenavir (1400 mg Telzir™ qd): 200 mg ritonavir qd (this once-daily combination is not suitable for treatment-experienced patients!)
- Tipranavir (500 mg Aptivus™ qd) + 200 mg ritonavir bid

**Side effects:** very frequent when used as single PI (600 mg bid): nausea, vomiting, diarrhea, headache, perioral paresthesia and electric sensations on arms and legs. Elevated transaminases and  $\gamma$ GT, often significant dyslipidemia, reduced glucose tolerance and, rarely, diabetes mellitus. Lipodystrophy.

**Comments/Warnings:** even the low boosting doses used in combination with other PIs have multiple drug interactions! The following are contraindicated: rifampin, amiodarone, astemizole, bepridil, terfenadine, encainide, flecainide, cisapride, triazolam, ergotamine, simvastatin, lovastatin, quinidine, and St. John's wort. Sildenafil should be avoided!

Caution should be taken and plasma levels measured for both ritonavir and (if possible) the following comedications: methadone, immunosuppressants (cyclosporine, tacrolimus), macrolide antibiotics (erythromycin, clarithromycin), steroids, calcium antagonists, tricyclic antidepressants, other antidepressants (fluoxetine, paroxetine, sertraline), neuroleptics (haloperidol, risperidone, thioridazine), antimycotic drugs (ketoconazole, itraconazole), carbamazepine, tolbutamide, rifabutin, theophylline, and warfarin.

**Internet sources:**

USA: <http://hiv.net/link.php?id=31>

**References:**

1. Cameron DW, Heath-Chiozzi M, Danner S, et al. Randomised placebo-controlled trial of ritonavir in advanced HIV-1 disease. *Lancet* 1998, 351:543-9. <http://amedeo.com/lit.php?id=9492772>
2. Cooper CL, van Heeswijk RP, Gallicano K, Cameron DW. A review of low-dose ritonavir in protease inhibitor combination therapy. *Clin Infect Dis* 2003; 36: 1585-92. <http://amedeo.com/lit.php?id=12802760>
3. Kempf DJ, Marsh KC, Kumar G, et al. Pharmacokinetic enhancement of inhibitors of the HIV protease by coadministration with ritonavir. *Antimicrob Agents Chemother* 1997, 41:654-60. <http://amedeo.com/lit.php?id=9056009>
4. Moreno S, Podzamczer D, Blazquez R, et al. Treatment of tuberculosis in HIV-infected patients: safety and antiretroviral efficacy of the concomitant use of ritonavir and rifampin. *AIDS* 2001; 15: 1185-7.
5. Pardo Rey C, Yebra M, Borrallo M, Vega A, Ramos A, Montero MC. Irreversible coma, ergotamine, and ritonavir. *Clin Infect Dis* 2003; 37: e72-3. <http://amedeo.com/lit.php?id=12942422>
6. Spiegel M, Schmidauer C, Kampf A, Sarcletti M, Poewe W. Cerebral ergotism under treatment with ergotamine and ritonavir. *Neurology* 2001, 57:743-4.

**Roferon** see Interferon

## Saquinavir

Saquinavir was the first PI to be licensed for HIV therapy in 1995. It is well tolerated except for gastrointestinal problems, and with no serious short-term problems. It is almost exclusively used together with a ritonavir boost. Since the introduction of the 500 mg capsule, the number of tablets taken has been significantly reduced.

**Trade name:** Invirase 500™, abbr. SQV.

500 mg film-coated tablets. The earlier soft gel capsules (200 mg Fortovase™) and hard gel capsules (200 mg Invirase™) have been taken off the market.

**Drug class:** protease inhibitor

**Manufacturer:** Hoffmann-La Roche

**Indications:** HIV infection

**Oral dose:** Combination with ritonavir is standard: 1,000 mg saquinavir bid + 100 mg ritonavir bid.

**Side effects:** Usually well tolerated. Side effects mainly gastrointestinal with diarrhea, nausea, abdominal discomfort, meteorism. Rarely elevation of transaminases or  $\gamma$ GT, headache. As with other PIs, lipodystrophy, dyslipidemia and reduced glucose tolerance may occur with long-term treatment.

**Comments/Warnings:** contraindicated for comedication with rifampin, astemizole, terfenadine, cisapride, triazolam, ergotamine, simvastatin, lovastatin, and St. John's wort.

If saquinavir is not combined with other PIs it must be taken with meals.

### Internet sources:

USA: <http://hiv.net/link.php?id=132>

### References:

1. Cameron DW, Japour AJ, Xu Y, et al. Ritonavir and saquinavir combination therapy for the treatment of HIV infection. *AIDS* 1999, 13: 213-24. <http://amedeo.com/lit.php?id=10202827>
2. Deeks SG, Grant RM, Beatty GW, et al. Activity of a ritonavir plus saquinavir-containing regimen in patients with virologic evidence of indinavir or ritonavir failure. *AIDS* 1998, 12: F97-102. <http://amedeo.com/lit.php?id=9677159>
3. Kirk O, Lundgren JD, Pedersen C, et al. A randomized trial comparing initial HAART regimens of nelfinavir/nevirapine and ritonavir/saquinavir in combination with two nucleoside reverse transcriptase inhibitors. *Antivir Ther* 2003; 8: 595-602. <http://amedeo.com/lit.php?id=14760893>
4. Piscitelli SC, Burstein AH, Welden N, et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis* 2002, 34: 234-8. <http://amedeo.com/lit.php?id=11740713>
5. Plosker G, Scott L. Saquinavir: A review of its use in boosted regimens for treating HIV infection. *Drugs* 2003; 63: 1299-1324. <http://amedeo.com/lit.php?id=12790697>
6. Stellbrink HJ, Hawkins DA, Clumeck N, et al. Randomised, multicentre phase III study of saquinavir plus zidovudine plus zalcitabine in previously untreated or minimally pretreated HIV-infected patients. *Clin Drug Invest* 2000, 20:295-307.
7. Trout H, Mentre F, Panhard X, Kodjo A, Escaut L, Pernet P et al. Enhanced saquinavir exposure in human immunodeficiency virus type 1-infected patients with diarrhea and/or wasting syndrome. *Antimicrob Agents Chemother* 2004; 48: 538-45. <http://amedeo.com/lit.php?id=14742207>

**Sempera™** see Itraconazole

**Sobelin™** see Clindamycin

**Stavudine** see d4T

## Sulfadiazine

**Drug class:** sulfonamide antibiotic

**Indications:** treatment and prophylaxis of cerebral toxoplasmosis, only in combination with pyrimethamine.

**Dose:** For treatment 2-3 500 mg tablets qid (daily dose 4-6 g). For prophylaxis halve the dose (500 mg qid)!

Renal insufficiency: creatinine clearance 50-10 ml/min: halve dose. At values below 10 ml/min: administer one third of the dose.

**Side effects:** very frequently allergies with pruritus, fever and urticaria, often treatment-limiting. Rare: Stevens-Johnson syndrome. Gastrointestinal complaints such as nausea, vomiting, diarrhea. Renal problems with renal failure, crystalluria, nephrolithiasis in up to 7 %. Anemia, leukopenia, thrombocytopenia. Elevated liver enzymes.

**Comments/Warnings:** sulfadiazine is contraindicated in sulfonamide hypersensitivity and allergies to sulfonylurea antidiabetics, acetazolamide or thiazide diuretics; also in G6PD deficiency, renal failure and severe hepatic disease or dysfunction (e.g. acute hepatitis); and during pregnancy and breastfeeding.

Sulfadiazine can increase levels of sulfonyl urea (oral antidiabetics), anticoagulants, diphenylhydantoin.

Concurrent dosing with antacids reduces absorption of sulfadiazine (separate administration 1-2 hours apart). Ensure sufficient intake of fluids (at least 2 l daily).

Monitor blood count, ALT, creatinine, and BUN at least weekly initially.

Monitor urine! In case of crystalluria: alkalinize urine.

### References:

1. Caumes E, Bocquet H, Guernonprez G, et al. Adverse cutaneous reactions to pyrimethamine/sulfadiazine and pyrimethamine/clindamycin in patients with AIDS and toxoplasmic encephalitis. *Clin Infect Dis* 1995, 21: 656-8. <http://amedeo.com/lit.php?id=8527561>
2. Chirgwin K, Hafner R, Lepout C, et al. Randomized phase II trial of atovaquone with pyrimethamine or sulfadiazine for treatment of toxoplasmic encephalitis in patients with AIDS: ACTG 237/ANRS 039 Study. *Clin Infect Dis* 2002, 34: 1243-50. <http://amedeo.com/lit.php?id=11941551>
3. Dannemann B, McCutchan JA, Israelski D, et al. Treatment of toxoplasmic encephalitis in patients with AIDS. A randomized trial comparing pyrimethamine plus clindamycin to pyrimethamine plus sulfadiazine. *Ann Intern Med* 1992, 116: 33-43. <http://amedeo.com/lit.php?id=1727093>
4. Katlama C, De Wit S, O'Doherty E, et al. Pyrimethamine-clindamycin vs. pyrimethamine-sulfadiazine as acute and long-term therapy for toxoplasmic encephalitis in patients with AIDS. *Clin Infect Dis* 1996, 22: 268-75. <http://amedeo.com/lit.php?id=8838183>
5. Molina JM, Belenfant X, Doco-Lecompte T, et al. Sulfadiazine-induced crystalluria in AIDS patients with toxoplasma encephalitis. *AIDS* 1991, 5: 587-9. <http://amedeo.com/lit.php?id=1863412>
6. Podzamczar D, Miro JM, Bolao F, et al. Twice-weekly maintenance therapy with sulfadiazine-pyrimethamine to prevent recurrent toxoplasmic encephalitis in patients with AIDS. *Ann Intern Med* 1995, 123: 175-80. <http://amedeo.com/lit.php?id=7598298>

**Stocrin™** see Efavirenz

**Sustiva™** see Efavirenz

## T-20 (Enfuvirtide)

T-20 is an entry inhibitor, which is licensed for treatment-experienced adults and children above 6 years who have received at least one drug out of each of the drug classes PI, NNRTI, and NRTI, and subsequently developed treatment failure or intolerance. T-20 is well tolerated, but must be injected subcutaneously. However, this drug is important in salvage therapy. Treatment costs of more than 2,000 Euro per month double the price of HAART.

**Trade name:** Fuzeon™

90 mg/ml powder and solvent. 1 ml of the reconstituted solution contains 90 mg T-20.

**Drug class:** fusion inhibitor (or entry inhibitor)

**Manufacturer:** Hoffmann-La Roche

**Indications:** treatment of HIV-1 infection in patients with evidence of HIV-1 replication despite ongoing HAART.

**Dose:** 90 mg subcutaneously bid.

**Side effects:** generally well tolerated. However, almost all patients have local injection site reactions: erythema, inflammation, induration, rash (change injection sites!). There may be inflammation at more than one site. In the licensing studies, approximately 10 % of patients required intermittent use of analgesics or were temporarily affected in their daily activities. However, only 3 % stopped therapy.

Patients on T-20 possibly have an increased risk of contracting bacterial pneumonia. Therefore, it is important to be particularly vigilant in patients with risk factors for pneumonia (low baseline CD4+ T-cell count, high viral load, iv drug users, smokers, history of pulmonary disease).

Hypersensitivity reactions with rash, fever, nausea, chills, hypotension or elevated transaminases are rare (< 1 %).

**Comments/warnings:** interactions are not known.

Injection sites: upper arm, ventral hip, and abdomen. Change injection sites! Do not inject at sites with inflammatory signs from previous injections. Do not inject at sites with naevi, scars or disrupted skin integrity.

### Internet sources:

USA: <http://hiv.net/link.php?id=225>

### References:

1. Ball RA, Kinchelov T. Injection site reactions with the HIV-1 fusion inhibitor enfuvirtide. *J Am Acad Dermatol* 2003; 49: 826-31. <http://amedeo.com/lit.php?id=14576660>
2. Cervia JS, Smith MA. Enfuvirtide (T-20): a novel HIV type 1 fusion inhibitor. *Clin Infect Dis* 2003; 37: 1102-6. <http://amedeo.com/lit.php?id=14523775>
3. Clotet B, Raffi F, Cooper D, et al. Clinical management of treatment-experienced, HIV-infected patients with the fusion inhibitor enfuvirtide: consensus recommendations. *AIDS* 2004; 18: 1137-46. <http://amedeo.com/lit.php?id=15166529>
4. Dando TM, Perry CM. Enfuvirtide. *Drugs* 2003; 63: 2755-66 <http://amedeo.com/lit.php?id=14664654>
5. Hardy H, Skolnik PR. Enfuvirtide, a new fusion inhibitor for therapy of human immunodeficiency virus infection. *Pharmacotherapy* 2004; 24: 198-211. <http://amedeo.com/lit.php?id=14998221>
6. Lalezari JP, Henry K, O'Hearn M, et al. Enfuvirtide, an HIV-1 fusion inhibitor, for drug-resistant hiv infection in north and south america. *N Engl J Med* 2003; 348:2175-85. <http://amedeo.com/lit.php?id=12637625>

7. Lazzarin A, Clotet B, Cooper D, et al. Efficacy of enfuvirtide in patients infected with drug-resistant HIV-1 in Europe and Australia. *N Engl J Med* 2003; 348: 2186-95. <http://amedeo.com/lit.php?id=12773645>
8. Trottier B, Walmsley S, Reynes J, et al. Safety of Enfuvirtide in Combination With an Optimized Background of Antiretrovirals in Treatment-Experienced HIV-1-Infected Adults Over 48 Weeks. *J AIDS* 2005; 40: 413-421. Abstract: <http://amedeo.com/lit.php?id=16280695>

## Tenofovir

Tenofovir DF is the prodrug of the acyclic **nucleotide** analog tenofovir, and has good oral bioavailability. It also has efficacy against hepatitis B virus. Tenofovir has a good tolerability profile and probably only low mitochondrial toxicity. However, interactions must be considered (particularly with ddI and atazanavir!), as well as weak efficacy in many triple nuke regimens. Caution when using in patients with renal disease.

**Trade name:** Viread™. Abbr.: TDF

Film-coated tablets 300 mg tenofovir disoproxilfumarate or 245 mg tenofovir disoproxil (N1 = 30 tablets).

Also in Truvada™ in combination with emtricitabin (see Emtricitabin).

**Drug class:** nucleotide reverse transcriptase inhibitor

**Manufacturer:** Gilead

**Indications:** HIV infection

**Oral dose:** 300 mg qd, to be taken with a meal. Dose adjustments:

Viread™, adjust dose in renal insufficiency

	Creatinine clearance (ml/min)		Hemodialysis patients
	30 - 49	10 - 29	
Recommended dose interval	Every 48 hours	Every 72 to 96 hours	Every 7 days following the completion of a hemodialysis*

\*See leaflet in packet for more information

Truvada™, adjust dose in renal insufficiency\*

	Creatinine clearance (ml/min)	
	≥ 50	30 - 49
Recommended dose interval	Every 24 hours	Every 48 hours

\*Do not use Truvada™ if creatinine clearance is below 30 ml/min

**Side effects:** generally well tolerated. However, there a potential risk of nephrotoxicity. In most cases, there is only a mild disturbance of renal function. Severe renal side effects are rare (renal failure, Fanconi's syndrome, nephrogenic diabetes insipidus). Patients with renal disease should either not receive tenofovir or otherwise reduce the dose (see above). Controls of creatinine clearance and serum phos-

phate before starting tenofovir, then every four weeks during the first year, and every three months thereafter. More frequent controls are useful if there is disturbance of renal function (actual or in the medical history) or renal insufficiency.

Rarely elevation of liver enzymes. It is not currently known whether long-term treatment with tenofovir can lead to bone density changes. Animal studies showed changes in bone density at doses 30 times higher than the therapeutic dose.

**Comments/Warnings:** when serum phosphate is < 1.5 mg/dl (0.48 mmol/l) or creatinine clearance < 50 ml/min: check renal function again within one week. Simultaneous determination of blood glucose and potassium, as well as glucose in the urine. Interruption of therapy may be necessary if creatinine clearance is < 50 ml/min or serum phosphate is < 1.0 mg/dl (0.32 mmol/l).

Creatinine clearance in ml/min is calculated as follows:

Women:  $(1.04 \times (140 - \text{age}) \times \text{kg}) / \text{creatinine } (\mu\text{mol/l})$

Men:  $(1.23 \times (140 - \text{age}) \times \text{kg}) / \text{creatinine } (\mu\text{mol/l})$

Concurrent administration of tenofovir and drugs that are also eliminated via active tubular secretion can lead to increased serum concentrations of both drugs: didanosine, acyclovir, valacyclovir, ganciclovir, valganciclovir.

Use with caution in combination with ddI: co-medication with tenofovir increases the C<sub>max</sub> and AUC of ddI by 28 % and 44 %, respectively. Pancreatitis may occur, and therefore the dose of ddI should be reduced to 250 mg. Combinations with ddI should be avoided for various reasons (see HAART chapter).

Atazanavir and lopinavir increase tenofovir levels.

Larger controlled studies on the use of tenofovir in pregnancy are yet to come. In monkey studies, tenofovir was effective in the prophylaxis of SIV transmission, but also resulted in growth disorders.

### Internet sources:

USA: <http://hiv.net/link.php?id=134>

### References:

- Gallant JE, Deresinski S. Tenofovir disoproxil fumarate. *Clin Infect Dis* 2003; 37: 944-50. <http://amedeo.com/lit.php?id=13130407>
- Gallant JE, Staszewski S, Pozniak AL, et al. Efficacy and safety of tenofovir DF vs stavudine in combination therapy in antiretroviral-naïve patients: a 3-year randomized trial. *JAMA* 2004; 292: 191-201. <http://amedeo.com/lit.php?id=15249568>
- Guo Y, Fung HB. Fatal lactic acidosis associated with coadministration of didanosine and tenofovir disoproxil fumarate. *Pharmacotherapy* 2004; 24: 1089-94. <http://amedeo.com/lit.php?id=15338857>
- Izzedine H, Isnard-Bagnis C, Hulot JS, et al. Renal safety of tenofovir in HIV treatment-experienced patients. *AIDS* 2004; 18: 1074-6. <http://amedeo.com/lit.php?id=15096814>
- Mauss S, Berger F, Schmutz G. Antiretroviral therapy with tenofovir is associated with mild renal dysfunction. *AIDS* 2005; 19: 93-5. Abstract: <http://amedeo.com/lit.php?id=15627039>
- Murphy MD, O'Hearn M, Chou S. Fatal lactic acidosis and acute renal failure after addition of tenofovir to an antiretroviral regimen containing Didanosine. *Clin Infect Dis* 2003; 36: 1082-5. <http://amedeo.com/lit.php?id=12684925>
- Peyriere H, Reynes J, Rouanet I, et al. Renal tubular dysfunction associated with tenofovir therapy: report of 7 cases. *J Acquir Immune Defic Syndr* 2004; 35: 269-73. <http://amedeo.com/lit.php?id=15076241>
- Schaaf B, Aries SP, Kramme E, Steinhoff J, Dalhoff K. Acute renal failure associated with tenofovir treatment in a patient with acquired immunodeficiency syndrome. *Clin Infect Dis* 2003; 37: e41-3. <http://amedeo.com/lit.php?id=12884188>



9. Squires K, Pozniak AL, Pierone G Jr, et al. Tenofovir disoproxil fumarate in nucleoside-resistant HIV-1 infection: a randomized trial. *Ann Intern Med* 2003; 139: 313-20. <http://amedeo.com/lit.php?id=12965939>
10. Taburet AM, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. *Antimicrob Agents Chemother* 2004; 48: 2091-6. <http://amedeo.com/lit.php?id=15155205>

## Tipranavir

Tipranavir is the first nonpeptidic protease inhibitor (PI), which was recently licensed in the USA and in Europe. This new drug has a favorable resistance profile. In two large studies on intensively PI-treatment-experienced patients, it was superior to other ritonavir-boosted PIs (lopinavir, amprenavir, indinavir, saquinavir). Tipranavir is always boosted with ritonavir.

**Trade name:** Aptivus™. Abbr.: TPV

250 mg soft capsules

**Drug class:** non-peptide protease inhibitor (NPPI)

**Manufacturer:** Boehringer Ingelheim

**Indications:** HIV-infected adult patients who are either highly treatment-experienced or who have multiple PI resistances.

**Oral dose:** 500 mg bid tipranavir + 200 mg bid ritonavir

**Side effects:** The most frequent side effects are gastrointestinal: diarrhea and nausea. The following occur (in decreasing frequency): fatigue, vomiting, headache, bronchitis, abdominal pain, depression, lack of strength, and insomnia. In the studies published so far, 8 % of patients terminated therapy with tipranavir.

Increased transaminases (sometimes severe) have been observed in at least 6 % of patients, with clinical hepatitis and liver failure in rare cases. Dyslipidemia (20 %).

Rash (urticarial or maculopapular) seems to be more common in women than in men.

**Interactions:** combination of tipranavir and ritonavir inhibits the activity of CYP3A and induces p-glycoprotein. Therefore, elevated serum drug levels have to be expected for those drugs that are primarily metabolized by CYP3A (see following table). Further information in the US product description at <http://hiv.net/link.php?id=256>

### Drugs that are contraindicated on tipranavir therapy

Antiarrhythmics	Amiodarone, bepridil, flecainide, propafenone, quinidine
Antihistamines	Astemizole, terfenadine
Ergotamine derivatives	(Dihydro)-ergotamine, (methyl)-ergonovine
Prokinetics	Cisapride
Neuroleptics	Pimozide
Sedatives/hypnotics	Midazolam, triazolam

Tipranavir reduces the serum level of lopinavir, saquinavir and amprenavir, so a double PI regime with these substances is not recommended.

Fluconazole and clarithromycin increase the serum level of tipranavir. Careful monitoring is required on concurrent therapy.

Antacids reduce tipranavir levels by 30 %: stagger doses.

Rifampicin reduces tipranavir levels by 80 %: avoid.

TPV/r increases the serum level of atorvastatin, therefore, begin with the smallest dose of atorvastatin, or – better still – change to another substance.

The same applies to rifabutin. Consequently: rifabutin 150 mg every two days or three times a week.

ddI should only be taken at a two-hour interval to tipranavir.

**Comments/Warnings:** tipranavir is contraindicated in patients with moderate to severe hepatic impairment (Child-Pugh B and C). Patients with chronic hepatitis B or C infection have a 2.5 times higher risk of increased transaminases on tipranavir treatment. Determine liver function parameters, cholesterol, and triglycerides before and during treatment.

Women who take an estrogen-based contraceptive appear to have a higher incidence of rash. Occasionally alternative methods of contraception have to be used. Tipranavir should be taken with meals.

#### **Internet sources:**

US: <http://hiv.net/link.php?id=256>

#### **References:**

1. Cooper D, Hicks C, Cahn P, et al. 24-week RESIST study analysis: the efficacy of tipranavir/ritonavir (TPV/r) is superior to lopinavir/ritonavir (LPV/r) and the TPV/r treatment response is enhanced by inclusion of genotypically active antiretrovirals in the optimized background regimen (OBR) Abstract 560, 12<sup>th</sup> CROI 2005, Boston.
2. Hicks C. RESIST-1: a phase 3, randomized, controlled, open-label, multicenter trial comparing tipranavir/ritonavir to an optimized comparator protease inhibitor/r regimen in antiretroviral experienced patients: 24 week data. Abstract H-1137a, 44th ICAAC 2004, Washington.
3. Larder BA, Hertogs K, Bloor S, et al. Tipranavir inhibits broadly protease inhibitor-resistant HIV-1 clinical samples. AIDS 2000, 14:1943-8. <http://amedeo.com/lit.php?id=10997398>
4. Plosker G, Figgitt D. Tipranavir. Drugs 2003; 63: 1611-8. <http://amedeo.com/lit.php?id=12887268>
5. Yeni P. Tipranavir: a protease inhibitor from a new class with distinct antiviral activity. J Acquir Immune Defic Syndr 2003; 34 Suppl 1: S91-4. <http://amedeo.com/lit.php?id=14562864>

## **Trizivir™**

Trizivir™ is a fixed combination of AZT+3TC+abacavir. It is frequently used to simplify HAART regimens. However, once daily dosage is not possible. Another disadvantage of Trizivir™ is that it does not seem to be as effective as “divergent” combinations comprised of several drug classes. It is an option for patients with compliance problems; and when treatment with additional drugs (tuberculostatics, coumarin derivatives, etc.) bears the potential of important drug interactions.

**Trade name:** Trizivir

Tablets containing 150 mg 3TC **and** 300 mg AZT **and** 300 mg abacavir.

**Drug class:** NRTI

**Manufacturer:** GlaxoSmithKline

**Indications:** HIV infection

**Oral dose:** 1 tablet bid. In cases of impaired renal function (creatinine clearance less than 50 ml/min), the individual drugs should be given separately to allow for dose adjustment of 3TC and AZT.

**Side effects:** mostly gastrointestinal, see the individual drugs. Hypersensitivity reaction with abacavir (see under abacavir!). There are possibly additive effects with regard to mitochondrial toxicity.

**Comments/Warnings:** watch closely for hypersensitivity reactions (see abacavir). See individual drugs.

**Internet sources:** USA: <http://hiv.net/link.php?id=51>

**References:**

1. Gulick RM, Ribaldo HJ, Shikuma CM, et al. Triple-nucleoside regimens versus efavirenz-containing regimens for the initial treatment of HIV-1 infection. *N Engl J Med.* 2004, 350:1850-1861. <http://amedeo.com/lit.php?id=15115831>
2. Ibbotson T, Perry C. Lamivudine/Zidovudine/Abacavir: triple combination tablet. *Drugs* 2003; 63: 1089-98. <http://amedeo.com/lit.php?id=12749741>
3. Opravil M, Hirschel B, Lazzarin A, et al. A randomized trial of simplified maintenance therapy with abacavir, lamivudine, and zidovudine in HIV infection. *J Infect Dis* 2002, 185: 1251-60. <http://amedeo.com/lit.php?id=12001042>
4. Staszewski I S, Keiser P, Montaner J, et al. Abacavir-lamivudine-zidovudine vs indinavir-lamivudine-zidovudine in antiretroviral-naive HIV-infected adults: A randomized equivalence trial. *JAMA* 2001, 285: 1155-63. <http://amedeo.com/lit.php?id=11231744>

## Truvada™

Truvada™ is a fixed-dose combination preparation, containing tenofovir (300 mg tenofovir disoproxilfumarate) and emtricitabine (200 mg FTC). Overall tolerability is good. Truvada™ is a component of many once-daily HAART regimens.

**Drug class:** nucleoside and nucleotide reverse transcriptase inhibitor (NRTI).

**Manufacturer:** Gilead

**Indications:** HIV infection

**Oral dose:** 1 film-coated tablet daily

With reduced creatinine clearance of 30-49 ml/min, dose should be reduced to 1 tablet every two days. Truvada should not be prescribed at values lower than this.

**Side effects:** see chapter on tenofovir

**Comments/Warnings:** refer to information in the tenofovir chapter.

In HIV patients with chronic hepatitis B coinfection, exacerbation of hepatitis may occur after discontinuing Truvada™. In such cases, clinical and laboratory monitoring is recommended for several months.

Absorption of Truvada is not affected by food intake.

**Internet sources:**

USA: <http://hiv.net/link.php?id=241>

**References:**

1. Dando TM, Wagstaff AJ. Emtricitabine/tenofovir disoproxil fumarate. *Drugs* 2004; 64: 2075-82  
<http://amedeo.com/lit.php?id=15341498>
2. Molina JM, Gathe J, Lim JL, et al. Comprehensive resistance testing in antiretroviral naive patients treated with once-daily lopinavir/ritonavir plus tenofovir and emtricitabine: 48-week results from study 418. Abstract WePeB5701, XV Int AIDS Conf 2004, Bangkok.

**Valcyte™** see Valganciclovir

## Valganciclovir

Valganciclovir is the first CMV drug with good efficacy that can be administered orally. Valganciclovir is a prodrug of ganciclovir and therefore has a similar toxicity profile: neutropenia, anemia and thrombocytopenia. Due to the improved bioavailability, valganciclovir has largely replaced the earlier form of ganciclovir.

**Trade name:** Valcyte™

450 mg tablets

**Drug class:** virostatic

**Manufacturer:** Hoffmann-La Roche

**Indications:** oral induction and maintenance therapy of CMV retinitis.

**Dose:** for induction therapy 900 mg bid for 3 weeks (or until scar formation of CMV lesions), then suppressive therapy with 900 mg qd.

The following doses should be used for renal failure:

CrCl (ml/min)	Induction therapy	Suppressive therapy
≥ 60	900 mg bid	900 mg qd
40 – 59	450 mg bid	450 mg qd
25 – 39	450 mg qd	450 mg q 48 h
10 – 24	450 mg q 48 h	450 mg 2 x/week

**Side effects:** frequently leukopenia, but also thrombocytopenia, anemia. Gastrointestinal complaints such as nausea, vomiting and diarrhea are more frequent than with intravenously-administered ganciclovir.

**Comments/Warnings:** monitoring of blood count at least 2-3 x/week during induction. Discontinuation if neutrophils below 500/μl (G-CSF if needed!). Contraindicated in neutropenia < 500/μl, thrombocytopenia < 25,000/μl and concurrent chemotherapy. Caution when concurrent dosing with ddI, as valganciclovir can double levels of ddI (increased toxicity!).

Valganciclovir is potentially teratogenic; reliable contraception is required.

Valganciclovir must be taken with meals.

The drug is extremely expensive! It should be discontinued when sufficient immune reconstitution has been reached (see OI chapter).

**Internet sources:**

USA: <http://hiv.net/link.php?id=135>

**References:**

1. Boivin G, Gilbert C, Gaudreau A, et al. Rate of emergence of cytomegalovirus mutations in leukocytes of patients with AIDS who are receiving valganciclovir as induction and maintenance therapy for CMV retinitis. *J Infect Dis* 2001, 184:1598-1602. <http://amedeo.com/lit.php?id=11740736>
2. Lalezari J, Lindley J, Walmsley S, et al. A safety study of oral valganciclovir maintenance treatment of cytomegalovirus retinitis. *J AIDS* 2002, 30: 392-400. <http://amedeo.com/lit.php?id=12138345>
3. Martin DF, Sierra-Madero J, Walmsley S, et al. A controlled trial of valganciclovir as induction therapy for cytomegalovirus retinitis. *NEJM* 2002, 346: 1119-26. <http://amedeo.com/lit.php?id=11948271>

**Vfend™** see Voriconazole

**Videx™** see ddI

**Viracept™** see Nelfinavir

**Viramune™** see Nevirapine

**Viread™** see Tenofovir

**Vistide™** see Cidofovir

## Voriconazole

Voriconazole is a very promising oral broad spectrum antimycotic. A comparative study of voriconazole and amphotericin B for the treatment of invasive aspergillosis showed significantly better treatment results with voriconazole after 12 weeks (53 % versus 32 %).

**Trade name:** Vfend™

50 mg and 200 mg tablets

Bottles for injection with 200 mg

**Drug class:** antimycotic

**Manufacturer:** Pfizer

**Indications:** treatment of invasive aspergillosis; treatment of fluconazole-resistant, severe *Candida* infections (including *C. krusei*); treatment of severe fungal infections caused by *Scedosporium* spp and *Fusarium* spp.

**Dose:** 200 mg bid po

For intravenous dosing: 3 to 6 mg/kg every 12 hours.

**Side effects:** elevated transaminases, rash and impairment of vision most commonly led to discontinuation of treatment in clinical studies.

Visual impairments (overly bright images, blurred vision, light sensitivity or altered color vision) occurred in approximately 30 %, usually appearing within 30 minutes of taking voriconazole, and lasting approximately 30 minutes.

More rarely fever, nausea, vomiting, diarrhea, headache, abdominal pain.

**Comments/warnings:** voriconazole is metabolized via the cytochrome 450 enzymatic pathway. Serum levels of voriconazole may be significantly reduced by several drugs, which are therefore contraindicated for co-administration: rifampin, carbamazepine, barbiturates.

Serum levels of several drugs are significantly elevated by voriconazole, and therefore comedication is contraindicated: sirolimus, ergotamine derivatives, terfenadine, astemizole, cisapride, pimozide, quinidine.

Concurrent administration of rifabutin is also contraindicated.

Administration together with NNRTIs or protease inhibitors (exception: indinavir) may require dose modifications, as is the case with a number of other drugs: cyclosporine, tacrolimus, anticoagulants, digoxin, statins, calcium antagonists, vincristine, vinblastine, phenytoin, omeprazole (see product information).

Voriconazole tablets should be taken one hour before or two hours after a meal.

Avoid strong sun exposure, and driving at night (due to potential visual impairment).

### References:

1. Arikan S, Lozano-Chiu M, Paetznick V, Nangia S, Rex JH. Microdilution susceptibility testing of amphotericin B, itraconazole, and voriconazole against clinical isolates of *Aspergillus* and *Fusarium* species. *J Clin Microbiol* 1999, 37:3946-3951. <http://hiv.net/link.php?id=10565912>
2. Chavez M, Bernal S, Valverde A, et al. In-vitro activity of voriconazole (UK-109,496), LY303366 and other antifungal agents against oral *Candida* spp. isolates from HIV-infected patients. *J Antimicrob Chemother* 1999, 44: 697-700. <http://amedeo.com/lit.php?id=10552989>
3. Clancy CJ., Nguyen MH. In vitro efficacy and fungicidal activity of voriconazole against *Aspergillus* and *Fusarium* species. *Eur J Clin Microbiol Infect Dis* 1998, 17:573-575. <http://amedeo.com/lit.php?id=9796657>
4. Espinel-Ingroff A. In vitro activities of the new triazole voriconazole (UK-109,496) against opportunistic filamentous and dimorphic fungi and common and emerging yeast pathogens. *J Clin Microbiol* 1998, 36:198-202. <http://amedeo.com/lit.php?id=9431946>
5. Martin CA, Roberts S, Greenberg RN. Voriconazole treatment of disseminated *paecilomyces* infection in a patient with AIDS. *Clin Infect Dis* 2002, 35: e78-81. <http://amedeo.com/lit.php?id=12228840>
6. Nguyen MH, Yu CY. Voriconazole against fluconazole-susceptible and resistant *Candida* isolates: in-vitro efficacy compared with that of itraconazole and ketoconazole. *J Antimicrob Chemother* 1998, 42:253-256. <http://hiv.net/link.php?id=9738846>
7. Odds FC, Cheesman SL, Abbott AB. Antifungal effects of fluconazole (UK 49858), a new triazole antifungal, in vitro. *J Antimicrob Chemother* 1986, 18:473-478. <http://hiv.net/link.php?id=3021710>
8. Ruhnke M, Schmidt-Westhausen A, Trautmann M. In vitro activities of voriconazole (UK-109,496) against fluconazole-susceptible and -resistant *Candida albicans* isolates from oral cavities of patients with HIV. *Antimicrob Agents Chemother* 1997, 41: 575-7. <http://amedeo.com/lit.php?id=9055995>
9. Sanati H, Belanger P, Fratti R, Ghannoum M. A new triazole, voriconazole (UK-109,496), blocks sterol biosynthesis in *Candida albicans* and *Candida krusei*. *Antimicrob Agents Chemother* 1997, 41:2492-2496. <http://hiv.net/link.php?id=9371355>
10. Scherpelier HJ, Hilhorst MI, Kuijpers TW. Liver failure in a child receiving highly active antiretroviral therapy and voriconazole. *Clin Infect Dis* 2003; 37: 828-30. <http://amedeo.com/lit.php?id=12955645>
11. Weig M, Muller FM. Synergism of voriconazole and terbinafine against *Candida albicans* isolates from HIV-infected patients with oropharyngeal candidiasis. *Antimicrob Agents Chemother* 2001, 45: 966-8. <http://amedeo.com/lit.php?id=11181393>
12. Wildfeuer A, Seidl HP, Paule I, Haberreiter A. In vitro evaluation of voriconazole against clinical isolates of yeasts, moulds and dermatophytes in comparison with itraconazole, ketoconazole, amphotericin B and griseofulvin. *Mycoses* 1998, 41:309-319. <http://hiv.net/link.php?id=9861837>

**Zerit™** see d4T

**Ziagen™** see Abacavir

**Zidovudine** see AZT

**Zovirax™** see Acyclovir

## 33. Drug-Drug Interactions

Leonie Meemken and Laura Dickinson

In an attempt to predict or avoid drug-drug interactions, a complete medication history, including herbal remedies and recreational drug use is necessary. In particular, combinations involving inducers (e.g. rifampicin) and inhibitors (e.g. ketoconazole) can result in unfavorable plasma concentrations of antiretroviral agents. For example, inhibitors can increase concentrations of some drugs to such an extent that toxicity develops and inducers can reduce concentrations to a point where resistance can occur. If there are no clear clinical data about a specific drug-drug interaction, theoretical consideration can help to exclude severe drug-drug interactions. It is important to look at the bilateral effect of ART. ART can influence co-medication and vice versa. Dose adjustments of ARVs and/or co-medication may need to be considered. For further information on drug-drug interactions refer to the website [www.hiv-druginteractions.org](http://www.hiv-druginteractions.org)

Drug plasma concentrations can also be influenced by many different factors such as age, gender, liver disease and genetic polymorphism. Individualized dosing with the use of TDM is, in many cases, very important.

### Individual drugs

Comment: plasma concentrations of drugs are affected by many factors: such as ethnicity, kidney and liver failure, age or sex. Prediction of possible interactions can be challenging and in a number of cases therapeutic drug monitoring (TDM) may be useful. Abbreviations used in the table: AUC = area under the curve, QD = once daily, BID = twice daily, TID = three times daily, ↓↑ = AUC decreases or increases, TDM = therapeutic drug monitoring

### 3TC (Lamivudine, Epivir™; in Combivir™, Trizivir™, Kivexa™)

Approved dose: 150 mg BID or 300 mg QD. Elimination: renal

Drugs	Interactions (IA)	Comments
<b>NRTIs</b>		
FTC [1-2]	Antagonism	<b>Avoid combination</b>
<b>NNRTIs</b> [1-2]	No clinically significant IA	
<b>PIs</b> [1-2]	No clinically significant IA	

### References

1. Tseng A. [www.tthhivclinic.com](http://www.tthhivclinic.com), General Hospital, Toronto 2006 Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
2. US Department of Health and Human Services (DHHS) and National Institutes of Health (NIH). The living document: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Retrieved April 14, 2004. [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov).

## Abacavir (ABC, Ziagen™; also in Trizivir™, Kivexa™)

Approved dose: 300 mg BID or 600 mg QD. Metabolism via alcohol dehydrogenase and glucuronidation pathway

Drugs	Interactions (IA)	Comments
Alcohol [1-3]	ABC ↑ 41 %	Clinically not significant
<b>NRTIs</b> [1-2]	No clinically significant IA	
<b>NNRTIs</b> [1-2]	No clinically significant IA	Caution when starting ABC and NNRTI (allergy/HSR)
<b>PIs</b>		
TPV/r [4]	ABC: 40 % ↓	Clinical relevance unknown. No dose adjustment at the moment

\* HSR = hypersensitivity reaction

### References

1. Tseng A. www.tthivclinic.com, General Hospital, Toronto 2004.
2. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
3. McDowell JA, Chittick GE, Pilati-Stevens C, et al. Pharmacokinetic interaction of abacavir and ethanol in HIV-infected adults. Antimicrob Agents Chemother 2000 ; 44: 1686-90. <http://www.amedeo.com/lit.php?id=10817729>
4. Aptivus™, Boehringer Ingelheim.

## Atazanavir (ATV, Reyataz™)

Approved dose: ATV/RTV: 300/100 mg. Metabolism: atazanavir (ATV) is primarily metabolized by CYP3A4 and inhibits CYP3A4, CYP2C9, CYP1A2 and UDP-glucuronosyltransferase (UGT)-1A1 [1].

Drugs	Interactions	Comments
<b>NRTIs</b>		
TDF [2,31]	ATV 400 + TDF 300 QD [2]: ATV ↓ 25 % ( $C_{min}$ 40 % ↓)  ATV/r 300/100 +TDF 300 QD: ATV ↓ 11 % ( $C_{min}$ 20 % ↓) TDF ↑ 37 % ( $C_{min}$ 29 % ↑)	ATV/RTV 300/100 QD [2,3], taken with a light meal.  Boosted ATV levels are 2-4-fold higher than unboosted ATV without TDF.
<b>NNRTIs</b>		
EFV [3-5]	ATV 400 + EFV 600 QD: ATV ↓ up to 74 % [4,5]	ATV/RTV 400/100 QD [3], taken with a light meal.
NVP [24]	Theoretically: NVP ↓	No data.
<b>PIs</b>		
IDV/r [3,6] SQV/r [8,9]	Risk of hyperbilirubinemia ATV 300 + SQV/r 1600/100 QD: SQV ↑ 60 %, RTV ↑ 41 % [9] ATV 200 + SQV 1500 BID: SQV: 75 % > 0.1 ug/ml [8]	<b>Avoid combination.</b> TDM. Synergistic effect [9].
NLF [26]	NLF 1250 BID + ATV 400 QD: $C_{min}$ NLF: 57 % ↑, M8: 124 % ↑	



Drugs	Interactions	Comments
FPV/r [27,30]	ATV 300 QD + FPV/r 700/100 BID: controversial data	TDM.
LPV/r [28,34,35]	ATV 400 QD + LPV/r 400/100 BID: 1. LPV ↓ 16 % ( $C_{\min}$ 35 % ↓) [28] 2. ATV ( $C_{\min}$ 45 % ↑) [34] 3. ATV ↓ 38 % ( $C_{\min}$ 38 % ↓) [35]	Controversial data => TDM.  1. HIV-patients. 2. Healthy volunteers. 3. HIV-patients
TPV/r [33]	ATV 300 QD + TPV/r 500/100 BID: ATV ↓ 68 % ( $C_{\min}$ 81 % ↓) TPV ( $C_{\min}$ 75 % ↑)	<b>Avoid combination.</b>
DNV (TMC 114)/r [36]	ATV 300 QD + DNV/r 400/100 BID: ATV ( $C_{\min}$ 50 % ↑) RTV ↑ 50-59 %	Increased risk of hyperbilirubinemia, icterus. Combination possible if necessary
<b>Antiarrhythmics</b>		
Amiodarone, bepridil, quinidine, flecainide, lidocaine [3,11]	Theoretically: antiarrhythmic drugs ↑	<b>Avoid combination:</b> bepridil, quinidine [3]. Possible: dose adjustment of antiarrhythmics
<b>Antibiotics</b>		
Clarithromycin [12]	Clarithromycin ↑ 1.9-fold (caution: QT-prolongation), active clarithromycin metabolite ↓ 70 %, ATV ↑ 30 %	<b>Avoid combination</b> or 50 % dose reduction of clarithromycin. Theoretical alternative: azithromycin.
Erythromycin [13]	Theoretically: ATV ↑	
<b>Anticoagulants</b>		
Warfarin	Theoretically: warfarin ↑	Check INR
<b>Antidepressants</b>		
Tricyclic antidepressants [14]	Theoretically: tricyclic antidepressants ↑	Monitor for anticholinergic effects.
St. John's Wort [3]	Theoretically: ATV ↓	<b>Avoid combination.</b>
<b>Antiepileptics</b>		
Carbamazepine, phenytoin, primidon [3]	Theoretically: ATV ↓	Theoretical alternative: gabapentin, lamotrigine, valproic acid.
<b>Antifungal drugs</b>		
Itra-, keto-, vori-conazole [18]	Theoretically: ATV ↑	Theoretical alternative: fluconazole.
<b>Antihistamines</b>		
Loratadine (> 20 mg), terfenadine [3,15,16]	Theoretically: antihistamines ↑ risk of QT-prolongation ↑	<b>Avoid combination:</b> terfenadine, loratadine (> 20 mg) [3]. Theoretical alternative: cetirizine, fexofenadine [15,16].
<b>Antihypertensives</b>		
<b>Calcium channel blockers</b> [17] such as bepridil, diltiazem, nifedipine, verapamil		
Bosentan [11,23]	Bepridil, diltiazem ↑ 2-fold Theoretically: calcium channel blockers ↑  Theoretically: ATV ↓	Theoretically: dose reduction of calcium channel blockers. 50 % dose reduction of diltiazem.  <b>Avoid combination</b> or TDM.

Drugs	Interactions	Comments
<b>Antipsychotics</b> several neuroleptics	Theoretically: antipsychotics ↑	<b>Avoid combination</b> with pimozide. Monitor for side-effects. Prefer: atypical neuroleptics (less anticholinergic)
<b>Antituberculosis drugs</b> Rifampicin [21]	90 % AUC-reduction of PIs	<b>Avoid combination.</b>
Rifabutin [21]	ATV 400 + rifabutin 150 QD: rifabutin ↑ 2-fold	ATV 400 QD + rifabutin 150 mg 3 times a week.
<b>Cytotoxic drugs</b> Paclitaxel, vinca-alkaloids [22], irinotecan [3]	Theoretically: cytotoxic drugs ↑	Monitor for side-effects.
<b>Gastritis-/ Ulcer healing drugs</b> Proton pump inhibitors (PPIs)	Omeprazole 40 + ATV/r 300/100: ATV ↓ 76 % (Cmin 78 % ↓)	<b>Avoid combination:</b> PPIs are not recommended.
H2-receptor antagonists, antacids [25,29]	Famotidin + 1. ATV 400 QD = ATV 40-50 % ↓ 2. ATV/r 300/100 QD = ATV-level of ATV/TDF 3. ATV/r 400/100 QD = ATV-level = ATV 300/100 QD	<b>At least 12h time-lag:</b> H2-receptor antagonists, antacids.  ATV/r + H2-receptor antagonists: concurrent intake could be possible.
<b>Hypnotics</b> Barbexalclone, phenobarbital	Theoretically: ATV ↓	<b>Avoid combination</b> or TDM.
Benzodiazepines, zolpidem [10]	Theoretically: benzodiazepines ↑	<b>Avoid combination:</b> midazolam, triazolam. Alternatives: oxazepam, lorazepam, temazepam.
<b>Immunosuppressants</b> Cylosporine, sirolimus, tacrolimus [11]	Theoretically: immunosuppressants ↑	Dose adjustment of immunosuppressants with TDM.
<b>Lipid-lowering drugs</b> Atorvastatin, lovastatin, simvastatin [19]	Theoretically: statins ↑	<b>Avoid combination:</b> lovastatin, simvastatin. Alternatives: pravastatin, fluvastatin, rosuvastatin.
<b>Oral contraceptives</b> [11]	ATV: ethinyl estradiol ↑ 48 %, norethindrone ↑ 110 % RTV: ethinyl estradiol ↓	Monitor for side-effects, when necessary, reduce dose.
<b>PDE5 inhibitors</b> Sildenafil, tadalafil vardenafil [11]	Theoretically: PPH ↑	Start with lowest dose.

Drugs	Interactions	Comments
<b>Substitution</b>		
Methadone [32]	No interaction	
<b>Others</b>		
Ergot alkaloids [11]	Theoretically: ergotamines ↑	<b>Avoid combination:</b> Theoretical alternative: triptans.

## References

1. Tseng A. www.tthhivclinic.com, General Hospital, Toronto; 2004.
2. Kaul S, Bassi K, Damle BD, et al. Pharmacokinetic evaluation of the combination of atazanavir, enteric coated didanosine, and tenofovir disoproxil fumarate for a once daily antiretroviral regimen. Abstract A-1616, 43rd ICAAC 2003, Chicago.
3. Atazanavir. Bristol Myers-Squibb.
4. Preston S, Pillero P, O'Mara E, et al. Evaluation of steady-state interaction between atazanavir and efavirenz. Abstract 443, 9th CROI 2002, Seattle. <http://63.126.3.84/2002/Abstract/13543.htm>
5. Tackett D, Child M, Agarwala S, et al. Atazanavir: A summary of two pharmacokinetic drug interaction studies in healthy volunteers. Abstract 543, 10th CROI 2003, Boston.
6. Robinson BS, Riccardi KA, Gong YF, et al. BMS- 232632, a highly potent HIV protease inhibitor that can be used in in combination with other available antiretroviral agents. Antimicrob Agents Chemother 2000; 44: 2093-9. <http://www.amedeo.com/lit.php?id=10898681>
7. King J, Paul Lundy S, Kakuda TN et al. Pharmacokinetics of saquinavir with low-dose ritonavir or atazanavir twice daily in seronegativ volunteers. ASPIRE II. Abstract 586. 13th CROI 2006, Denver.
8. DeJesus E, Grinsztejn B, Rodriguez C, et al. Efficacy and safety of atazanavir with ritonavir or saquinavir vs lopinavir/ritonavir in patients who have experienced virologic failure on multiple HAART regimens: 48-Week results from BMS A1424-045. Abstract 54, 11th CROI 2004, San Francisco. <http://www.retroconference.org/2004/cd/Abstract/547.htm>
9. Boffito M, Kurowski M, Kruse G, et al. Atazanavir enhances saquinavir hard gel concentration in a ritonavir boosted once daily regimen. AIDS 2004; 18: 1292-7. <http://www.amedeo.com/lit.php?id=15362661>
10. Agarwala S, Russo R, Mummaneni V, et al. Steady-state pharmacokinetic interaction study of atazanavir with ritonavir in healthy subjects. Abstract H1716, 42nd ICAAC 2002, San Diego.
11. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
12. Mummaneni V, Randall D, Chabuel D, et al. Steady-state pharmacokinetic interaction study of atazanavir with clarithromycin in healthy subjects. Abstract H1717, 42nd ICAAC 2002, San Diego.
13. Benedek ICH, Joshi A, Fiske WD, et al. Pharmacokinetic studies in healthy volunteers with efavirenz and the macrolide antibiotics, azithromycin and clarithromycin. Abstract 347, 5th CROI 1998, Chicago.
14. Richelson E. Pharmacokinetic interactions of antidepressiva. J Clin Psychiatry 1998; 59: 22-6. <http://www.amedeo.com/lit.php?id=9720479>
15. Pratt CM, Mason J, Russell T. Cardiovascular safety of fexofenadine HCL. Am J Cardiol 1999; 84: 278-9. <http://www.amedeo.com/lit.php?id=10444240>
16. Abernethy DR, Barbey JT. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QT-prolongation. Clin Pharmacol Ther 2001; 69: 96-103. <http://www.amedeo.com/lit.php?id=11240972>
17. Rossi DR, Rathbun C, Slater LD. Symptomatic orthostasis with extended-release nifedipine and protease inhibitors. Ann Pharmacother 2002; 22: 1312-6. <http://www.amedeo.com/lit.php?id=12389881>
18. O'Mara E, Randall D, Uderman H, et al. Steady-state pharmacokinetics interaction study between BMS-232632 and ketoconazole in healthy subjects. Abstract 1646, 40th ICAAC 2000, Toronto.
19. Fichtenbaum CJ, Gerber JG, Rosenkranz S. Pharmacokinetic interaction between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS 2002; 16: 569-77. <http://www.amedeo.com/lit.php?id=11873000>
20. Antoniou T, Lin-in Tseng. Interactions between recreational drugs and antiretroviral agents. Annals Pharmacother 2002; 36: 1598-613. <http://www.amedeo.com/lit.php?id=12243611>
21. CDC. Notice to Readers: Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR 2004; 53:37. <http://www.amedeo.com/lit.php?id=11795500>

## 772 Interactions

22. Lam M, Ignoffo R, Meibohm B. Ein Leitfaden für klinisch-relevante Arzneimittel-Interaktionen in der Onkologie.
23. Ghofrani HA, Olschewski H, Seeger W, et al. Sildenafil for treatment of severe pulmonary hypertension and commencing right-heart failure. *Pneumologie* 2002; 56: 665-72. <http://amedeo.com/lit.php?id=12442206>
24. Alexander CS, Montaner JG, Langridge S, et al. Interaction between atazanavir/Ritonavir (ATV/r) and nevirapine (NVP) is observed in a clinical setting. Abstract P275, 7th Int Congr Drug Ther HIV Inf 2004, Glasgow.
25. Roter Hand Brief, Bristol Myers-Squibb, December 2004
26. Kurowski M, Breske A, Kruse G, et al. Atazanavir (ATV) enhances through concentrations of nelfinavir (NFV) and its M8 metabolite in a treatment regimen without ritonavir (RTV). Abstract 90, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
27. Guttanti M, Raffaella de Pascalis C, Seminari E, et al. Pharmacokinetics of amprenavir given once or twice a day when combined with atazanavir in heavily pre-treated patients. *AIDS* 2003, 17: 2669-70. <http://www.amedeo.com/lit.php?id=14685066>
28. Colombo S, Buclin T, Franc C. Ritonavir-boosted atazanavir-lopinavir combination: a pharmacokinetic interaction study of total, unbound plasma and cellular exposures. *Antivir Ther.* 2006;11:53-62.
29. Agarwala S, Child M, Wang Y et al. Pharmacokinetic effect of famotidine on atazanavir with and without ritonavir in healthy subjects. Abstract 11, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
30. Wire MB et al. The pharmacokinetic interaction between fosamprenavir/ritonavir and atazanavir in healthy adult subjects (APC 10018). Abstract 4.3/9. 10th EACS Conference 2005, Dublin.
31. Agarwala S, Eley T, Villegas C, et al. Pharmacokinetic interaction between tenofovir and atazanavir co-administered with ritonavir in healthy subjects. Abstract 16, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
32. Friedland G, Andrews L, Schreiber T et al. Lack of an effect of atazanavir on steady-state pharmacokinetics of methadone in patients chronically treated for opiate addiction. *AIDS* 2005; 19:1635-41. <http://amedeo.com/lit.php?id=16184033>
33. Sekar V, De Marez T, Spinosa-Guzman S et al. Pharmacokinetic Interaction between TMC114/RTV and Atazanavir in healthy volunteers. Abstract PE4/3.4, 10th EACS Conference 2005, Dublin.
34. Pham P, Parson T, Flexner C et al. Beneficial Pharmacokinetic Interaction between Atazanavir and Lopinavir/r. 13th CROI Denver 2006, abstract 585.
35. Vezina HE, Tschampa JM, Jennings C et al. Steady-state pharmacokinetic of lopinavir/ritonavir co-administered with atazanavir in HIV-infected subjects. Abstract 48. 7th Int Worksh Clin Pharmacol HIV Ther 2005, Lissabon.
36. Sabo JP, Elgadi M, Wruck J et al. The pharmacokinetic interaction between atazanavir/ritonavir and steady-state tipranavir/ritonavir in healthy volunteers. Abstract 41, 7th Int Worksh Clin Pharmacol HIV Ther 2005, Lissabon.

## AZT (Zidovudine, Retrovir™; also in Trizivir™, Combivir™)

Approved dose: 250 or 300 mg BID. Metabolism: glucuronidation pathway, elimination: renal

Drugs	Interactions	Comments
<b>NRTIs</b>		
d4T [1-3]	Antagonism	<b>Avoid combination.</b>
<b>NNRTIs</b>		
	No significant interaction	
<b>PIs</b>		
TPV/r [15]	AZT ↓ 33-43 %	<b>Avoid comb. if possible.</b>
<b>Antibiotics</b>		
Atovaquone	AZT ↑ 35 % ± 23 %	Monitor for AZT side-effects.
Clarithromycin [4]	AZT ↓ 10-25 %	Take 2 - 4 h apart
Cotrimoxazol [2]	Haematotoxicity ↑	
Dapsone [5]	Haematotoxicity ↑	

Drugs	Interactions	Comments
<b>Antiepileptics</b>		
(Fos-)Phenytoin [2]	Clearance of AZT ↓ 30 % and phenytoin ↑↓	Monitor for AZT side-effects, TDM of phenytoin.
Valproic acid [2]	AZT ↑ 79 %	Monitor for AZT side-effects.
<b>Antifungal drugs</b>		
Fluconazole [2]	AZT ↑ 74 %	Monitor for AZT side-effects.
<b>Antimalarials</b>		
Pyrimethamine [2]	Increased hematotoxicity ↑	
<b>Antiviral Drugs</b>		
Acyclovir [7]	Case report: profound lethargy	See: probenecid.
Cidofovir [8]	Increased hematotoxicity ↑	
Foscarnet [6]	Increased risk of anaemia ↑ (less risky than with ganciclovir)	
Ganciclovir [9-10], Valganciclovir	Increased hematotoxicity ↑	<b>Avoid combination.</b> Th. alternatives: foscarnet + AZT, ganciclovir + ddI.
Interferon [11]	Increased hematotoxicity ↑	<b>Avoid combination.</b>
Ribavirin [12]	Increased hematotoxicity and mitochondrial toxicity (lactic acidosis), AZT-antagonism	<b>Avoid combination.</b>
<b>Cytotoxic drugs</b>		
Doxorubicin [2] among many others	Increased hematotoxicity ↑	<b>Avoid combination</b> or control blood counts closely.
<b>Substitution</b>		
Methadone [14]	AZT ↑ 41 %	Monitor for AZT side-effects.
<b>Uricosuric drug</b>		
Probenecid [13]	AZT ↑ 80 %	Monitor for AZT side-effects. Take 50 % of AZT dose when combined with cidofovir and probenecid.

## References

1. Tseng A. www.tthivclinic.com, General Hospital, Toronto, 2006.
2. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
3. Product information: Retrovir™. Glaxo Smithkline.
4. Polis MA, Piscitelli SC, Vogel S, et al. Clarithromycin lowers plasma zidovudine levels in persons with HIV-infection. *Antimicrob Agents Chemother* 1997; 41: 1709-14. <http://www.amedeo.com/lit.php?id=9257746>
5. US Department of Health and Human Services (DHHS) and National Institutes of Health (NIH). The living document: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Retrieved April 14, 2004. [www.aidsinfo.nih.gov](http://www.aidsinfo.nih.gov).
6. Foscavir™. Astra Zeneca.
7. Cooper DA, Pehrson PO, Pedersen C, et al. The efficacy and safety of zidovudine alone or as co-therapy with acyclovir for the treatment of AIDS and AIDS-related complex: a double-blind randomized trial. European-Australian Collaborative Group. *AIDS* 1993; 7: 197-207. <http://www.amedeo.com/lit.php?id=8096703>
8. Bach MC. Possible drug interaction during therapy with azidothymidine and acyclovir for AIDS [letter]. *N Engl J Med* 1987; 317: 547. <http://www.amedeo.com/lit.php?id=3468354>
9. Hochster H, Dieterich D, Bozzette S, et al. Toxicity of combined ganciclovir and zidovudine for cytomegalovirus disease associated with AIDS. *Ann Intern Med* 1990; 113: 111-7. <http://www.amedeo.com/lit.php?id=2163228>

10. Cimoch PJ, Lavelle J, Pollard R, et al. Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine and probenecid in HIV-infected subjects. *JAIDS* 1998; 17: 227-34. <http://www.amedeo.com/lit.php?id=9495222>
11. Ruedy J, Schlechter M, Montaner JS. Zidovudine for early HIV-infection: who, when, and how? *Ann Intern Med* 1990; 112: 721-3.
12. Sim SM, Higgard PG, Sales SD, et al. Effect of ribavirin on zidovudine efficacy and toxicity in vitro: a concentration-dependent interaction. *AIDS Res Hum Retr* 1998; 14: 1661-7.
13. Kornhauser DM, Petty BG, Hendrix CW, et al. Probenecid and zidovudine metabolism. *Lancet* 1989; 2: 473-5. <http://www.amedeo.com/lit.php?id=2570186>
14. Antoniou T, Lin-in Tseng. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; 36: 1598-613. <http://www.amedeo.com/lit.php?id=12243611>
15. Roszko PJ, Curry K, Brazina B, et al. Standard doses of efavirenz, zidovudine, tenofovir, and didanosine may be given with tipranavir/ritonavir. Abstract 865, 2nd IAS 2003, Paris. <http://www.aegis.com/conferences/2ndIASHIVPT/865.html>

## d4T (Stavudine, Zerit™)

Approved dose: 30-40 mg BID (< 60 kg: 30 mg BID). Elimination: 34-43 % renal

Drugs	Interactions	Comments
<b>NRTIs</b>		
AZT	Antagonism	
ddI [1]	Risk of lactic acidosis, pancreatitis, neuropathy ↑	Not recommended for first line therapy.
ddC [1]	Risk of neuropathy ↑	<b>Avoid combination.</b>
<b>Co-medication</b>		
Dapsone [1]	Risk of neuropathy ↑	<b>Avoid combination.</b>
Isoniazid	Risk of neuropathy ↑	<b>Avoid combination.</b>
Pentamidine [3]	Additive pancreas toxicity when given i.v.	<b>Avoid combination.</b> Start d4T after one week.
Ribavirin [4-6]	Increased risk of mitochondrial toxicity (lactic acidosis), pancreatitis	Closely monitor for amylase, lipase, lactate.
Vinca Alkaloids [1]	Risk of neuropathy ↑	<b>Avoid combination.</b>

## References

1. Tseng A. [www.tthivclinic.com](http://www.tthivclinic.com), General Hospital, Toronto, 2004.
2. *Clinical Pharmacology*, Gold Standard Multimedia, 2004. <http://www.gsm.com>
3. Foisy MM, Slayter KL, Hewitt RG, et al. Pancreatitis during intravenous pentamidine therapy in an AIDS patient with prior exposure to didanosine. *Ann Pharmacother* 1994; 28: 1025-8. <http://www.amedeo.com/lit.php?id=7803875>
4. Landau A, Batisse D, Piketty C, et al. Lack of interference between ribavirin and nucleoside analogues in HIV/HCV co-infected individuals undergoing concomitant antiretroviral and anti-HCV combination therapy. *AIDS* 2000; 14: 1857-8. <http://www.amedeo.com/lit.php?id=10985327>
5. Hittinger G. Mitochondrial toxicity in HIV/HCV co-infected patients treated with ribavirin, interferon alpha and antiretroviral therapy. Abstract TuPeB4516, XIV Int AIDS Conference 2002, Barcelona.
6. Smith DM, Puoti M, Sulkowski, et al. Symptomatic hyperlactatemia during a large hepatitis C treatment trial in HIV/HCV co-infected participants on stable antiretroviral therapy. Abstract MoOrB1059, XIV Int AIDS Conference 2002, Barcelona.

## Darunavir (DRV, TMC 114, Prezista™)

Dose (approved in US): TMC 114/r: 600/100 mg BID taken with a meal [5]. Metabolism: TMC 114 is metabolized by the isoenzyme CYP3A4 [5]. By means of boosting with RTV, TMC 114 becomes to be an inhibitor of CYP3A4.

Substance	Interactions	Comments
<b>NRTIs</b>		
ddI [5]		ddI 2h before or after
TDF [1]	TDF 300 QD + DRV/r 300/100 BID: TDF ↑ 22 %	No dose adjustment.
<b>NNRTIs</b>		
EFV [5]	EFV 600 QD + DRV 300/100 BID: DRV ↓ 13 % ( $C_{\min}$ 31 % ↓) EFV ↑ 21 % ( $C_{\min}$ 17 % ↑)	Clinical relevance unclear. Combine with caution.
NVP [5]	NVP 200 BID + DRV 300/100 BID: NVP ↑	Combination possible.
<b>PIs</b>		
ATV [2]	ATV 300 QD + DRV/r 400/100 BID: ATV ↑ ( $C_{\min}$ 87 % ↑) RTV ↑ 50-59 %	Increased incidence of hyperbilirubinemia, ocular icterus.
IDV [5]	IDV 800 BID + DRV/r 400/100 BID: IDV ↑, DRV ↑	Combination possible, if clinically necessary.
LPV/r [5]	LPV/r 400/100 + DRV/r 300/100 BID: DRV ↓ 53 %, LPV/r ↑	<b>Avoid combination.</b> No appropriate dosages known as yet.
SQV [5]	SQV 1000 BID + DRV/r 400/100 BID: DRV ↓ 26 %	<b>Avoid combination.</b>
<b>Antiarrhythmics</b>		
Amiodarone, lidocaine, chinidine [5]	Theoretically: antiarrhythmics ↑, potential for severe arrhythmia	<b>Close monitoring.</b>
<b>Antibiotics</b>		
Clarithromycin [5]	Clarithromycin 500 BID + DRV/r 400/100 BID: clarithromycin ↑	Only dose adjustment in renal failure.
<b>Antidepressants</b>		
Trazodone, sertraline, paroxetine [5]	Trazodone side effects ↑: syncope, sickness, hypotension sertraline 50 QD + DRV/r 400/100 BID: sertraline ↓, paroxetine 20 QD + DRV/r 400/100 BID: paroxetine ↓	<b>Caution.</b> Possibly dose reduction. Start with low dose. Look out for antidepressive effects.
<b>Antihistamines</b>		
Astemizole, terfenadine [5]	Astemizole, terfenadine ↑	<b>Avoid combination:</b> astemizole, terfenadine.
<b>Antihypertensives</b>		
Calcium channel blockers [5]	Calcium channel blockers ↑	If necessary, dose reduction of calcium channel blockers.

Substance	Interactions	Comments
<b>Antifungal drugs</b>		
Ketoconazole, itraconazole, voriconazole [5]	Ketoconazole 200 BID + DRV/r 400/100 BID: DRV ↑, ketoconazole ↑, itraconazole ↑, voriconazole + RTV 100 BID: voriconazole ↓ 39 %	Dose of ketoconazole, itraconazole: < 200 mg.  <b>Avoid combination.</b> No data, apart from RTV.
<b>Antituberculosis drugs</b>		
Rifampicin Rifabutin [5]	DRV ↓ DRV ↓	<b>Avoid combination.</b> DRV + rifabutin 150 mg every other day.
<b>Corticoids</b>		
Dexamethasone, fluticasone [5]	Theoretically: dexamethasone + DRV: DRV ↓, fluticasone + DRV: fluticasone ↑	Look for alternative by longtime use.
<b>Ergotamines</b> [5]	Theoretically: ergotamines ↑. Possibly life-threatening ergotism	<b>Avoid combination.</b>
<b>Gastritis-/ Ulcer healing drugs</b>		
Ranitidine [3] Omeprazole [3]	DRV/r 400/100 BID alone + ranitidine 150 BID or omeprazole 20 QD: no level fluctuations	No interaction.
Cisapride [5]		<b>Avoid combination.</b>
<b>Hypnotics</b>		
Mida-, triazolam [5]	Prolonged sedation.	<b>Avoid combination.</b>
<b>Immunosuppressants</b>		
Ciclosporine, sirolimus tacrolimus [5]	Immunosuppressants ↑	TDM of immunosuppressants.
<b>Lipid-lowering drugs</b>		
Atorvastatin [4]	Atorvastatin 10 + DRV/r 300/100 BID versus atorvastatin 40 alone: atorvastatin 10 ↓ 15 %	Start with a low initial dose of 10 mg atorvastatin. <b>Avoid combination:</b> lovastatin, simvastatin.
<b>Neuroleptics</b>		
Pimozide [5]	Potential for severe, life-threatening cardiac arrhythmia.	<b>Avoid combination.</b>
<b>Oral contraceptives</b> [5]		
	Ethinyl estradiol ↓ Norethindrone ↓	Use additional contraceptive method.
<b>PDE5 inhibitors</b>		
Sildenafil, tadalafil, vardenafil [5]	PDE5 inhibitors ↑, sildenafil 100 QD+ DRV/r 400/100 BID: sildenafil ↑	Sildenafil 25 mg in 48h. Tadalafil 10 mg in 72h. Vardenafil 2.5 mg in 72h.
<b>Substitution</b>		
Methadone [5]	Methadone ↓	Monitor f. withdr. symptoms.
<b>Others</b> [5]		
St. John's Wort Warfarin	DRV ↓ Warfarin ↓	<b>Avoid combination.</b> Check for INR levels.



## References

1. Hoetelmans R, Marien K, De Pauw M et al. Pharmacokinetic Interaction between TMC114/RTV and Tenofovir in healthy volunteers. XVth World AIDS Conference 2004, Bangkok.
2. Sekar V, De Marez T, Spinosa-Guzman S et al. Pharmacokinetic Interaction between TMC114/RTV and Atazanavir in healthy volunteers. Abstract PE4/3.4, 10th European AIDS Conference 2005, Dublin.
3. Sekar VJ, Hoetelmans R, De Marez T et al. Pharmacokinetics of TMC114: Effect of Omeprazole and Ranitidin. Poster 2.10, 6<sup>th</sup> Inter Worksh on Clin Pharmacol of HIV-Ther 2005, Quebec
4. Hoetelmans R, Lasure A, Koester A et al. The effect of TMC114, a potent next generation HIV Protease Inhibitor with low-dose Ritonavir on Atorvastatin Pharmacokinetics. Abstract H-885, 44<sup>th</sup> ICAAC 2004, Washington
5. US product information on Prezista®.

## ddI (Didanosine, Videx™)

Approved dose: < 60 kg: 250 mg QD, > 60 kg: 400 mg QD. Metabolism: Hypoxanthine-oxidase; elimination: 30-50 % renal

Drugs	Interactions	Comments
<b>NRTIs</b>		
d4T [1-3]	Risk of lactic acidosis, pancreatitis, neuropathy ↑	Not recommended for first line therapy.
TDF [3-5]	ddI EC 250 QD + 300 TDF QD has equivalent ddI AUC compared to ddI 400 mg alone. Dose recommendation: Patients ≥ 60 kg: ddI 250 mg Patients < 60 kg: ddI 200 mg  Despite dose reduction increased risk of lactic acidosis/pancreatitis	<b>Probably unfavourable combination.</b> Virological failure in patients with high viral load and low CD4 cells [4]. Closely monitor for amylase, lipase, lactate. Take ddI and TDF together with food.
<b>PIs</b>		
ATV [1,3]	ddI tablets: ATV ↓ 87 %, ddI-EC: no data	Take ddI 2 h apart from ATV.
<b>Co-medication</b>		
Allopurinol [6]	ddI ↑ 122 % (Cmax ↑ 116 %)	<b>Avoid combination.</b>
Cimetidine [1]	Theoretically: ddI ↑	Monitor for side-effects.
Dapsone [7]	Increased risk of neuropathy ↑	<b>Avoid combination.</b>
Ganciclovir (GCV), Valganciclovir (VGCV) [8-10]	Risk of lactic acidosis and pancreatitis ↑ GCV i.v.: ddI ↑ 70 %	Closely monitor for amylase, lipase, lactate.
Isoniazid	Risk of neuropathy ↑	<b>Avoid combination.</b>
Methadone [11]	ddI 41 % ↓	Not clinically significant.
Pentamidine [12]	Additive pancreas toxicity when given i.v.	<b>Avoid combination.</b>
Ribavirin [13]	ddI + metabolite ↑, risk of lactic acidosis, pancreatitis, neuropathy ↑	<b>Avoid combination.</b> Never combine ddI and RBV!
Vinca Alkaloids [1]	Risk of neuropathy ↑	Vinblastine: less neurotoxic than vincristine.

## References

1. Tseng A. www.tthhivclinic.com, General Hospital, Toronto, 2004.
2. US Department of Health and Human Services (DHHS) and National Institutes of Health (NIH). The living document: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Retrieved April 14, 2004.
3. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
4. Moyle G, Maitland D, Hand J, et al. Early virological failure in persons with viral loads > 100,000 cps/ml and CD4 counts < 200/mm<sup>3</sup> receiving DDI/tenofovir/ efavirenz as initial therapy: Results from a randomised comparative trial. Abstract H-566, 44th ICCAC 2004, Washington.
5. Kearney BP, Isaacson E, Sayre J, et al. Didanosine and tenofovir DF drug-drug interaction: assessment of didanosine dose reduction. Abstract 533, 10th CROI 2003, Boston.
6. Liang D, Breaux K, Rodriguez-Barradas M, et al. Allopurinol increases didanosine adsorption in HIV-infected patients. Abstract A498, 41st ICAAC 2001, Chicago.
7. Sahai J, Garber G, Gallicano K, et al. Effects of the antacids in didanosine tablets on dapsone pharmacokinetics. *Ann Intern Med* 1995; 123: 584-7. <http://www.amedeo.com/lit.php?id=7677298>
8. Cimoch PJ, Lavelle J, Pollard R, et al. Pharmacokinetics of oral ganciclovir alone and in combination with zidovudine, didanosine and probenecid in HIV-infected subjects. *JAIDS* 1998; 17: 227-34. <http://www.amedeo.com/lit.php?id=9495222>
9. Jung D, Griffy K, Dorr A, et al. Effect of high dose oral ganciclovir on didanosine disposition in HIV-positive patients. *J Clin Pharmacol* 1998; 38: 1057-62. <http://www.amedeo.com/lit.php?id=9824788>
10. Frascino RJ, Gaines Griffy K, Jung D, et al. Multiple dose crossover study of IV ganciclovir induction dose (5 mg/kg IV q12h) and didanosine (200 mg po q12h) in HIV-infected persons. Abstract A-27, 3th CROI 1995, San Francisco.
11. Rainey PM, Friedland G, McCance-Katz EF, et al. Interaction of Methadone with didanosine and stavudine. *JAIDS* 2000; 24: 241-8. <http://www.amedeo.com/lit.php?id=10969348>
12. Foisy MM, Slayter KL, Hewitt RG, et al. Pancreatitis during intravenous pentamidine therapy in an AIDS patient with prior exposure to didanosine. *Ann Pharmacother* 1994; 28: 1025-8. <http://www.amedeo.com/lit.php?id=7803875>
13. Product nformation: Videx™, Bristol Myers-Squibb.
14. Roszko PJ, Curry K, Brazina B, et al. Standard doses of efavirenz, zidovudine, tenofovir, and didanosine may be given with tipranavir/ritonavir. Abstract 865, 2nd IAS 2003, Paris. <http://www.aegis.com/conferences/2ndIASHIVPT /865.html>

## Efavirenz (EFV, Sustiva™, Stocrin™)

Approved dose: 600 mg QD. Metabolism: efavirenz is mainly metabolized by CYP2B6 and minor by CYP3A4 and CYP1A2. In vitro EFV is an inducer of CYP3A4 and a poor inhibitor of CYP3A4, -2C9 and -2C19 [1]. Note: wrong positive Cannabinoid urine result with CEDIA DAU multilevel THC assay [2] possible.

Drugs	Interactions (IAs)	Comments
<b>NRTIs</b>	No clinically significant IAs [1]	
<b>NNRTIs</b>		
Nevirapine NVP [3,34]	NVP 400 QD + EFV [3]: EFV ↓ 22 % (C <sub>min</sub> 36 % ↓)	<b>Unfavourable combination.</b> Less efficacy, increased toxicity [33].
<b>PIs</b>		
FPV/r [4]	FPV/r 700/100 BID + EFV: no clinically significant IA	Off label use: when use FPV/r QD, increase RTV to 300 mg.
ATV [7,8]	ATV 400 QD + EFV: ATV ↓ up to 74 %	ATV/r: 300/100 QD.
IDV/r [9,10]	IDV/r 800/100 BID + EFV: IDV ↓ 19 % (C <sub>min</sub> 48 % ↓) [9]	IDV/r 800/100, probably higher doses for pre-treated patients are necessary [10].

Drugs	Interactions (IAs)	Comments
LPV/r [1,5, 11]]	Capsules: LPV/r 400/100 + EFV: LPV ↓ 25 % ( $C_{min}$ 44 % ↓) Tablets: LPV/r 600/150 BID + EFV: LPV ↑ 35 %, RTV ↑ 56-92 %	Capsules: LPV/r: 533/133 BID. TDM  Tablets: LPV/r 400/100 BID: may be used in ART-naive patients. LPV/r 600/150 BID: recommended for pretreated pts [1].
SQV/r [12-15]	SQV 1200 TID + EFV: SQV ↓ 62 % [12,13]	SQV/r 400/400 BID or SQV/r 1200/100 QD [14,15]. No data with new SQV tablets (TDM)
NFV [6,16]	NFV 1250 BID + EFV: NFV ↓ 38 % ( $C_{min}$ 65 % ↓) [16]	TDM.
TPV/r [34]	EFV ↓ 1-31 % TPV ↓ ( $C_{max}$ ↓, $C_{min}$ ↓)	Limited data. No dose adjustment necessary as yet.
TMC/r [32]	TMC/r 300/100 BID + EFV: TMC ↓ 13 % ( $C_{min}$ 31 %) EFV ↑ 21 % ( $C_{min}$ 17 %) TMC/r 300/100 BID + EFV: TMC ↓ 13 % ( $C_{min}$ 31 %) EFV ↑ 21 % ( $C_{min}$ 17 %)	Limited data. Use combination with caution.
<b>Antiarrhythmics</b>		
Amiodarone, quinidine, flecainide, lidocaine	Theoretically: antiarrhythmic ↓ ↑	<b>Avoid combination.</b>
<b>Antibiotics</b>		
Clarithromycin [2,17,18]	CLM 500 BID + EFV 400 QD: CLM metabolite ↑ 34 % ( $C_{max}$ 49 % ↑), 46 % exanthema [2,18]	Theoretical alternative: azithromycin [17].
Erythromycin [17]	Theoretically: EFV ↑	Monitor for EFV side-effects. Th. alternative: azithromycin.
<b>Antiepileptics</b>		
Carbamazepine, phenytoin, primidone [2]	Theoretically: EFV ↓	<b>Avoid combination</b> or TDM. Theoretical alternative: gabapentin, valproic acid, lamotrigine.
<b>Antifungal drugs</b>		
Itraconazole, ketoconazole, voriconazole [2,21]	Theoretically: EFV ↑, azole ↓ Voriconazole + EFV: voriconazole 77 % ↓ ( $C_{max}$ 61 % ↓) EFV ↑ 44 % ( $C_{max}$ 38 % ↑)	<b>Avoid combination:</b> voriconazole. Itra-/ketoconazole: no data. Theoretical alternative: fluconazole [1].
<b>Antihistamines</b>		
Astemizole, loratadine (> 20 mg), terfenadine [1,2,19,21]	Theoretically: antihistamines ↓ ↑ Risk of QT-prolongation [1,21]	<b>Avoid combination:</b> Terfenadine. Th. alternative: cetirizine, fexofenadine [2,19].

Drugs	Interactions (IAs)	Comments
<b>Antihypertensives</b>		
Calcium channel bl. felodipine, nifedipine, verapamil [23]	Theoretically: calcium channel blockers ↓ ↑	Perhaps reduce dose of calcium channel blockers.
Bosentan [18,31]	Theoretically: EFV ↓ [18]	<b>Avoid combination</b> or TDM. Off label use sildenafil [31].
<b>Antipsychotics</b>		
Several drugs [2,18,28]	1. Theoretically: antipsychotics ↓ ↑ 2. Clozapine (active metabolite ↑) 3. QT-prolongation of pimozide	<b>Avoid combination</b> with pimozide. Prefer atypical neuroleptics (less anticholinergic)
<b>Antituberculosis drugs</b>		
Rifabutin [2,16,29]	Rifabutin ↓ 38 % ( $C_{max}$ 32 % ↓)	Rifabutin 450 mg QD or 600 mg two or three times/week
Rifampicin [2,29,36,37]	EFV ↓ 26 % ( $C_{max}$ 20 % ↓)	EFV 800 QD; EFV 600 for pts < 50 kg only with TDM.
<b>Cytotoxic drugs</b>		
Cyclophosphamide [18,30]	Theoretically: neurotoxic metabolite ↑	Avoid additional neurotoxic drugs.
<b>Hypnotics</b>		
Barbexaclone, phenobarbital	Theoretically: EFV ↓	<b>Avoid combination</b> or TDM.
Benzodiazepines, zolpidem [2,22]	Theoretically: benzodiazepines ↓	<b>Avoid combination:</b> mida-, triazolam [2]. Th. alternative: lora/oxa/tema-zepam [22].
<b>Immunosuppressants</b>		
Cyclosporine, sirolimus, tacrolimus	Dose reduction of cyclosporine when combined with EFV [35].	Dose adjustment of immunosuppressants via TDM.
<b>Herbals</b>		
St. John's Wort [2]	Theoretically: EFV ↓	<b>Avoid combination.</b>
<b>Lipid-lowering drugs</b>		
Ator-, lo-, sim-vastatin [24-26]	Atorvastatin 48 % ↓ and simvastatin 58 % ↓	Th. alternative: Pravastatin, fluvastatin, rosuvastatin.
<b>Oral contraceptives</b> [2]		
	Oestrogen ↑, ethinylestradiol ↑ 37 %	Use additional contraception method. Not enough data.
<b>PDE5 inhibitors (PPHs)</b>		
Sildenafil, tadalafil, vardenafil	Theoretically: PPHs ↓ ↑	Caution: low initial dose.
<b>Recreational drugs</b>		
Cocaine [27]	Theoretically: norcocaine ↑	Caution: liver toxicity.
<b>Substitution</b>		
Methadone [27]	Methadone: 60 % ↓	If necessary, increase methadone dose up to 100 %. Dose reduction of methadone when stopping EFV therapy.

## References

1. Tseng A. [www.tthhivclinic.com](http://www.tthhivclinic.com), General Hospital, Toronto, 2004.
2. Sustiva™, Bristol-Myers Squibb.
3. Veldkamp AI, Harris M, Montaner JSG, et al. The steady-state pharmacokinetics of efavirenz und nevirapine when used in HIV-1 infected patients. *J Infect Dis* 2001; 184: 37-42. <http://www.amedeo.com/lit.php?id=11398107>
4. Wire MB, Ballou C, Preston SL, et al. Pharmacokinetics and safety of GW433908 and ritonavir, with and without efavirenz, in healthy volunteers. *AIDS* 2004, 18: 897-907. <http://www.amedeo.com/lit.php?id=15060437>
5. Klein C, ZHU T, Chiu YL et al. Effect of efavirenz on lopinavir/ritonavir pharmacokinetics from a new tablet formulation. Abstract 4.3/2, 10<sup>th</sup> EACS 2005, Dublin.
6. Alvarez-Amao D, Pace W, Gold M. Switch from high to low dose amprenavir in combination with efavirenz and ritonavir. Abstract 2.7, 3rd Int Worksh Clin Pharmacol HIV Ther 2002, Washington.
7. Preston S, Piliero P, O'Mara E, et al. Evaluation of steady-state interaction between atazanavir and efavirenz. Abstract 433, 9th CROI 2002, Seattle.
8. Reyataz™, Bristol-Myers Squibb.
9. Aarnoutse RE, Grinjtjes KJT, Telgt DS, et al. The influence of efavirenz on the pharmacokinetics of a twice daily combination of indinavir and low-dose ritonavir in healthy subjects. *JAIDS* 2003; 34: 134-9. <http://www.amedeo.com/lit.php?id=11823758>
10. Boyd MA, Aarnoutse RE, Ruxrungtham K, et al. Pharmacokinetics of indinavir/ritonavir (800/100 mg) in combination with efavirenz (600 mg) in HIV-infected subjects. *JAIDS* 2003; 34: 134-9. <http://www.amedeo.com/lit.php?id=14526202>
11. Bertz R, Lam W, Hsu A, et al. Assessment of the pharmacokinetic interaction between ABT – 378/r and efavirenz in healthy volunteers and in HIV+subjects. Abstract 424, 40th ICAAC 2000, Toronto.
12. Jorga K, Buss NE. Pharmacokinetic drug interaction with saquinavir sgc. Abstract 339, 39th ICAAC 1999, San Francisco.
13. Hendrix CW, Fiske WD, Fuchs EJ, et al. Pharmacokinetics of the triple combination of saquinavir, ritonavir and efavirenz in HIV+subjects. Abstract 424, 11th CROI 2000, San Francisco.
14. van Heeswijk RP, Cooper C, Gallicano A, et al. The pharmacokinetics of SQV/RTV 400/400 mg BID before, and after short- and long term co-administration of efavirenz 600 mg QD. Abstract 7.4, 3rd Int Worksh Clin Pharmacol HIV-Ther 2002, Washington.
15. Lopez-Cortes LF, Viciano P, Ruiz-Valderas R, et al. Pharmacokinetics, efficacy and safety of once-daily saquinavir-sgc plus low-dose ritonavir (1200/100 mg) in combination with efavirenz in HIV-pretreated patients. Abstract 441, 9th CROI 2002, Seattle.
16. Fiske WD, Benedek IH, White SJ, et al. Pharmacokinetic interaction between efavirenz and nelfinavir mesylate in healthy volunteers. Abstract 349, 5th CROI 1998, Chicago.
17. Benedek ICH, Joshi A, Fiske WD, et al. Pharmacokinetic studies in healthy volunteers with efavirenz and the macrolide antibiotics, azithromycin and clarithromycin. Abstract 347, 5th CROI 1998, Chicago.
18. *Clinical Pharmacology*, Gold Standard Multimedia, 2004. <http://www.gsm.com>
19. Pratt CM, Mason J, Russell T. Cardiovascular safety of fexofenadine HCL. *Am J Cardiol* 1999; 84: 278-9. <http://www.amedeo.com/lit.php?id=10335761>
20. Abernethy DR, Barbey JT. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QT-prolongation. *Clin Pharmacol Ther* 2001; 69: 96-103. <http://www.amedeo.com/lit.php?id=11240972>
21. Vfend™, Pfizer.
22. Michalets E: Update: Clinically Significant Cytochrome P-450 Drug Interaction. *Ann Pharmacother* 1998; 18: 84-112. <http://www.amedeo.com/lit.php?id=9469685>
23. Rossi DR, Rathbun C, Slater LD. Symptomatic ortostasis with extended-release nifedipine and protease inhibitors. *Ann Pharmacother* 2002; 22:1312-16. <http://www.amedeo.com/lit.php?id=12389881>
24. Gerber JG, Fichtenbaum CJ, Rosenkranz S, et al. Efavirenz is a significant inducer of simvastatin and atorvastatin metabolism: results of ACTG A5108 study. Abstract 603, 11th CROI 2004, San Francisco.
25. Fichtenbaum CJ, Gerber JG, Rosenkranz S. Pharmacokinetic interaction between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. *AIDS* 2002; 16: 569-77. <http://www.amedeo.com/lit.php?id=11873000>
26. Doser N, Kubli S, Telenti A. Efficacy and safety of fluvastatin in hyperlipidemic protease inhibitor-treated HIV-infected patients. *AIDS* 2002; 16: 1982-3. <http://www.amedeo.com/lit.php?id=12351967>

## 782 Interactions

27. Antoniou T, Lin-in Tseng. Interactions between recreational drugs and antiretroviral agents. *Ann Pharmacother* 2002; 36: 1598-613. <http://www.amedeo.com/lit.php?id=12243611>
28. Tseng AL, Foisy MM. Significant interactions with new antiretrovirals and psychotropic drugs. *Ann Pharmacother* 1999; 33: 461-73. <http://www.amedeo.com/lit.php?id=10332538>
29. Centers for Disease Control and Prevention (CDC). Notice to Readers: Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR*; 2004; 53: 37. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4909a4.htm>
30. Lam M, Ignoffo R, Meibohm B. Ein Leitfadens für klinisch-relevante Arzneimittel-Interaktionen in der Onkologie, Institute for Applied Healthcare Science.
31. Ghofrani HA, Olschewski H, Seeger W, et al. Sildenafil for treatment of severe pulmonary hypertension and commencing right-heart failure. *Pneumologie* 2002; 56: 665-72. <http://www.amedeo.com/lit.php?id=12442206>
32. Sekar V, DePauw M, Marien K et al. No clinically significant pharmacokinetic drug-drug interaction is observed between the HIV protease inhibitor TMC 114 and the NNRTI Efavirenz. Abstract 55. 7<sup>th</sup> Int Worksh Clin Pharmacol HIV Ther 2005, Lissabon.
33. van Leth F, Phanuphak P, Ruxrungtham K, et al. Comparison of first-line antiretroviral therapy with regimens including nevirapine, efavirenz, or both drugs, plus stavudine and lamivudine: a randomised open-label trial, the 2NN Study. *Lancet* 2004, 363:1253-63. <http://www.amedeo.com/lit.php?id=15094269>
34. Roszko PJ, Curry K, Brazina B, et al. Standard doses of efavirenz, zidovudine, tenofovir, and didanosine may be given with tipranavir/ritonavir. Abstract 865, 2nd IAS 2003, Paris.
35. Tseng A, Nguyen ME, Cardella C, et al. Probable interaction between efavirenz and Cyclosporine. *AIDS* 2002,16:505-6.
36. Sheehan NL, Richter C, Koopmans P et al. Efavirenz is not associated with subtherapeutic EFV concentrations when given concomitantly with rifampin. Abstract 28. 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
37. Almond L, Gibbons S, Davies G et al. A retrospective survey of the Liverpool TDM service: Factors influencing Efavirenz concentrations in patients taking Rifampicin. Abstract 19. 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.

### Emtricitabine (FTC, Emtriva™; also in Truvada™)

Approved dose: 200 mg QD. Elimination: renal

Drugs	Interactions	Comments
<b>NRTIs</b>		
3TC	Antagonism	<b>Avoid combination.</b>
<b>NNRTIs</b>	No significant interaction	
<b>PIs</b>	No significant interaction	

### Fosamprenavir (FPV, Lexiva™, Telzir™)

Approved dose: FPV/r: 700/100 mg BID. Metabolism: FPV is a prodrug of amprenavir (APV) and is hydrolysed in the gut epithelium by cellular phosphatases during absorption to the active compound. APV is metabolized by CYP3A4 and is an inhibitor of CYP3A4 (as potent as indinavir and nelfinavir). Additionally, there are reports suggesting that APV is also an inducer of CYP3A4 [35]. Except the drug interaction between APV and LPV/r, the inducing effect may not be seen with the dose commonly used for boosting.

Drugs	Interactions (IAs)	Comments
<b>NRTIs</b> [3,30,31]	No significant IAs	
<b>NNRTIs</b>		
EFV [4-6]	EFV 600 QD + FPV/r: no clinically significant IAs	Off label use FPV/r QD: increase RTV to 300/d [6].
NVP [7,8]	NVP 200 BID + FPV/r: no clinically significant IAs	In this study, no dose adjustment was necessary.
<b>PIs</b>		
ATV [17,18]	ATV 300 QD + FPV/r: 1. ATV ↓ 22 % ( $C_{\min}$ 24 % ↓) [17] 2. Adequate levels of both dr. [18]	Controversial data => TDM.
IDV [19]	APV 800 + IDV 800 TID: APV ↑ 33 %, IDV ↓ 38 % ( $C_{\min}$ 27 % ↓)	In this study, no dose adjustment was necessary.
LPV/r [9-16]	FPV/r 700/100 + LPV/r 400/100 BID: APV ↓ 63 % ( $C_{\min}$ 65 % ↓) LPV ↑ 37 % ( $C_{\max}$ 30 % ↑) [10] FPV 700 + LPV/r 400/100 BID: APV ↓ 64 % ( $C_{\min}$ 69 % ↓) LPV ↓ 48 % ( $C_{\min}$ 61 % ↓) [9] FPV 700 + LPV/r 533/133 BID: APV ↓ 26 % ( $C_{\min}$ 42 % ↓) LPV: adequate concentrations [10]	<b>Avoid combination</b> or TDM. [5].  Dose separation corrected LPV-levels, but not APV plasma concentrations [11]
NFV [2,19]	APV 800 + NFV 750 TID [19]: APV: $C_{\min}$ 3-fold ↑, NFV ↑ 15 %	In this study, no dose adjustment was necessary [2].
SQV/r [20,21]	FPV 700 + SQV/r 1000/ <b>100</b> BID: FPV not affected, SQV ↓ 14 % (C <sub>trough</sub> SQV 24 % ↓) FPV 700 + SQV/r 1000/ <b>200</b> BID: FPV not affected, SQV ↑ 12 %	FPV + SQV + RTV <b>100</b> : unsafe => TDM of SQV. FPV + SQV + RTV <b>200</b> : safe.
TPV/r [34]	TPV/r 500/200 + APV 600 BID: APV ↓ 44 % ( $C_{\min}$ ↓ 56 %)	<b>Avoid combination.</b>
<b>Antiarrhythmics</b>		
Amiodarone, flecainide, lidocaine [3]	Theoretically: antiarrhythmics ↑	<b>Avoid combination.</b>
<b>Antibiotics</b>		
Clari-, erythromycin [2,3]	Theoretically: APV ↑, erythromycin, clarithromycin ↑	Dose reduction of clarithromycin in pts with renal failure
<b>Anticoagulants</b>		
Warfarin [3]	Theoretically: warfarin ↑↓	Check INR.
<b>Antidepressants</b>		
Tricyclic antidepressants [2,3]	Theoretically: APV and tricyclic antidepressants ↑	Monitor for side-effects of both drugs.
Paroxetine [33]	FPV 700/100 BID + Paroxetine 20 QD: paroxetine ↓ 60 % ↓	Dose adjustment if necessary.
St. John's Wort [2,3]	Theoretically: APV ↓	<b>Avoid combination.</b>

Drugs	Interactions (IAs)	Comments
<b>Antiepileptics</b>		
Carbamazepine, Phenytoin [2,3,27]	Theoretically: APV ↓, antiepileptics ↑	Th. alternatives: gabapentin, lamotrigine, valproic acid.
<b>Antifungal drugs</b>		
Itra-, Keto-conazole, voriconazole [1,2]	Theoretically: APV ↑, azole ↑ [2]. Caution: toxicity of both drugs [1]	Theoretical alternative: fluconazole [1].
<b>Antihistamines</b>		
Astemizole, loratadine (> 20 mg), terfenadine [3,28,29]	Theoretically: antihistamines ↑ and risk of QT-prolongation ↑	<b>Avoid combination:</b> terfenadine [2,3], loratadine > 20 mg. Th. alternatives: cetirizine, fexofenadine [28,29].
<b>Antihypertensives</b>		
Calcium channel blockers felodipine, nifedipine, verapamil [2]	Theoretically: calcium channel blockers ↑	<b>Avoid combination</b> or reduce dose of calcium channel blockers if necessary.
Bosentan [26]	Theoretically: APV ↓	<b>Avoid combination</b> or TDM.
<b>Antipsychotics</b>		
several drugs [2]	Theoretically: antipsychotic drugs ↑	<b>Avoid combination:</b> pimozide, clozapine. Prefer: atypical neuroleptics (less anticholinergic effects).
<b>Antituberculosis drugs</b>		
Rifampicin [2,25]	APV + rifampicin 600 QD APV ↓ 82 % ( $C_{\min}$ 92 % ↓)	<b>Avoid combination.</b>
Rifabutin [6,25]	Rifabutin ↑ 200 %	Rifabutin: 150 mg 3x/week. Monitor for side-effects.
<b>Gastritis-/ Ulcer healing drugs</b>		
PPIs [32]	Esomeprazole + FPV/±r: adequate steady-steady APV-levels	
Antacids [22]	FPV/r: adequate absorption	
H2-blockers Cimetidine [3,22]	theoretically: cimetidine ↑ weak interaction with ranitidine APV ↓ 18-30 % ( $C_{\min}$ unchanged, $C_{\max}$ 35-51 % ↓)	Higher potential for drug-interaction with cimetidine. Prefer: ranitidine.
<b>Hypnotics</b>		
Barbexaclone, phenobarbital	Theoretically: APV ↓	<b>Avoid combination</b> or TDM.
Benzodiazepines, zolpidem [1-3]	Theoretically: benzodiazepines ↑ prolonged sedation	Caution with all benzodiazepines. Lora-, oxa-, temazepam possible.
<b>Immunosuppressants</b>		
Cyclosporine, sirolimus, tacrolimus	Theoretically: immunosuppressants ↑	Dose adjustment of immunosuppressants via TDM.



Drugs	Interactions (IAs)	Comments
<b>Lipid-lowering drugs</b>		
Atorvastatin, lovastatin, simvastatin [1,2,23]	FPV/r 700/100 BID or FPV/r 1400/200 QD + 10 mg Atorvastatin QD [23] FPV/r ↑ 230 % (C <sub>max</sub> : 404 % ↑) FPV ↑ 253 % (C <sub>max</sub> : 284 % ↑)	<b>Avoid combination:</b> simvastatin, lovastatin [1,2], atorvastatin ≥ 20 mg. Th. alternatives: pravastatin, fluvastatin.
<b>Oral contraceptives</b> [2]		
	APV ↓ 22 % (C <sub>min</sub> 20 % ↓) Ethinylestradiol (C <sub>min</sub> 32 % ↑) Norethindrone ↑ 18 % (C <sub>min</sub> 45 % ↑)	<b>Avoid combination</b> or TDM of APV and use additional contraceptive methods.
<b>PDE5 inhibitors (PPHs)</b>		
Sildenafil, tadalafil, vardenafil [6,26]	Theoretically: PPHs ↑ [26] Sildenafil + FPV/r: Sildenafil ↑ 210 % [6]	<b>Not recommended:</b> sildenafil, vardenafil, tadalafil: low initial dose.
<b>Substitution</b>		
Methadone [2,24]	Active methadone enantiomers: 13 % ↓ (C <sub>max</sub> 25 % ↓) Comparison with historical studies: APV ↓ 30 % (C <sub>min</sub> 25 % ↓)	TDM of APV, if necessary, adjust dose of both drugs.
<b>Others</b>		
Dexamethasone Ergotamines	Theoretically: APV ↓ Theoretically: APV ↑	<b>Avoid combination.</b> Theoretical alternative: triptans. TDM of theophylline.
Theophylline	Theoretically: theophylline ↓	

## References

1. Tseng A. <http://www.tthivclinic.com/>, General Hospital, Toronto, 2006.
2. Agenerase™, GlaxoSmithKline.
3. Telzir™, GlaxoSmithKline.
4. Piscitelli S, Bechtel C, Sadler B, et al. The addition of a second protease inhibitor eliminates amprenavir-efavirenz drug interaction and increases plasma amprenavir concentrations. Abstract 78, 7th CROI 2000, San Francisco. <http://www.retroconference.org/2000/abstracts/78.htm>
5. Alvarez-Amao D, Pace W, Gold M. Switch from high to low dose amprenavir in combination with efavirenz and ritonavir. Abstract 2.7, 3rd Int Worksh Clin Pharmacol HIV Ther, 2002, Washington.
6. Wire MB, Ballou C, Preston SL, et al. Pharmacokinetics and safety of GW433908 and ritonavir, with and without efavirenz, in healthy volunteers. AIDS 2004, 18: 897-907. <http://www.amedeo.com/lit.php?id=15060437>
7. Goujard C, Meynard JL, Choudet N, et al. Steady-state pharmacokinetics of amprenavir 600 mg BID and ritonavir 100 mg BID with or without NNRTI in HIV-1 infected patients. Abstract S92, 5th Int Congr Drug Ther HIV Inf 2000, Glasgow. <http://www.aegis.com/conferences/hiv5/P268.html>
8. DeJesus E, Piliero P, Summers K, et al. Evaluation of the pharmacokinetic drug interaction between fosamprenavir (FPV), FPV plus ritonavir (RTV) and nevirapine (NVP) in HIV-infected patients (APV10014). Abstract A447, 44th ICAAC 2004, Washington.
9. Kashuba ADM, Tierney C, Downey GF, et al. Combining fosamprenavir, 908 with lopinavir/ritonavir in HIV-1 infected adults in substantial reduction in amprenavir and lopinavir concentrations: pharmacokinetic results from Adult ACTG Protocol A5143. Abstract 855, 43rd ICAAC 2003, Chicago.
10. Wire MB, Naderer OJ, Masterman AL, et al. The pharmacokinetic interaction between GW433908 and lopinavir/ritonavir (APV10011 and APV 10012). Abstract 612, 11th CROI 2004, San Francisco. <http://www.amedeo.com/lit.php?id=15060437>

11. Corbett AH, Davidson L, Park JJ, et al. Dose separation strategies to overcome the pharmacokinetic interaction of a triple protease inhibitor regimen containing fosamprenavir, lopinavir and ritonavir. Abstract 611, 11th CROI 2004, San Francisco.
12. Khanlou H, Graham E, Brill M, et al. Drug interaction between amprenavir and lopinavir/ritonavir in salvage therapy. *AIDS* 2002; 16: 797-8. <http://www.amedeo.com/lit.php?id=11964539>
13. Bertz RJ, Foit C, Ashbrenner E, et al. Effect of amprenavir on the steady-state pharmacokinetics of lopinavir/ritonavir in HIV+ and healthy subjects. Abstract A1823, 42nd ICAAC 2002, San Diego.
14. Taburet AM, Raguin G, Le Tiec C, et al. Interaction between Amprenavir and lopinavir –ritonavir combination in heavily pretreated patients infected by HIV. *Clin Pharmacol Ther* 2004; 75: 310-23. <http://www.amedeo.com/lit.php?id=15060509>
15. Mauss S, Scholten S, Wolf E, et al. A prospective, controlled study assessing the effect of lopinavir on amprenavir concentrations boosted by ritonavir. *HIV Med* 2004; 5: 15-7. <http://www.amedeo.com/lit.php?id=14731164>
16. Wynn Vezina HE, Brundage RC, Bushman L, et al. Pharmacologic management of the drug-drug interaction between lopinavir/ritonavir and amprenavir. Abstract 609, 11th CROI 2004, San Francisco. <http://www.retroconference.org/2004/cd/PDFs/609.pdf>
17. Wire MB et al. The pharmacokinetic interaction between fosamprenavir/ritonavir and atazanavir in healthy adult subjects (APC 10018). Abstract 4.3/9. 10th EACS Conference 2005, Dublin
18. Guttanti M, Raffaella de Pascalis C, Seminari E, et al. Pharmacokinetics of amprenavir given once or twice a day when combined with atazanavir in heavily pre-treated patients. *AIDS* 2003, 17: 2669-70. <http://www.amedeo.com/lit.php?id=14685066>
19. Sadler BM, Gillotin C, Lou Y, et al. Pharmacokinetic study of human immunodeficiency virus protease inhibitors used in combination with amprenavir. *Antimicrob Agents Chemother* 2001, 45: 3663-8. <http://www.amedeo.com/lit.php?id=11709366>
20. Boffito M, Dickinson L, Hill A, et al. Steady state pharmacokinetics of saquinavir hard gel/fosamprenavir 1000/700 plus 100 and 200 mg of Ritonavir twice daily in HIV+ Patients. Abstract 608, 11th CROI 2004, San Francisco.
21. Wolfe PR, Anderson PG, Gunawan S. Simultaneous administration of amprenavir and saquinavir does not appear to lower plasma levels of either agent when coadministered with low dose ritonavir. Abstract 7.11, 3rd Int Worksh Clin Pharmacol HIV Ther 2002, Washington.
22. Ford SL, Wire MB, Lou Y, et al. The effect of antacids and ranitidine on the pharmacokinetic of GW433908 (APV10007). Abstract A-1606, 43rd ICAAC 2003, Chicago.
23. Wire MB, Baker KL, Moore KHP, et al. The pharmacokinetic interaction of GW 433908 with atorvastatin and 908/ritonavir with atorvastatin (APV 10013). Abstract A1622, 43rd ICAAC 2003, Chicago.
24. Hendrix C, Wakeford J, Wire MB, et al. Pharmacokinetic and pharmacodynamic evaluation of methadone enantiomers following coadministration with amprenavir in opioid-dependent subjects. Abstract 1649, 40th ICAAC 2000, Toronto.
25. Centers for Disease Control and Prevention (CDC). Notice to Readers: Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors 2004. *MMWR*; 53: 37. <http://www.amedeo.com/lit.php?id=11795500>
26. Nandwani R, Gourlay Y. Possible Interaction between sildenafil and HIV combination therapy. *Lancet* 1999; 353: 840. <http://www.amedeo.com/lit.php?id=10459981>
27. Hugen PWH, Burger DM, Brinkman K, et al. Carbamazepine-indinavir interaction causes antiretroviral therapy failure. *Ann Pharmacother* 2000; 34: 465-70. <http://www.amedeo.com/lit.php?id=10772431>
28. Pratt CM, Mason J, Russell T. Cardiovascular safety of fexofenadine HCL. *Am J Cardiol* 1999; 84: 278-9. <http://www.amedeo.com/lit.php?id=10335761>
29. Abernethy DR, Barbey JT. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QT-prolongation. *Clin Pharmacol Ther* 2001; 69: 96-103. <http://www.amedeo.com/lit.php?id=11240972>
30. Kurowski M, Walli R, Breske et al. Co-administration of tenofovir 300 mg QD with fosamprenavir/ritonavir 1400/100 mg QD or 1400/200 mg QD does not affect amprenavir pharmacokinetics. Abstract 10, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
31. Peytavin G, Rouault A, Agher R, et al. Plasma concentrations of amprenavir, ritonavir and tenofovir in HIV-infected patients treated with fosamprenavir / ritonavir (700 / 100 mg BID) and tenofovir (300 mg QD) containing regimen. Abstract 32, 6th Int. Worksh Clin Pharmacol HIV Ther 2005, Quebec.
32. Shelton MJ, Wire MB, Lou Y, et al. Co-administration of esomeprazole (ESO) with fosamprenavir (FPV) has no impact on steady-state plasma amprenavir (APV) pharmacokinetics (APV10031). Abstract 24, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.

33. Blenke A, van der Lee M, Verweij-van Wissen C, et al. Combined use of paroxetine and fosamprenavir / ritonavir: a pharmacokinetic interaction study in healthy volunteers. Abstract 13, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
34. Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir alone or in combination with saquinavir, amprenavir, or lopinavir: interim analysis of B1182.51. Abstract 34, 5th Int Worksh Clin Pharmacol HIV-Ther 2004, Rome.

## Indinavir (IDV, Crixivan™)

Approved dose: IDV: 800 mg TID, IDV/r: 800/100 mg BID. Metabolism: IDV is primarily metabolized by CYP3A4 and is an inhibitor of CYP3A4. For optimal adsorption an acidic gut pH is necessary. IDV should be taken with a light meal [1].

Drugs	Interactions	Comments
<b>NRTIs</b>		
ddI [2-4]	ddI EC + IDV: no interaction [4]	Take ddI 1 h apart [2,3].
<b>NNRTIs</b>		
EFV [2,5-7]	IDV/r 800/100 BID + EFV 600 QD: IDV ↓ 19 % ( $C_{\min}$ 48 % ↓) [6]	IDV/r 800/100, probably higher doses for pre-treated patients are necessary [6]. No QD-IDV [7].
NVP [2,5,8-9]	IDV/r 800/100 BID + NVP: IDV: $C_{\min}$ 57 % RTV: $C_{\min}$ 59 % but IDV > 100 ng/ml [8]	1. IDV: 1000 TID [2] 2. IDV/r: 800/100 BID [8] Consider higher doses in pre-treated patients [8]. NVP QD may decrease IDV/r more than NVP BID [9].
<b>PIs</b>		
ATV [10]	increased bilirubin levels	<b>Avoid combination.</b>
APV [11]	IDV 800 + APV 800 TID APV ↑ 33 %, IDV ↓ 38 % ( $C_{\min}$ 27 % ↓)	In this study, no dose adjustment was necessary.
LPV/r [16-21]	IDV 800 BID + LPV/r 400/100 BID: PK-value of LPV insignificantly lower [16]	TDM of both drugs.
NFV [12]	IDV 1200 + NFV 1250 BID	In this study, no dose adjustment was necessary.
<b>Antiarrhythmics</b>		
Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone	Theoretically: antiarrhythmics ↑	<b>Avoid combination.</b> If necessary, reduce dose of antiarrhythmic drugs.
<b>Antidepressants</b>		
St. John's Wort [2]	Theoretically: IDV ↓	<b>Avoid combination.</b>
Trazodone [5]	Theoretically: trazodone ↑	Avoid combination or possibly reduce trazodone dose.
<b>Antiepileptics</b>		
Carbamazepine, Phenytoin, primidone [2,23]	Theoretically: IDV ↓, antiepileptics ↑	Theoretical alternative: gabapentin, lamotrigine, valproic acid.

Drugs	Interactions	Comments
<b>Antifungal drugs</b>		
Itraconazol, ketocozazole, voriconazole [5,26]	Theoretically: IDV and azole ↑ IDV 400 + Ketoconazole 400: IDV ↑ 68 % [5]	IDV: 600 TID [5]. Theoretical alternative: fluconazole [26].
<b>Antihistamines</b>		
Astemizole, loratadine (> 20 mg), terfenadine [2,24,25]	Theoretically: antihistamines and risk of QT-prolongation ↑	<b>Avoid combination:</b> terfenadine [2]. Theoretical alternative: cetirizine, fexofenadine [24,25].
<b>Antihypertensives</b>		
Calcium channel blockers such as felodipine, nifedipine, verapamil	Theoretically: calcium channel blockers ↑ [2]	Reduce dose of calcium channel blockers if necessary.
Bosentan [5,32]	Theoretically: IDV ↓ [5]	<b>Avoid combination</b> or TDM. Off label use: sildenafil [32].
<b>Antipsychotics</b>		
Several drugs [2]	Theoretically: IDV and antipsychotic drugs ↑	<b>Avoid combination</b> with pimoziide. Monitor for side-effects. Prefer: atypical neuroleptics (less anticholinergic).
<b>Antituberculosis drugs</b>		
Rifabutin [2,3,30]	Rifabutin ↑ 173 % IDV ↓ 33 % [30]	IDV: 1000 TID +Rifabutin: 150 mg/d [2]. IDV/r: 800/100 BID + Rifabutin: 150 mg 3x/week.
Rifampicin [2]	IDV ↓ 89 %	<b>Avoid combination</b> [2].
<b>Gastritis-/ Ulcer healing drugs</b>		
Antacids [2]	IDV requires acidic pH for adequate absorption, possible: IDV ↓	Antacids 1h apart from IDV.
H2-blockers	Theoretically: IDV ↓	TDM of IDV.
Proton pump inhibitors (PPIs), e.g. omeprazole [5,22]		TDM of IDV.
<b>Hypnotics</b>		
Barbexaclone, phenobarbital	Theoretically: IDV ↓	<b>Avoid combination</b> or TDM.
Benzodiazepines, zolpidem [2,5]	Prolonged sedation	<b>Avoid combination:</b> Alpra-, mida-, triazolam [2]. <b>Caution:</b> clorazepate, diazepam, flurazepam [5]. Th. alternative: lorazepam, oxazepam, temazepam [5].

Drugs	Interactions	Comments
<b>Immunosuppressants</b>		
Cyclosporine, siroli - mus, tacrolimus [27]	Theoretically: immunosuppressants ↑	Dose adjustment of immunosuppressants by TDM.
<b>Lipid-lowering drugs</b>		
Atorvastatin, lovastatin, simvastatin [2,5]	Theoretically: Atorvastatin, lovastatin ↑	<b>Avoid combination:</b> simva-, lova-[2], atorvastatin [5]. Theoretical alternative: pravastatin [5], fluvastatin.
<b>Oral contraceptives</b> [5]	Estradiol ↑ 24 % Norethindrone ↑ 26 %	No dose adjustment necessary.
<b>PDE5 inhibitors (PPHs)</b>		
Sildenafil, tadalafil, vardenafil [5,31]	Theoretically: PPHs ↑ IDV 800 TID + Sildenafil 25: Sildenafil ↑ 304 % [31] IDV + Vardenafil: Vardenafil ↑ 16-fold IDV ↓ 30 % (Cmax 40 % ↓) [5]	Sildenafil: 12.5 mg every 48h [5].  Avoid combination or TDM.
<b>Others</b>		
Dexamethasone [2]	Theoretically: IDV ↓	TDM of IDV.
Ergotamine [2]	Theoretically: IDV ↑	<b>Avoid combination.</b>
Grapefruit juice [1]	AUC of IDV: 26 % ↓	<b>Avoid combination</b> [1].
Interleukin [5,28]	IL-2 + IDV: IDV ↑ 88 %	TDM of IDV.
L-Tyroxin [5,29]	Thyroxin ↑ because IDV inhibits UDP-GT [29]	Perhaps l-tyroxin dose could be reduced.
Vitamine C [32]	IDV 800 TID + 1 g vitamine C: Cmin IDV 32 % ↓ (not significant)	Avoid high doses of vitamine C.

## References

1. Tseng A. <http://www.tthhivclinic.com/>, General Hospital, Toronto, 2004.
2. Crixivan™, MSD.
3. Shelton MJ, Mei JH, Hewitt RG, et al. If taken 1 hour before indinavir, didanosine does not affect indinavir exposure, despite persistent buffering effects. *Antimicrob Agents Chemother* 2001; 45: 298-300. <http://www.amedeo.com/lit.php?id=11120981>
4. Damle BD, Mummaneni V, Kaul S, et al. Lack of effect of simultaneously administered didanosine encapsulated enteric coated formulation (Videx EC) on oral absorption of indinavir, ketoconazol or ciprofloxacin. *Antimicrob Agents Chemother* 2002; 46: 385-91. <http://www.amedeo.com/lit.php?id=11796346>
5. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
6. Aarnoutse RE, Burger DM, Hugen PWH, et al. A Pharmacokinetic Study to investigate the influence of efavirenz on a BID indinavir 800 mg/ritonavir 100 mg in healthy volunteers. Abstract 423, 40th ICAAC 2000, Toronto.
7. Saah A, Winchell G, Rhodes R, et al. Multiple-dose pharmacokinetics and tolerability of indinavir with ritonavir and efavirenz combinations in a once daily regimen in healthy volunteers (Merck 093). Abstract 284, 5th Int Congr Drug Ther HIV Inf 2000, Glasgow. <http://www.aegis.com/conferences/hiv5/P284.html>
8. Burger DM, Prins JM, van der Ende ME, et al. The effect of nevirapine on the pharmacokinetics of indinavir/ritonavir 800/100 mg BID. *JAIDS* 2004; 35: 97-8. <http://www.amedeo.com/lit.php?id=14707800>

## 790 Interactions

9. Crommentuyn KML, van Heeswijk RPG, Veldkamp AI, et al. Nevirapine once daily versus twice daily: implications for drug-drug interactions. Abstract 1.11, 2nd Int Worksh Clin Pharmacol HIV Ther 2001, Noordwijk.
10. Reyataz™, Bristol Myers-Squibb.
11. Sadler BM, Gillotin C, Lou Y, et al. Pharmacokinetic study of human immunodeficiency virus protease inhibitors used in combination with amprenavir. *Antimicrob Agents Chemother* 2001; 45: 3663-8. <http://www.amedeo.com/lit.php?id=11709366>
12. Riddler S, Havlir D, Squires KE, et al. Coadministration of indinavir and nelfinavir in human immunodeficiency virus type 1-infected adults: safety, pharmacokinetics and antiretroviral activity. *Antimicrob Agent Chemother* 2002; 46: 3877-82. <http://www.amedeo.com/lit.php?id=12435691>
13. Mc Crea J, Buss N, Stone J, et al. Indinavir-saquinavir single dose pharmacokinetic study. 4th CROI 1997, Washington.
14. Manion D, Merrill DP, Hirsch MS. Combination drug regimens against multidrug resistant HIV-1 in vitro. 4th CROI 1997, Washington.
15. Buss N. Saquinavir soft gel capsule (Fortovase): Pharmacokinetics and drug interactions. Abstract 354, 5th CROI 1998, Chicago.
16. Tseng A, Phillips E, Antoniou A, et al. Steady-state pharmacokinetics and tolerability of indinavir when administered with lopinavir/r in antiretroviral-experienced subjects. Abstract 8.10, 4th Int Worksh Clin Pharmacol HIV Ther 2003, Cannes.
17. Bertz R, Foit C, Ashbrenner E, et al. Assessment of the steady-state pharmacokinetic interaction of lopinavir/ritonavir with either indinavir or saquinavir in healthy subjects. Abstract A1822, 42nd ICAAC 2002, San Diego.
18. Burger DM, Schmitz K, Schneider K, et al. Pharmacokinetics of lopinavir and reduced dose indinavir as a part of salvage therapy regimen. 4th Abstract 8.2, 4th Int Worksh Clin Pharmacol HIV Ther 2003, Cannes.
19. Harris M, Alexander C, Ting L, et al. Rescue therapy with indinavir 600 mg twice daily and lopinavir/ritonavir: baseline resistance, virologic response and pharmacokinetics. Abstract P170, 6th Int Congr Drug Ther HIV Inf 2002, Glasgow.
20. Isaac A, Taylor S, Rubin G, et al. Lopinavir /ritonavir combined with twice daily indinavir: pharmacokinetics in blood, CSF and semen (the Protect Study). Abstract 531, 10th CROI 2003, Boston.
21. DHHS: Guidelines for the use of antiretroviral agents in HIV-infected adults and adolescents. Retrieved April 14, 2004. <http://www.amedeo.com/lit.php?id=11364535>
22. Burger DM, Hugen PW, Kroon FP, et al. Pharmacokinetic interaction between the proton pump inhibitor omeprazole and the HIV protease inhibitor indinavir. *AIDS* 1998; 12: 2080-2. <http://www.amedeo.com/lit.php?id=9814882>
23. Hugen PWH, Burger DM, Brinkmann K, et al. Carbamazepine-indinavir interaction causes antiretroviral failure. *Ann Pharmacother* 2000; 34: 465-70. <http://www.amedeo.com/lit.php?id=10772431>
24. Pratt CM, Mason J, Russell T. Cardiovascular safety of fexofenadine HCL. *Am J Cardiol* 1999; 84: 278-9. <http://www.amedeo.com/lit.php?id=10335761>
25. Abernethy DR, Barbey JT. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QT-prolongation. *Clin Pharmacol Ther* 2001; 69: 96-103. <http://www.amedeo.com/lit.php?id=11240972>
26. Michalets E: Update: Clinically Significant Cytochrome P-450 Drug Interaction. *Ann Pharmacother* 1998; 18: 84-112. <http://www.amedeo.com/lit.php?id=9469685>
27. Brinkmann K, Huysmans F, Burger DM. Pharmacokinetic interaction between Saquinavir and Cyclosporine. *Ann Intern Med* 1998; 129: 914-5. <http://www.amedeo.com/lit.php?id=9867740>
28. Piscitelli SC, Vogel S, Figg WD, et al. Alteration in indinavir clearance during interleukin-2 infusions in patients infected with the human immunodeficiency virus. *Ann Pharmacother* 1998; 18: 1212-6. <http://www.amedeo.com/lit.php?id=9855318>
29. Lanzafame M, Trevenzoli M, Faggian F, et al. Interaction between levothyroxine and indinavir in a patient with HIV infection. *Infection* 2002; 30: 54-8. <http://www.amedeo.com/lit.php?id=11876520>
30. Centers for Disease Control and Prevention (CDC). Notice to Readers: Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR*; 2004; 53: 37. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4909a4.htm>
31. Merry C, Barry MG, Ryan M, et al. Interaction of sildanafinil and indinavir when coadministered to HIV-positive patients. *AIDS* 1999; 13: 101-7. <http://www.amedeo.com/lit.php?id=10546851>
32. Slain D, Amsden JR, Khakoo RA, et al. Effect of high-dose vitamin C on the steady-state pharmacokinetics of the protease inhibitor indinavir in healthy volunteers. Abstract A-1610, 43rd ICAAC 2003, Chicago.

**Lopinavir/r (LPV/r, Kaletra™)**

Approved dose: LPV/r 400/100 mg BID. Metabolism: LPV is co-formulated with ritonavir and primarily metabolized by CYP3A4. LPV/r is a strong inhibitor of CYP3A4 and induces the glucuronidation pathway as well as CYP2C9 and CYP2C19 [1].

<b>Drugs</b>	<b>Interactions</b>	<b>Comments</b>
<b>NRTIs</b>		
TDF [41,42]	TDF ↑ 32 % ( $C_{\max}$ 15 % ↑), LPV/r: Adequate plasma levels 18 heavily pre-treated patients: $C_{\min}$ LPV 34 % ↓, $C_{\min}$ RTV 44 % ↓ [41]	no increase in side-effects observed.  LPV/r: TDM.
<b>NNRTIs</b>		
EFV [2,3,50]	Capsules: EFV 600 QD + LPV/r [3]: LPV ↓ 25 % ( $C_{\min}$ 44 % ↓)  Tablets: EFV 600 QD + LPV/r 600/150 BID: LPV ↑ 35 %, RTV ↑ 56-92 % [50]	Capsules: LPV/r: 533/133 BID [2].  Tablets: LPV/r 400/100 BID: may be used in naïve pts => TDM. LPV/r 600/150 BID: recom- mended in pre-treated pts [1].
NVP [2,4,45]	NVP 200 BID + LPV/r: 1. Extensively pre-treated patients [4]: LPV/r ↓ 27 % ( $C_{\min}$ 51 % ↓) 2. 31 patients with VL < 80 c/ml: adequate levels of both drugs [45]	Clinical experiences: LPV/r: 533/133 BID [2].
<b>PIs</b>		
ATV [14,46,51]	ATV400 QD + LPV/r 400/100 BID: 1. LPV ↓ 16 % ( $C_{\min}$ 35 % ↓) [14] 2. ATV ( $C_{\min}$ 45 % ↑) [51] 3. ATV ↓ 38 % ( $C_{\min}$ 38 % ↓) [46]	Controversial data. => TDM  1. HIV-patients. 2. Healthy volunteers. 3. HIV-patients.
FPV/r [5-8] APV/r [9-13]	1. FPV/r 700/100 BID + LPV/r: APV ↓ 63 % ( $C_{\min}$ 65 % ↓), LPV ↓ 37 % ( $C_{\min}$ 52 % ↓) [6] 2. FPV/r 700/100 + LPV/r 533/133 BID [7]: APV ↓ 26 % ( $C_{\min}$ 42 % ↓), LPV: adequate plasma levels 3. Dose separation corrects LPV concentration, but not APV plasma concentrations [8]	<b>Unfavourable combination,</b> wide variability of concen- trations => TDM.  Tablets: LPV/r 400/100 BID in naïve, LPV/r 600/150 BID in pre- treated patients [1]. TDM.
IDV/r [15-19]	IDV 800 BID + LPV/r	TDM.

Drugs	Interactions	Comments
NFV [24]	NFV 1000 BID + LPV/r: LPV/r ↓ 27 % ( $C_{\min}$ 33 % ↓)	TDM. Tablets: LPV/r 400/100 BID in naïve, LPV/r 600/150 BID in pre- treated patients [1]. TDM.
SQV/r [20-23]	SQV 1000 BID + LPV/r: adequate SQV- and LPV-levels	Synergic effect, favourable combination: TDM.
TPV/r [49]	TPV 500 BID + LPV/r: LPV ↓ 55 % ( $C_{\min}$ ↓ 52-70 %)	<b>Avoid combination.</b>
TMC/r [52]	TMC/r 300/100 BID + LPV/r: TMC ↓ 53 %, LPV/r ↑	<b>Avoid combination.</b>
<b>Antiarrhythmics</b>		
Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone	Theoretically: antiarrhythmics ↑	<b>Avoid combination:</b> amioda- rone [2]. Monitor for side- effects, dose reduction.
<b>Antibiotics</b>		
Clarithromycin [25-27]	Clarithromycin ↑ Dose reduction with patients of liver and renal failure [25]	Dose reduction in liver and renal failure. Alternative: Azithromycin [26,27].
<b>Anticoagulants</b>		
Warfarin [25]	Warfarin ↓	Monitor for INR.
<b>Antidepressants</b>		
Nefazodone [28]	Theoretically: LPV/r ↑	Monitor for side-effects. Th. alternative: SSRIs.
St. John's Wort [2]	Theoretically: LPV/r ↓	<b>Avoid combination.</b>
<b>Antiepileptics</b>		
Carbamazepine, phenytoin, primidone, [2,25,40]	Theoretically: LPV/r ↓ antiepileptics ↑	Theoretical alternative: gabapentin.
Lamotrigine [47]	Lamotrigine 100 QD + LPV/r 400/100 BID: lamotrigine $C_{\min}$ : 56 % ↓	Dose adjustment of 200 % for lamotrigine, not for LPV/r.
<b>Antifungal drugs</b>		
Itra-, keto-, vori- conazole [1,2,25]	LPV/r and azole ↑ Caution: possible dose-related toxicity of both drugs.	<b>Avoid combination:</b> Itra-, ketoconazole. Th. alter- native: fluconazole [1].
<b>Antihistamines</b>		
Astemizole, loratadine (> 20 mg), terfenadine [2,29,30]	Theoretically: antihistamines ↑ and increased risk of QT-prolongation	<b>Avoid combination:</b> terfen- adine. Th. alternative: ceti- rizine, fexofenadine [29,30].



Drugs	Interactions	Comments
<b>Antihypertensives</b>		
Calcium channel blockers [2,31] such as Amlodipine, nifedipine, verapamil	Theoretically: calcium channel blockers ↑	Theoretically dose reduction of calcium channel blockers.
Bosentan [25,39]	Theoretically: LPV/r ↓	<b>Avoid combination</b> or TDM.
<b>Antipsychotics</b>		
Several drugs[25,28]	Theoretically: LPV/r and antipsychotic drugs ↑	<b>Avoid combination</b> with pimozide. Monitor for side-effects. Prefer: atypical neuroleptics (less anticholinergic).
<b>Antituberculosis drugs</b>		
Rifabutin [2,37]	Rifabutin: 303 % ↑, rifabutin-metabolite ↑ 47.5-fold, no effect of LPV/r	Rifabutin: 150 mg 3x/week. Monitor for side-effects.
Rifampicin [2,37]	LPV/r + rifampicin 600/QD: LPV/r ↓ 75 % (Cmin 99 % ↓)	<b>Avoid combination.</b>
<b>Cytotoxic drugs</b>		
Docetaxel, etoposide, paclitaxel, tamoxifen, vinca alkaloids [38]	Theoretically: cytotoxic drugs ↑	Monitor for side-effects of the cytotoxic drugs.
<b>Gastritis-/ Ulcer healing drugs</b>		
Antacids, H2-blockers, proton pump inhibitors (PPIs) [44]	No significant interactions after 48 week therapy	
<b>Hypnotics</b>		
Barbexaclone, Phenobarbital	Theoretically: LPV ↓	<b>Avoid combination</b> or TDM.
Benzodiazepines, zolpidem [25]	Theoretically: Benzodiazepines ↑ Prolonged sedation	<b>Avoid combination:</b> midazolam, triazolam. Theoretical alternative: lorazepam, oxazepam, temazepam.
<b>Immunosuppressants</b>		
Cyclosporine, sirolimus tacrolimus [2,25,43,48]	Theoretically: immunosuppressants ↑ Tacrolimus + LPV/r: (3 patients) Tacrolimus 10-20-fold ↑ [43]	Dose adjustment of immunosuppressants with TDM.
<b>Lipid-lowering drugs</b>		
Ator-, Lo-, Simvastatin [32-35]	Atorvastatin, pravastatin + LPV/r: Atorvastatin ↑ 5.9-fold Pravastatin ↑ 30 %	Low initial dose: atorvastatin. Alternatives: pravastatin, fluvastatin.
<b>Oral contraceptives</b> [2,25]		
	Ethinylestradiol ↓ 42 % Norethindrone ↓ 17 %	Use additional contraceptive method.

Drugs	Interactions	Comments
<b>PDE5 inhibitors (PPHs)</b>		
Sildenafil, tadalafil, vardenafil [2,25]	Theoretically: PPHs ↑ Sildenafil 100 QD + RTV 500 BID: sildenafil ↑ 1000 %	Sildenafil 25 mg every 48h.
<b>Substitution</b>		
Methadone [36]	Methadone ↓ 36 % (Cmax 44 % ↓)	Monitor for opiate withdrawal; if necessary, increase methadone dose.
<b>Others</b>		
Atovaquone	Theoretically: atovaquone ↓	If necessary, increase dose.
Disulfiram [2]	Kaletra liquid contains alcohol.	<b>Avoid combination.</b>
Dexamethasone [2]	Theoretically: LPV/r ↓	
Metronidazole [2]	Kaletra liquid contains alcohol and can cause sickness when combined with metronidazole	<b>Avoid combination.</b>
Theophylline [2]	Theoretically: theophylline ↓	TDM of theophylline.

## References

1. Tseng A. www.tthivclinic.com, General Hospital, Toronto, 2006
2. Kaletra™, Abbott.
3. Bertz R, Lam W, Hsu A, et al. Assessment of the pharmacokinetic interaction between ABT-378/ritonavir and efavirenz in healthy volunteers and in HIV + subjects. Abstract 424, 40th ICAAC 2000, Toronto.
4. Bertz R, Foit C, Burt D, et al. Assessment of the Effect of Nevirapine on the Pharmacokinetics of Lopinavir/Ritonavir after Multiple Dosing in HIV-infected Adults. Abstract TUPEB4565, XIV Int AIDS Conf 2002, Barcelona.
5. Telzir™, GlaxoSmithKline.
6. Kashuba ADM, Tierney C, Downey GF, et al. Combining fosamprenavir, 908 with lopinavir/Ritonavir in HIV-1 infected adults in substantial reduction in Amprenavir and lopinavir concentrations: pharmacokinetic results from Adult ACTG Protocol A5143. Abstract H-855a, 43rd ICAAC 2003, Chicago.
7. Wire MB, Naderer OJ, Masterman AL, et al. The pharmacokinetic interaction between GW433908 and lopinavir/ritonavir (APV10011 and APV 10012). Abstract 612, 11th CROI 2004, San Francisco. <http://www.retroconference.org/2004/cd/PDFs/612.pdf>
8. Corbett AH, Davidson L, Park JJ, et al. Dose separation strategies to overcome the pharmacokinetic interaction of a triple protease inhibitor regimen containing fosamprenavir, lopinavir and ritonavir. Abstract 611, 11th CROI 2004, San Francisco.
9. Khanlou H, Graham E, Brill M, et al. Drug interaction between amprenavir and lopinavir/ritonavir in salvage therapy. AIDS 2002; 16: 797-8. <http://www.amedeo.com/lit.php?id=11964539>
10. Bertz RJ, Foit C, Ashbrenner E, et al. Effect of amprenavir on the steady-state pharmacokinetics of lopinavir/ritonavir in HIV+ and healthy subjects. Abstract A1823, 42nd ICAAC 2002, San Diego.
11. Taburet AM, Raguin G, Le Tiec C, et al. Interaction between Amprenavir and lopinavir – ritonavir combination in heavily pretreated patients infected by HIV. Clin Pharmacol Ther 2004; 75: 310-23. <http://www.amedeo.com/lit.php?id=15060509>
12. Mauss S, Scholten S, Wolf E, et al. A prospective, controlled study assessing the effect of lopinavir on amprenavir concentrations boosted by ritonavir. HIV Med 2004; 5: 15-7. <http://www.amedeo.com/lit.php?id=14731164>
13. Wynn Vezina HE, Brundage RC, Bushman L, et al. Pharmacologic management of the drug-drug interaction between lopinavir/ritonavir and amprenavir. Abstract 609, 11th CROI 2004, San Francisco.
14. Colombo S, Buclin T, Franc C. Ritonavir-boosted atazanavir-lopinavir combination: a pharmacokinetic interaction study of total, unbound plasma and cellular exposures. Antivir Ther. 2006;11:53-62.

15. Tseng A, Phillips E, Antoniou A, et al. Steady-state pharmacokinetics and tolerability of indinavir when administered with lopinavir/r in antiretroviral-experienced subjects. Abstract 8.10, 4th Int Worksh Clin Pharmacol HIV Ther 2003, Cannes.
16. Bertz R, Foit C, Ashbrenner E, et al. Assessment of the steady-state pharmacokinetic interaction of lopinavir/ritonavir with either indinavir or saquinavir in healthy subjects. Abstract A1822, 42nd ICAAC 2002, San Diego.
17. Burger DM, Schmitz K, Schneider K, et al. Pharmacokinetics of lopinavir and reduced dose indinavir as a part of salvage therapy regimen. Abstract 8.2, 4th Int Worksh Clin Pharmacol HIV Ther 2003, Cannes.
18. Burger DM, Schmitz K, Schneider K, et al. Rescue therapy with indinavir 600 mg twice daily and lopinavir/ritonavir: baseline resistance, virologic response and pharmacokinetics. Abstract P170, 6th Int Congr Drug Ther HIV Inf 2002, Glasgow.
19. Isaac A, Taylor S, Rubin G, et al. Lopinavir /ritonavir combined with twice daily indinavir: pharmacokinetics in blood, CSF and semen (the Protect Study). Abstract 531, 10th CROI 2003, Boston.
20. La Porte CJ, Wasmuth JC, Schneider K, et al. Lopinavir/ritonavir plus saquinavir in salvage therapy; pharmacokinetics, tolerability and efficacy. AIDS 2003; 17: 1700-2.  
<http://www.amedeo.com/lit.php?id=12853756>
21. Ribera E, Diaz M, Pou L, et al. Steady-state pharmacokinetics of double boosting regimen of lopinavir, plus minidose Ritonavir, plus Saquinavir soft-gel in HIV-infected adults. Abstract TUPE4545, XIV Int AIDS Conf 2002, Barcelona.
22. Staszewski S, Dauer B, Von Hentig N, et al. The LopSaq study: 24 week analysis of the double protease inhibitor salvage regimen containing lopinavir plus saquinavir without any additional antiretroviral therapy. Abstract 583, 2nd IAS Conference on HIV Pathogenesis and Treatment 2003, Paris.
23. Stefan C, Von Hentig N, Kourbeti I, et al. Saquinavir drug exposure is not impaired by the boosted double protease inhibitor combination of lopinavir/Saquinavir. AIDS 2004; 18: 503-8.  
<http://www.amedeo.com/lit.php?id=15090803>
24. Klein C, Bertz R, Ashbrenner E, et al. Assessment of the multiple dose pharmacokinetic interaction of lopinavir/ritonavir with nelfinavir. Abstract 536, 10th CROI 2003, Boston.
25. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
26. Michalets E. Update: Clinically Significant Cytochrome P-450 Drug Interaction. Ann Pharmacother 1998; 18: 84-112. <http://www.amedeo.com/lit.php?id=9469685>
27. Benedek ICH, Joshi A, Fiske WD, et al. Pharmacokinetic studies in healthy volunteers with efavirenz and the macrolide antibiotics, azithromycin and clarithromycin. Abstract 347, 5th CROI 1998, Chicago.
28. Tseng AL, Foisy MM. Significant Interactions with New Antiretrovirals and Psychotropic Drugs. Ann Pharmacother 1999; 33: 461-73. <http://www.amedeo.com/lit.php?id=10332538>
29. Pratt CM, Mason J, Russell T. Cardiovascular safety of fexofenadine HCL. Am J Cardiol 1999; 84: 278-9. <http://www.amedeo.com/lit.php?id=10335761>
30. Abernethy DR, Barbey JT. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QT-prolongation. Clin Pharmacol Ther 2001; 69: 96-103.  
<http://www.amedeo.com/lit.php?id=11240972>
31. Rossi DR, Rathbun C, Slater LD. Symptomatic orthostasis with extended-release nifedipine and protease inhibitors. Ann Pharmacother 2002; 22: 1312-6. <http://www.amedeo.com/lit.php?id=12389881>
32. Fichtenbaum CJ, Gerber JG, Rosenkranz S. Pharmacokinetic interaction between protease inhibitors and statins in HIV seronegative volunteers: ACTG Study A5047. AIDS 2002; 16: 569-77.  
<http://www.amedeo.com/lit.php?id=11873000>
33. Carr RA, Andre AK, Bertz RJ, et al. Concomitant administration of ABT-378/ritonavir results in a clinically important pharmacokinetic interaction with atorvastatin but not pravastatin. Abstract 1644, 40th ICAAC 2000, Toronto.
34. Doser N, Kubli S, Telenti A et al. Efficacy and safety of fluvastatin in hyperlipidemic protease inhibitor-treated HIV-infected patients. AIDS 2002; 16: 1982-3. <http://www.amedeo.com/lit.php?id=12351967>
35. Dube MP, Sprecher D, Henry WK, et al. Preliminary guidelines for the evaluation and management of dyslipidemia in HIV-infected adults receiving antiretroviral therapy. Recommendations of the adult ACTG Cardiovascular Disease Focus Group. Clin Infect Dis 2000; 31: 1216-24.  
<http://www.amedeo.com/lit.php?id=11073755>
36. Antoniou T, Lin-in Tseng. Interactions between recreational drugs and antiretroviral agents. Annals Pharmacother 2002; 36: 1598-613. <http://www.amedeo.com/lit.php?id=12243611>
37. Centers for Disease Control and Prevention (CDC). Notice to Readers: Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. MMWR; 2004; 53: 37.  
<http://www.amedeo.com/lit.php?id=11795500>

38. Lam M, Ignoffo R, Meibohm B: Ein Leitfaden für klinisch-relevante Arzneimittel-Interaktionen in der Onkologie, Institute for Applied Healthcare Science.
39. Ghofrani HA, Olschewski H, Seeger W et al. Sildenafil for treatment of severe pulmonary hypertension and commencing right-heart failure. *Pneumologie*. 2002; 56: 665-72. <http://www.amedeo.com/lit.php?id=12442206>
40. DiCenzo R, Petersen D, Cruttenden K, et al. Effect of Valproic Acid Coadministration on Plasma Efavirenz and Lopinavir Concentrations in Human Immunodeficiency Virus-Infected Adults. *Antimicrobial Agents and Chemotherapy* 2004; 48: 4328-31. <http://www.amedeo.com/lit.php?id=15504860>
41. Breilh D, Rouzes A, Djabarouti S et al. Pharmacokinetic drug interaction of lopinavir/ritonavir in combination with tenofovir in experienced HIV+patients. Abstract A-445, 44th ICAAC 2004, Washington.
42. Kearney BP, Mittan A, Sayre J, et al. Pharmacokinetic drug interaction and long term safety profile of tenofovir DF and lopinavir/ritonavir. Abstract A-1617, 43rd ICAAC 2003, Chicago. [http://www.natap.org/2003/ICAAC/day5\\_2.htm](http://www.natap.org/2003/ICAAC/day5_2.htm)
43. Jain AB, Venkataramanan R, Eghtesad B, et al. Effect of coadministered lopinavir and ritonavir (Kaletra) on tacrolimus blood concentration in liver transplantation patients. *Liver Transpl* 2003, 9:954-60. <http://amedeo.com/lit.php?id=12942457>
44. Bertz RJ, Chiu YL, Naylor C et al. Lack of Effect of gastric acid reducing agents on lopinavir/ritonavir plasma concentrations in HIV-infected patients. Abstract 201, 7th Int Congr Drug Ther HIV Inf 2004, Glasgow.
45. Negrodo E, Moltó J, Burger D et al. Lopinavir/ritonavir plus nevirapine as a nucleoside-sparing approach in antiretroviral-experienced patients (NEKA study). *JAIDS* 2005; 38: 47-52. <http://www.amedeo.com/lit.php?id=15608524>
46. Vezina HE, Tschampa JM, Jennings C et al. Steady-state pharmacokinetic of lopinavir/ritonavir co-administered with atazanavir in HIV-infected subjects. Abstract 48. 7th Int Worksh Clin Pharmacol HIV Ther 2005, Lissabon.
47. Van der Lee MJ, Dawood L, ter Hofstede H, et al. The effect of lopinavir / ritonavir on the pharmacokinetic of lamotrigine in healthy subjects. Abstract 12, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
48. Faivre L, T. H., Vincent I, Abbara C, et al (2005). Potent drug interactions between tacrolimus and lopinavir / ritonavir therapy in HIV-infected liver transplant recipients. Abstract 26, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
49. Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir alone or in combination with saquinavir, amprenavir, or lopinavir: interim analysis of B1182.51. Abstract 34 , 5th Int Worksh Clin Pharmacol HIV-Ther 2004, Rome.
50. Klein C, ZHU T, Chiu YL et al. Effect of efavirenz on lopinavir/ritonavir pharmacokinetics from a new tablet formulation. Abstract 4.3/2, 10th EACS 2005, Dublin.
51. Pham P, Parson T, Flexner C et al. Beneficial Pharmacokinetic Interaction between Atazanavir and Lopinavir/r. Abstract 585.13th CROI 2006, Denver.
52. US product information on Prezista®.

## Nelfinavir (NFV, Viracept™)

Approved dose: 1250 mg BID. Metabolism: nelfinavir (NFV) is primarily metabolized by CYP2C19 more than CYP3A4 and CYP2D6. NFV is an inhibitor of CYP3A4. It is metabolized to an active metabolite M8 (approx. 30 % of parent compound), with equal potency to NLF. M8 is metabolized by CYP3A4 [1,2].

Drugs	Interactions	Comments
<b>NRTIs</b>		
ddI [1,2] TDF [3]	ddI: fasting, NFV: with a light meal No clinically significant interaction	Take ddI 2h apart.
<b>NNRTIs</b>		
EFV [2,4,5]	NFV 750 TID + EFV 600 QD: NFV ↑ 20 %, M8 ↓ 40 % NFV 1250 BID + EFV 600 QD: NFV ↓ 38 % (C <sub>min</sub> 65 % ↓)	No clinically significant interaction, possibly monitor for NLF by TDM.
NVP [6]	NFV 750 TID + NVP 200 BID	no dose adjustment.
<b>PIs</b>		
ATV [8,28]	NFV 1250 BID + ATV 400 QD: C <sub>min</sub> NFV: 57,4 % ↑, M8: 124 % ↑, No effect on AUC, C <sub>max</sub> , T <sub>max</sub>	
APV [9]	NFV 750 + APV 800 TID: APV: (C <sub>min</sub> 2.9-fold ↑), NFV ↑ 15 %	TDM.
IDV [10]	NFV 1250 + IDV 1200 BID	no dose adjustment.
LPV/r [1,7]	NFV 1000 + LPV/r 400/100 BID: LPV/r ↓ 27 % (C <sub>min</sub> 33 % ↓)	Tablets: LPV/r 400/100 BID in ART-naïve patients, LPV/r 600/150 BID in pre-treated patients [1]. TDM.
SQV [11-13,14]	NFV 1250 + SQV/r 1000/100 BID M8 ↑ 2.7-fold	no dose adjustment.
TPV/r	No data	<b>Avoid combination.</b>
TMC/r	No data.	<b>Avoid combination.</b>
<b>Antiarrhythmics</b>		
Amiodarone, bepridil, flecainide, lidocaine, propafenone [2]	Theoretically: antiarrhythmic drugs ↑	<b>Avoid combination</b> or monitor for toxic effects.
<b>Antibiotics</b>		
Azi-, Clari-, Ery-thromycin [1,15]	NFV 750 TID + azithromycin 1200 QD: NFV ↓ 28 %, M8 ↓ 23 % Azithromycin ↑ >100 %	Caution: azithromycin side-effects. No dose adjustment with Clari-, ery-thromycin.
<b>Antidepressants</b>		
Nefazodone	Theoretically: NFV ↑	<b>Avoid combination.</b> Th. alternative: SSRIs.
St. John's Wort [2]	Theoretically: NFV ↓	<b>Avoid combination.</b>

Drugs	Interactions	Comments
<b>Antiepileptics</b>		
Carbamazepine, phenytoin, primidone [2,18]	NFV + Phenytoin: NFV: adequate plasma concentration, phenytoin ↓	Caution: TDM of antiepileptics and NFV.
<b>Antifungal drugs</b>		
Caspofungin [1,19]	Caspofungin: approved dose 50 mg, theoretically increase dose up to 70 mg/QD	Azole: no dose adjustment is necessary.
<b>Antihistamines</b>		
Astemizole, Loratadine (> 20 mg), terfenadine [2,16,17]	Theoretically: antihistamines ↑ Increased risk of QT-prolongation	<b>Avoid combination:</b> terfenadine. Th. alternative: cetirizine, fexofenadine.
<b>Antihypertensives</b>		
Calcium channel blockers [20]	Theoretically: calcium channel blockers ↑	Theoretically: dose reduction of ccbs.
Bosentan [20,26]	Theoretically: NFV ↓	<b>Avoid combination</b> or TDM.
<b>Antimalarials</b>		
Mefloquine [18]	No clinically significant interaction	
<b>Antipsychotic drugs</b>		
several drugs [16]	Theoretically: NFV and antipsychotic drugs ↑	<b>Avoid combination</b> with pimozide. Monitor for side-effects. Prefer: atypical neuroleptics (less anticholinergic).
<b>Antituberculosis drugs</b>		
Rifabutin [23]	NFV 750 TID + Rifabutin 300 QD: NFV ↓ 32 % Rifabutin ↑ 207 %	Rifabutin: 150 mg/QD. 1. NFV: 1000 TID. 2. NFV: 1250 BID.
Rifampicin [2,23]	NFV ↓ 82 %	<b>Avoid combination.</b>
<b>Hypnotics</b>		
Barbexaclone, phenobarbital	Theoretically: NFV ↓	<b>Avoid combination</b> or TDM.
Benzodiazepines, zolpidem [2]	Benzodiazepines ↑, prolonged sedation	<b>Avoid combination:</b> midazolam, triazolam.
<b>Immunosuppressants</b>		
Cyclosporine, sirolimus, tacrolimus [20,27]	Theoretically: immunosuppressants ↑ NFV + Tacrolimus: tacrolimus dose needed 16-fold lower [27]	Dose adjustment of immunosuppressants with TDM.
<b>Lipid-lowering drugs</b>		
Atorvastatin, lovastatin, simvastatin [21,2]	NFV 1250 BID + Atorvastatin 10 or simvastatin 20 QD: Atorvastatin ↑ 74 % Simvastatin ↑ 506 %	<b>Avoid combination:</b> simvastatin. Low dose atorvastatin. T. alternative: pravastatin, fluvastatin.

Drugs	Interactions	Comments
<b>PDE5 inhibitors (PPHs)</b>		
Sildenafil, tadalafil, vardenafil [18,24,25]	Theoretically: PPHs ↑	Sildenafil 25 mg every 48h.
<b>Oral contraceptives</b> [2]	NFV 750 TID + 0.4 norethisterone + 35 µg estradiol: ethinyl estradiol ↓ 47 %, norethisterone ↓ 18 %	Use additional contraceptive methods.
<b>Substitution</b>		
Methadone [2,22]	NFV 1250 BID + methadone: methadone ↓ 47 %; in this study, no opiate withdrawal [22]	But monitor for opiate withdrawal.

## References

1. Tseng A. www.tthhivclinic.com, General Hospital, Toronto, 2004.
2. Viracept™, Hoffmann-La Roche.
3. Kruse G, Esser S, Stocker H, et al. Tenofovir does not impair the pharmacokinetic of Nelfinavir in HIV-infected patients. Abstract A446, 44th ICCAC 2004, Washington.
4. Lee CA, Liang BH, Wu EY, et al. Prediction of nelfinavir mesylate (Viracept) clinical drug interactions based on in vitro human P450 metabolism studies. 4th CROI 1997, Washington.
5. Smith PF, Robbins G, Shafer R, et al. Effect of efavirenz on the pharmacokinetics of nelfinavir and M8 in naïve, HIV-infected subjects receiving long-term HAART therapy. Abstract 148, 10th CROI 2003, Boston.
6. Vilaro J, Mascaro J, Colomer J, et al. The pharmacokinetics of combination therapy with nelfinavir plus nevirapine in HIV-positive patients. Abstract A497, 41st ICAAC 2001, Chicago.
7. Klein C, Bertz R, Ashbrenner E, et al. Assessment of the multiple dose pharmacokinetic interaction of lopinavir/ritonavir with nelfinavir. Abstract 536, 10th CROI 2003, Boston.
8. Robinson BS, Riccardi KA, Gong YF, et al. BMS- 232632, a highly potent human immunodeficiency virus protease inhibitor that can be used in combination with other available antiretroviral agents. Antimicrob Agents Chemother 2000; 44: 2093-9. <http://www.amedeo.com/lit.php?id=10898681>.
9. Sadler BM, Gillotin C, Lou Y, et al. Pharmacokinetic study of human immunodeficiency virus protease inhibitors used in combination with amprenavir. Antimicrob Agents Chemother 2001; 45: 3663-8. <http://www.amedeo.com/lit.php?id=11709366>
10. Riddler S, Havlir D, Squires KE, et al. Coadministration of indinavir and nelfinavir in human immunodeficiency virus type 1-infected adults: safety, pharmacokinetics and antiretroviral activity. Antimicrob Agent Chemother 2002; 46: 3877-82. <http://www.amedeo.com/lit.php?id=12435691>
11. Buss N. Saquinavir soft gel capsule (Fortovase): Pharmacokinetics and drug interactions. Abstract 354, 5th CROI 1998, Chicago.
12. Merry C, Barry MG, Mulcahy FM, et al. Saquinavir pharmacokinetics alone and in combination with nelfinavir in HIV infected patients. Abstract 352, 5th CROI 1998, Chicago.
13. Gallicano K, Sanai J, Kravcik S, et al. Nelfinavir increases plasma exposure of saquinavir in hard gel capsule in HIV+ patients. Abstract 353, 5th CROI 1998, Chicago.
14. Stocker H, Kruse G, Arasteh K, et al. Pharmacokinetic interaction between saquinavir/r und nelfinavir in HIV-Infected patients. Abstract A-454, 44th ICAAC 2004, Washington.
15. Amsden GW, Foulds G. The pharmacokinetics of azithromycin and nelfinavir when coadministered in healthy volunteers. Abstract 1651, 40th ICAAC 2000, Toronto.
16. Pratt CM, Mason J, Russell T. Cardiovascular safety of fexofenadine HCL. Am J Cardiol 1999; 84: 278-9. <http://www.amedeo.com/lit.php?id=10335761>
17. Abernethy DR, Barbey JT. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QT-prolongation. Clin Pharmacol Ther 2001; 69: 96-103. <http://www.amedeo.com/lit.php?id=11240972>
18. Schippers EF, Eugen PW, den Hartigh J, et al. No drug drug interaction between nelfinavir and indinavir mefloquine in HIV-1 infected patients. AIDS 2000; 14: 2794-5. <http://www.amedeo.com/lit.php?id=11125902>

19. Kerr B, Yuen G, Daniels R, et al. Strategic approach to nelfinavir mesylate (NFV) drug interactions involving CYP3A metabolism. 4th National CROI 1997, Washington.
20. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
21. Hsyu PH, Smith MD, Lillibridge JH, et al. Pharmacokinetic interactions between nelfinavir and 3-hydroxy-3-methylglutarylcoenzyme A reductase inhibitors atorvastatin and simvastatin. *Antimicrob Agents Chemother* 2001; 45: 3445-50. <http://www.amedeo.com/lit.php?id=11709322>
22. Smith PF, Booker BM, Difrancesco R, et al. Effect of methadone or LAAM on the Pharmacokinetics of nelfinavir & M8. Abstract A-491, 41st ICAAC 2001, Chicago.
23. Centers for Disease Control and Prevention. Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR Morbid Mortal Wkly Rep* 2004; 53:37. <http://www.amedeo.com/lit.php?id=11795500>
24. Nandwani R, Gourlay Y. Possible Interaction between sildenafil and HIV combination therapy. *Lancet* 1999; 353: 840. <http://www.amedeo.com/lit.php?id=10459981>
25. Bratt G, Stahle L. Sildenafil does not alter nelfinavir pharmacokinetics. *Therapeutic Drug Monitoring* 2003; 25: 240-2. <http://www.amedeo.com/lit.php?id=12657921>
26. Ghofrani HA, Olschewski H, Seeger W, et al. Sildenafil for treatment of severe pulmonary hypertension and commencing right-heart failure. *Pneumologie*. 2002; 56: 665-72. <http://www.amedeo.com/lit.php?id=12442206>
27. Jain AK, Venkataramanan R, Shapiro R, et al. The interaction between antiretroviral agents and tacrolimus in liver and kidney transplant patients. *Liver Transpl*. 2002, 8:841-5. <http://amedeo.com/lit.php?id=12200788>
28. Kurowski M, Breske A, Kruse G, et al. Atazanavir (ATV) enhances through concentrations of nelfinavir (NFV) and its M8 metabolite in a treatment regimen without ritonavir (RTV). Abstract 90, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.

## Nevirapine (NVP, Viramune™)

Approved dose: NVP 200 mg BID (lead-in period: 200 mg QD in the first 14 days)  
 Metabolism: nevirapine (NVP) is primarily metabolized by CYP3A4 and is an inducer of CYP3A4 and 2B6 [1,2].

Drugs	Interactions (IAs)	Comments
<b>NRTIs</b>	No clinically significant IA [1]	
<b>NNRTIs</b>		
EFV [2,4,32]	EFV 600 QD + NVP 400 QD [4]: EFV ↓ 22 % (C <sub>min</sub> 36 % ↓)	<b>Unfavourable combination:</b> less efficacy [32].
<b>PIs</b>		
ATV/r [2,30]	Possibly: ATV ↓	no recommendation of dose adjustment of ATV.
APV [6,7]	APV/r 600/100 BID + NVP: APV ↓ 35 % (C <sub>min</sub> 20 % ↓, C <sub>max</sub> 35 % ↓) [6]	TDM.
FPV [31]	FPV/r 700/100 BID + NVP: No clinically significant interaction	APV/r 450/200 BID [7]. no dose adjustment was necessary.
IDV and IDV/r [8,9,10]	IDV/r 800/100 BID + NVP: IDV: C <sub>min</sub> 57 % ↓ RTV: C <sub>min</sub> 59 % ↓ but IDV > 100 ng/ml [8]	1. IDV: 1000 TID [9] 2. IDV/r: 800/100 BID [8] Probably pre-treated patients need an increased dose of IDV [8]. NVP QD decreases IDV/r more than NVP BID [10].



Drugs	Interactions (IAs)	Comments
LPV/r [2,5,33,34]	Capsules: 1. LPV/r 400/100 + NVP: pre-treated patients of clinical trial LPV/r ↓ 27 % ( $C_{\min}$ 51 % ↓)  2. LPV/r 400/100 + NVP (VL < 80 c/ml, n=31): adequate levels of both drugs [33]	Capsules: LPV/r: 533/133 BID [2].  Tablets: LPV/r 400/100 BID in naïve, LPV/r 600/150 BID in pre- treated patients [1]. TDM.
NFV [11,12]	NFV 750 TID + NVP: NFV ↑ 4 % ( $C_{\max}$ 14 % ↑)	In this study, no dose ad- justment was necessary.
<b>Antiarrhythmics</b>		
Amiodarone, bepridil, quinidine, flecainide, lidocaine, propafenone	Theoretically: antiarrhythmics ↓	If necessary, increase dose of antiarrhythmic drugs.
<b>Antibiotics</b>		
Clarithromycin, erythromycin [1,15]	Clarithromycin 500 BID + NVP: Clarithromycin ↓ 35 %, active me- tabolite ↑ 58 %, NVP ↑ 26 %	No dose adjustment. Monitor liver function tests. Alternative: azithromycin.
<b>Antidepressants</b>		
Nefazodone	Theoretically: NVP ↑	<b>Avoid combination.</b>
St. John's Wort [2]	Theoretically: NVP ↓	<b>Avoid combination.</b>
<b>Antiepileptics</b>		
Carbamazepine, phenytoin	Theoretically: NVP ↓	<b>Avoid combination.</b> Th. alternative: gabapentin, lamotrigine, valproic acid.
<b>Antifungal drugs</b>		
Itra-, keto-, flu-, vori- conazole [2,16]	Theoretically: NVP ↑, Azole ↓ Ketoconazole 400 QD + NVP [16]: ketoconazole ↓ 63 % ( $C_{\max}$ 40 % ↓), NVP ↑ 15-28 % Fluconazole + NVP [2]: NVP ↑ 100% Voriconazole: no data	TDM of NVP.
<b>Antihypertensives</b>		
Calcium channel blockers such as amlodipine, nifedipine, verapamil	Theoretically: calcium channel blockers ↓	If necessary, increase dose of calcium channel block- ers.
Bosentan [3,26]	Theoretically: NVP ↓	Theoretical alternative: off label use of sildenafil for pulmonary hypertension.
<b>Antituberculosis drug</b>		
Rifabutin [21,22]		No dose adjustment.
Rifampicin [22-25]	NVP ( $C_{\min}$ 68 % ↓)	<b>Avoid combination.</b>
<b>Cytotoxic drugs</b>		
Cyclophosphamide [3]	Theoretically: neurotoxic metabolite ↑	Avoid combination with 2 or more neurotoxic drugs.

Drugs	Interactions (IAs)	Comments
<b>Drugs of abuse / recreational drugs</b>		
Cocaine [18]	Theoretically: norcocaine ↑ (liver toxicity)	<b>Avoid combination.</b>
<b>Gastritis-/ Ulcer healing drugs</b>		
Cimetidin	Theoretically: NVP ↑	Th. alternative: famotidin, nizatidin, ranitidin.
<b>Hypnotics</b>		
Barbexaclone, phenobarbital	Theoretically: NVP ↓	
Benzodiazepines, zolpidem	Theoretically: benzodiazepines ↓	Th. alternative: lorazepam, oxazepam, temazepam.
<b>Immunosuppressants</b>		
Cyclosporine, sirolimus, tacrolimus	Theoretically: immunosuppressants ↓	Dose adjustment of immunosuppressants with TDM.
<b>Lipid-lowering drugs</b>		
Atorvastatin, lovastatin, simvastatin [1,15,16]	Theoretically: statins ↓	Theoretical alternative: pravastatin.
<b>Oral contraceptives</b>		
[17]	Ethinyl estradiol 0.035 + norethindrone 1.0: estradiol ↓ 29 %, norethindrone ↓ 18 %	Use additional contraceptive method.
<b>PDE5 inhibitors (PPHs)</b>		
Sildenafil, tadalafil, vardenafil	Theoretically: PPHs ↓	Caution: adapt dose individually for each patient.
<b>Substitution</b>		
Methadone [2,19,20]	Methadone ↓ after 4-10 days: opiate withdrawal	Increase methadone dose in 10 mg steps.
<b>Others</b>		
Dexamethasone Warfarin [27]	Theoretically: NVP ↓ Warfarin ↓ ↑	Control INR.

## References

1. Tseng A. www.tthivclinic.com, General Hospital, Toronto, 2006
2. Viramune, Boehringer Ingelheim.
3. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
4. Veldkamp AI, Harris M, Montaner JSG, et al. The steady-state pharmacokinetics of efavirenz and nevirapine when used in combination in HIV type 1 infected persons. J Infect Dis 2001; 184: 37-42. <http://www.amedeo.com/lit.php?id=11398107>
5. Kaletra™, Abbott.
6. Goujard C, Meynard JL, Choudet N, et al. Steady-state pharmacokinetics of amprenavir 600 mg BID and ritonavir 100 mg BID with or without NNRTI in HIV-1 infected patients. Abstract P268, 5th Int Congr Drug Ther HIV Inf 2000, Glasgow. <http://www.aegis.com/conferences/hiv5/P268.html>
7. Degen O, Kurowski M, van Lunzen J, et al. Amprenavir and ritonavir: intraindividual comparison of different doses and influence of concomitant NNRTI on steady-state pharmacokinetics in HIV-infected patients. Abstract 739, 8th CROI 2001, Chicago. <http://www.retroconference.org/2001/abstracts/abstracts/abstracts/739.htm>

8. Burger DM, Prins JM, van der Ende ME, et al. The effect of nevirapine on the pharmacokinetics of indinavir/ritonavir 800/100 mg BID. *JAIDS* 2004; 35: 97-8. <http://www.amedeo.com/lit.php?id=14707800>
9. Murphy R, Gagnier P, Lamson M, et al. Effect of nevirapine on pharmacokinetics of indinavir and ritonavir in HIV-1 patients. Abstract 374, 4th CROI 1997, Washington.
10. Crommentuyn KML, van Heeswijk RPG, Veldkamp AI, et al. Nevirapine once daily versus twice daily: implications for drug-drug interactions. Abstract 1.11, 2nd Int Worksh Clin Pharmacol HIV Ther 2001, Noordwijk.
11. Skowron G, Leoung G, Kerr B, et al. Lack of pharmacokinetic interaction between nelfinavir and Nevirapine. *AIDS* 1998; 12: 1243-4. <http://www.amedeo.com/lit.php?id=9677174>
12. Vilaro J, Mascaro J, Colomer J, et al. The pharmacokinetics of combination therapy with nelfinavir plus nevirapine in HIV-positive patients. Abstract A497, 41st ICAAC 2001, Chicago.
13. Sahai J, Cameron W, Salgo M, et al. Drug interaction study between saquinavir (SQV) and nevirapine (NVP). Abstract 376, 4th National CROI 1997, Washington.
14. Sabo J, MacGregor T, Lamson M, et al. Pharmacokinetics of tipranavir and nevirapine. Abstract 249, 10th Annual Canadian Conference on HIV/AIDS Research 2001, Toronto.
15. Robinson P, Gigliotti M, Lamson M, et al. Effect of the reverse transcriptase inhibitor nevirapine, on the steady-state pharmacokinetics of clarithromycin in HIV positive patients. Abstract 374, 6th CROI 1999, Chicago.
16. Lamson M, Robinson P, Gigliotti M, et al. The pharmacokinetic interactions of nevirapine and ketocozazol. Abstract 12218, 12th World AIDS Conference 1998, Geneva.
17. Mildvan D, Yarrish R, Marshak A, et al. Pharmacokinetic interaction between nevirapine and ethinyl estradiol/norethindrone when administered concurrently to HIV-infected women. *Journal of the Acquired Immune Deficiency Syndrome* 2002; 29: 471-7. <http://www.amedeo.com/lit.php?id=11981363>
18. Antoniou T, Lin-in Tseng. Interactions between Recreational Drugs and antiretroviral agents. *Ann Pharmacother* 2002; 36: 1598-613. <http://www.amedeo.com/lit.php?id=12243611>
19. Altice FL, Friedland GH, Cooney E. Nevirapine induced opiate withdrawal among injection drug users with HIV infection receiving methadon. *AIDS* 1999; 13: 957-62. <http://www.amedeo.com/lit.php?id=10371177>
20. Clarke S, Mulcahy F, Back D, et al. Managing methadone and non-nucleoside reverse transcriptase inhibitors: guidelines for clinical practise. Abstract 88, 7th CROI 2000, San Francisco.
21. Maldonado S, Lamson M, Gigliotti M, et al. Pharmacokinetic interaction between nevirapine and rifabutin. Abstract 341, 39th ICAAC 1999, San Francisco.
22. Centers for Disease Control and Prevention (CDC). Notice to Readers: Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR*; 2004; 53: 37. <http://www.cdc.gov/mmwr/preview/mmwrhtml/mm4909a4.htm>
23. Robinson P, Lamson M, Gigliotti M, et al. Pharmacokinetic interaction between nevirapine and rifampin. Abstract 60623, 12th World AIDS Conference 1998, Geneva.
24. Ribera E, Pou L, Lopez RM, et al. Pharmacokinetic interaction between nevirapine and rifampicin in HIV-infected patients with tuberculosis. *JAIDS* 2001; 28: 450-3. <http://www.amedeo.com/lit.php?id=11744833>
25. Oliva J, Moreno S, Sanz J, et al. Co-administration of rifampin and nevirapine in HIV-infected patients with tuberculosis [letter]. *AIDS* 2003; 17: 637-8. <http://www.amedeo.com/lit.php?id=12598789>
26. Ghofrani HA, Olschewski H, Seeger W, et al. Sildenafil for treatment of severe pulmonary hypertension and commencing right-heart failure. *Pneumologie* 2002; 56: 665-72. <http://www.amedeo.com/lit.php?id=12442206>
27. Dioniso D, Mininni S, Bartolozzi D, et al. Need for increased dose of warfarin in HIV patients taking nevirapine. *AIDS* 2001; 15: 277-8. <http://www.amedeo.com/lit.php?id=11216940>
28. Tripranavir Investigators Broschüre, Boehringer Ingelheim, 2004.
29. Barry M, Mulcahy F, Merry C, et al. Pharmacokinetics and potential interactions among antiretroviral agents used to treat patients with HIV infection. *Clin Pharmacokinet*. 1999; 36: 289-304. <http://www.amedeo.com/lit.php?id=10320951>
30. Alexander CS, Montaner JG, Langridge S, et al. Interaction between atazanavir/Ritonavir (ATV/r) and nevirapine (NVP) is observed in a clinical setting. Abstract P275, 7th Int Congr Drug Ther HIV Inf 2004, Glasgow.
31. DeJesus E, Piliero P, Summers K, et al. Evaluation of the pharmacokinetic drug interaction between fosamprenavir (FPV), FPV plus ritonavir (RTV) and nevirapine (NVP) in HIV-infected patients (APV10014). Abstract A-447, 44th ICAAC 2004, Washington.

32. van Leth F., Hassink E., Phanuphak P. et al. Results of the 2NN Study: A randomized comparative trial of first-line antiretroviral therapy with regimens containing either NVP alone, EFV alone or both drugs combined, together with stavudine and lamivudine. Abstract 176, 10th CROI 2003.
33. Bertz R, Foit C, Burt D, et al. Assessment of the effect of nevirapine on the pharmacokinetics of lopinavir/ritonavir after multiple dosing in HIV-infected adults. Abstract TUPEB4565, XIV Int AIDS Conf 2002, Barcelona.
34. Negredo E, Moltó J, Burger D et al. Lopinavir/ritonavir plus nevirapine as a nucleoside-sparing approach in antiretroviral-experienced patients (NEKA study). JAIDS 2005; 38: 47-52. <http://www.amedeo.com/lit.php?id=15608524>

## Saquinavir (SQV, Invirase 500™)

Approved dose SQV: SQV/r: 1000/100 mg BID [3]. Metabolism: 90 % of SQV is metabolized by the isoenzyme CYP3A4. SQV is a weak inhibitor of CYP3A4. In vitro studies have shown that SQV is also a substrate of P-glycoprotein (P-gp) [1,2].

Drugs	Interactions	Comments
<b>NRTIs</b>		
ddI [1]		Take ddI 1h before or 2h after SQV.
TDF [4,5]	No clinically significant interactions	
<b>NNRTIs</b>		
EFV [6-9]	SQV 1200 TID + EFV 600 QD: SQV ↓ 62 % [6]	1. SQV/r 400/400 BID [7]. 2. SQV/r 1200/100 QD [8]. 3. SQV/r 1000/100 BID[9].
<b>PIs</b>		
ATV [16-19]	SQV 1600 QD + ATV/r 300/100 QD: SQV ↑ 60 %, RTV ↑ 41 % [16]  SQV 1000 BID + ATV/r 300/100 QD: SQV, ATV, RTV ↑ [19]	Synergistic effect.
APV [20]	SQV/r 1000/100 + APV 600 BID: => adequate plasma concentration	Insufficient data. => TDM.
FPV/r [21]	SQV 1000 + FPV/r 700/100 or 700/200 BID: no effect on FPV, but on 1. RTV 100: SQV ↓ 14 % 2. RTV 200: SQV ↑ 12 %	SQV + FPV + RTV <b>100</b> : TDM. SQV + FPV + RTV <b>200</b> : safe.
IDV [22-24]	IDV 800 TID + single dose SQV: SQV ↑ 5-8-fold [22,24]	Insufficient data.
LPV/r [3,12-15]	SQV 1000 + LPV/r 400/100 BID: adequate levels of SQV and LPV	Synergistic effect.
NFV [25-29]	SQV/r 1000/100 + NFV 1250 BID: NFV-M8 ↑ 2.7-fold	In this study no dose adjustment was necessary.
TPV/r [48]	TPV/r 500/200 + SQV 1000 BID: SQV ↓ 70 %, (C <sub>min</sub> 81 % ↓, C <sub>max</sub> 66 % ↓)	<b>Avoid combination.</b>
TMC/r [49]	TMC/r 400/100 + SQV 1000 BID TMC ↓ 26 %	<b>Avoid combination.</b>

Drugs	Interactions	Comments
<b>Antiarrhythmics</b>		
Amiodarone, flecainide, lidocaine, propafenone [3]	Theoretically: antiarrhythmics ↑	<b>Avoid combination.</b>
<b>Antibiotics</b>		
Clarithromycin	SQV 1200 TID + clarithromycin 500 BID: SQV ↑ 177 % Clarithromycin ↑ 45 %	Unboosted SQV: no dose adjustment was necessary.
Erythromycin [2,3]	SQV 1200 TID + Erythromycin 250 QD: SQV ↑ 99 % (Cmax 106 % ↑)	
<b>Antidepressants</b>		
Nefazodone [2]	Theoretically: SQV ↑	Monitor for side-effects. Th. alternative: SSRIs.
St. John's Wort [2]	Theoretically: SQV ↓	<b>Avoid combination</b> or TDM.
<b>Antiepileptics</b>		
Carbamazepine [3,30], phenytoin, primidone	Theoretically: SQV ↓, antiepileptics ↑	Theoretical alternative: gabapentin, lamotrigine, valproic acid [30].
<b>Antifungal drugs</b>		
Itraconazole, ketoconazole, voriconazole [2,33]	Theoretically: SQV ↑ Invirase 600 TID + 200 ketoconazole QD: SQV ↑ 160 %	No dose adjustment. Monitor for toxic effects.
<b>Antihistamines</b>		
Astemizole, loratadine (> 20 mg), terfenadine [2,31,32]	Risk of QT-prolongation ↑ (terfenadine ↑ 368 %)	<b>Avoid combination:</b> terfenadine. Theoretical alternative: cetirizine, fexofenadine.
<b>Antihypertensives</b>		
Calcium channel blockers [2] such as amlodipine, nifedipine, verapamil	Theoretically: calcium channel blockers ↑	Theoretical dose reduction of calcium channel blockers.
Bosentan [3,43]	Theoretically: SQV ↓	<b>Avoid combination</b> or TDM.
<b>Antipsychotic drugs</b>		
several drugs [2,40]	Theoretically: SQV and antipsychotic drugs ↑	<b>Avoid combination</b> with pimozide. Monitor for side-effects. Prefer: atypical neuroleptics (less anticholinergic).
<b>Antituberculosis drugs</b>		
Rifabutin [41]	SQV 1200 TID + rifabutin QD: SQV ↓ 40 %	SQV/r + rifabutin: 150 mg 3x/week.
Rifampicin [2,41,47]	SQV/r 1000/100 BID + rifampicin 600 QD: hepatotoxicity	<b>Avoid combination.</b>

Drugs	Interactions	Comments
<b>Gastritis-/ Ulcer healing drugs</b>		
Antacids, proton pump inhibitors (PPIs)	No data	Interactions unlikely.
H2-blockers Cimetidine [3,35]	SQV 1200 TID vs. SQV 1200 BID + cimetidine 400 BID: SQV ↑ 120 % (Cmax 179 % ↑)	Theoretical alternative: famotidine, nizatidine, ranitidine.
<b>Hypnotics</b>		
Barbexaclone, phenobarbital	Theoretically: SQV ↓	<b>Avoid combination</b> or TDM.
Benzodiazepines, zolpidem [2,3,51]	Prolonged sedation. SQV/r 1000/100 BID + midazolam: SQV ↑ 12.5-fold (Cmax 4.27-fold ↑), half life prolongation: from 4.4h to 14.6h [ 51]	<b>Avoid combination:</b> midazolam. Caution: alprazolam, triazolam. Theoretical alternative: lorazepam, oxazepam, temazepam [3].
<b>Immunosuppressants</b>		
Cyclosporine, sirolimus tacrolimus [3,46]	immunosuppressants ↑	Dose adjustment of immunosuppressants with TDM.
<b>Lipid-lowering drugs</b>		
Atorvastatin, lovastatin, simvastatin [2,34]	SQV/r 400/400 BID + 40 mg atorvastatin QD, pravastatin, simvastatin: atorvastatin ↑ 5.9-fold, pravastatin: ↓ 35 %, simvastatin ↑ 34.6-fold	<b>Avoid combination:</b> simvastatin, lovastatin. Th. alternative: pravastatin, fluvastatin.
<b>PDE5 inhibitors (PPHs)</b>		
Sildenafil, tadalafil, vardenafil [2,3,42]	Theoretically: PPHs ↑ Fortovase 1200 TID + sildenafil 100: Sildenafil ↑ 210 % (Cmax 140 % ↑)	Sildenafil 25 mg every 48h. Other PPIs: start with a low dose.
<b>Substitution</b>		
Methadone [36-39]	SQV/r + R- and S-methadone: No significant changes of SQV. R-methadone ↓ 20 %	Interactions unlikely.
<b>Others</b>		
Dexamethasone Ergot alkaloids [3]	Theoretically: SQV ↓ Theoretically: SQV ↑	TDM. <b>Avoid combination.</b> Theoretical alternative: triptans.
Garlic capsules [44] ingredients: allicin	SQV 1200 TID + allicin 300: SQV ↓ 51 %	<b>Avoid combination.</b>
Warfarin [3,45]	Report of hypoprothrombinaemia: 20 % lower warfarin concentration with SQV	If necessary, increase warfarin dose.

## References

1. Tseng A. <http://www.tthivclinic.com/>, General Hospital, Toronto, 2004.
2. Fortovase™, Hoffmann-La Roche.
3. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>

4. Ananworanich J, Siangphoe U, Mahanontharit A, et al. Saquinavir Cmin before and after switching NRTI to tenofovir in patients treated with once daily saquinavir-hard gel capsule/ritonavir 1600 mg/100 mg. Abstract 4.15, 5th Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
5. Boffito M, D'Avolio A, Di Perri G, et al. Repeated pharmacokinetics of tenofovir disoproxil fumarate (TDF) in HIV-infected-adults receiving saquinavir hard gel (SQV)/ritonavir (RTV) 1000/100 mg BID. Abstract 4.19, 5th Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
6. Jorga K, Buss NE. Pharmacokinetic drug interaction with saquinavir soft gelatine capsule. Abstract 339, 39th ICAAC 1999, San Francisco.
7. van Heeswijk RP, Cooper C, Gallicano, et al. The pharmacokinetics of SQV/RTV 400/400 mg BID before, and after short- and long term co-administration of efavirenz 600 mg QD. Abstract 7.4, 3rd Int Worksh Clin Pharmacol HIV-Ther 2002, Washington.
8. Lopez-Cortes LF, Viciano P, Ruiz-Valderas R, et al. Pharmacokinetics, efficacy and safety of once-daily saquinavir-sgc plus low-dose ritonavir (1200/100 mg) in combination with efavirenz in HIV-pretreated patients. Abstract 441-w, 9th CROI 2002, Seattle.
9. Boyd MA, Autar R, Burger D, et al. Saquinavir 1000 mg bid boosted with ritonavir 200 mg in the presence of efavirenz 600 mg results in adequate saquinavir minimum concentrations: HIV-NAT 012 pharmacokinetic study. Abstract 4.9, 5th Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
10. Sahai J, Cameron W, Salgo M, et al. Drug interaction study between saquinavir (SQV) and nevirapine (NVP). 4th National CROI 1997, Washington.
11. Crommentuyn KML, van Heeswijk RPG, Veldkamp AI, et al. Nevirapine once daily versus twice daily: implications for drug-drug interactions. Abstract 1.11, 2nd Int Worksh Clin Pharmacol HIV Ther 2001, Noordwijk.
12. La Porte CJ, Wasmuth JC, Schneider K, et al. Lopinavir/ritonavir plus saquinavir in salvage therapy: pharmacokinetics, tolerability and efficacy. AIDS 2003; 17: 1700-2.  
<http://www.amedeo.com/lit.php?id=12853756>
13. Ribera E, Diaz M, Pou L, et al. Steady-state pharmacokinetics of double boosting regimen of lopinavir, plus minidose Ritonavir, plus Saquinavir soft-gel in HIV-infected adults. Abstract TUPE4545, XIV Int AIDS Conf 2002, Barcelona.
14. Staszewski S, Dauer B, Von Hentig N, et al. The LopSaq study: 24 week analysis of the double protease inhibitor salvage regimen containing lopinavir plus saquinavir without any additional antiretroviral therapy. Abstract 583, 2nd IAS Conference on HIV Pathogenesis and Treatment 2003, Paris.
15. Stefan C, Von Hentig N, Kurowski, et al. Saquinavir drug exposure is not impaired by the boosted double protease inhibitor combination of lopinavir/Saquinavir. AIDS 2004; 18: 503-8.  
<http://www.amedeo.com/lit.php?id=15090803>
16. Boffito M, Kurowski M, Kruse G, et al. Atazanavir enhances saquinavir hard gel concentration in a ritonavir boosted once daily regimen. AIDS 2004; 18: 1292-7.  
<http://www.amedeo.com/lit.php?id=15362661>
17. Prelutsky D, Salvato P, Falcon R. Pharmacokinetics of saquinavir hard gel (invirase) when combined with atazanavir. Abstract 8.11, 4th Int Worksh Clin Pharmacol HIV Ther 2003, Cannes.  
[http://216.198.241.125/hiv/upload\\_doc/2/4PK Falcon 8.11.PDF](http://216.198.241.125/hiv/upload_doc/2/4PK Falcon 8.11.PDF)
18. DeJesus E, Grinsztejn B, Rodriguez C, et al. Efficacy and safety of atazanavir with ritonavir or saquinavir vs lopinavir/ritonavir in patients who have experienced virologic failure on multiple HAART Regimens: 48-Week results from BMS A1424-045. Abstract 54, 11th CROI 2004, San Francisco.  
<http://www.retroconference.org/2004/cd/Abstract/547.htm>
19. von Hentig N, Haberl A, Lutz T, et al. Pharmacokinetic interactions of atazanavir (ATV) and saquinavir (SQV) in a ritonavir (RTV) boosted protease inhibitor therapy regimen. Abstract P276, 7th Int Congr Drug Ther HIV Inf 2004, Glasgow.
20. Wolfe PR, Anderson PG, Gunawan S. Simultaneous administration of amprenavir and saquinavir does not appear to lower plasma levels of either agent when coadministered with low dose ritonavir. Abstract 7.11, 3rd Int Worksh Clin Pharmacol HIV Ther 2002, Washington.
21. Boffito M, Dickinson L, Hill A, et al. Steady state pharmacokinetics of saquinavir hard gel/fosamprenavir 1000/700 plus 100 mg und 200 mg of ritonavir twice daily in HIV+ patients. Abstract 608, 11th CROI 2004, San Francisco.
22. Mc Crea J, Buss N, Stone J, et al. Indinavir-saquinavir single dose pharmacokinetic study. 4th National CROI 1997, Washington.
23. Manion D, Merrill DP, Hirsch MS. Combination drug regimens against multidrug resistant HIV-1 in vitro. 4th National CROI, 1997, Washington.
24. Buss N. Saquinavir soft gel capsule (Fortovase): Pharmacokinetics and drug interactions. Abstract 354, 5th CROI 1998, Chicago.

25. Merry C, Barry MG, Mulcahy FM, et al. Saquinavir pharmacokinetics alone and in combination with nelfinavir in HIV-infected patients. *AIDS* 1997; 11: 117-20. <http://www.amedeo.com/lit.php?id=9084785>
26. Gallicano K, Sanai J, Kravcik S, et al. Nelfinavir increases plasma exposure of saquinavir in hard gel capsule in HIV+ patients. Abstract 353, 5th CROI 1998, Chicago.
27. Kravcik S, Sahai J, Kerr B, et al. Nelfinavir mesylate (NFV) increases saquinavir soft gel capsule (SQV- SGC) exposure in HIV+ patients. 4th National CROI, 1997, Washington.
28. Squires K, Currier J, Clark R, et al. Final 48-week result of a phase 2, randomized study of the safety, efficacy and pharmacokinetics of BID vs. TID nelfinavir and saquinavir in combination with lamivudine and stavudine in HIV-positive women. Abstract 330, 8th CROI 2001, Chicago.
29. Stocker H, Kruse G, Arasteh K, et al. Pharmacokinetic interaction between saquinavir/r und nelfinavir in HIV-Infected patients. Abstract A-454, 44th ICAAC 2004, Washington.
30. Hugen PWH, Burger DM, Brinkmann K, et al. Carbamazepine-indinavir interaction causes antiretroviral failure. *Ann Pharmacother* 2000; 34: 465-70. <http://www.amedeo.com/lit.php?id=10772431>
31. Pratt CM, Mason J, Russell T. Cardiovascular safety of fexofenadine HCL. *Am J Cardiol* 1999; 84: 278-9. <http://www.amedeo.com/lit.php?id=10335761>
32. Abernethy DR, Barbey JT. Loratadine and terfenadine interaction with nefazodone: Both antihistamines are associated with QT-prolongation. *Clin Pharmacol Ther* 2001; 69: 96-103. <http://www.amedeo.com/lit.php?id=11240972>
33. Cardiello P, Samor T, Burger D, et al. Pharmacokinetics of lower doses of saquinavir soft gel caps (800 and 1200 mg BID) boosted with itraconazole in HIV+ patients. *Antivir Ther* 2003; 8: 245-9. [amedeo.com/lit.php?id=12924542](http://www.amedeo.com/lit.php?id=12924542)
34. Fichtenbaum C, Gerber J, Rosenkranz S, et al. Pharmacokinetic interactions between protease inhibitors and selected HMG-CoA reductase inhibitors. Abstract LB6, 7th CROI 2000, San Francisco.
35. Boffito M, Trentini, Raiteri R, et al. Pharmacokinetics of saquinavir co-administered with cimetidine. *J Antimicrob Chemother*. 2002 ; 50:1081-4. <http://www.amedeo.com/lit.php?id=12461038>
36. Geletko SM, Erickson AD. Decreased methadone effect after ritonavir initiation. *Ann Pharmacother* 2000; 20: 93-4. <http://www.amedeo.com/lit.php?id=10641980>
37. Shelton M, Cloen D, Berenson C, et al. The effects of once daily saquinavir/mini-dose ritonavir on the pharmacokinetics of methadone isomers. *J Clin Pharmacol* 2004; 44: 293-304. <http://www.amedeo.com/lit.php?id=14973306>
38. Shelton MJ, Cloen D, Berenson C, et al. Pharmacokinetics of once daily saquinavir/ritonavir: effects on unbound methadone and alpha1-acid glycoprotein. Abstract A492, 41st ICAAC 2001, Chicago.
39. Gerber JG, Rosenkranz S, Segal Y. Effect of ritonavir/saquinavir on stereoselective pharmacokinetics of methadone: results of AIDS Clinical Trials Group (ACTG) 401. *J Acquir Immune Defic Syndr*. 2001; 27: 153-60. <http://www.amedeo.com/lit.php?id=11404537>
40. Tseng AL, Foisy MM. Significant Interactions wit New Antiretrovirals and Psychotropic Drugs, *Ann Pharmacother* 1999; 33: 461-73. <http://www.amedeo.com/lit.php?id=10332538>
41. Centers for Disease Control and Prevention (CDC). Notice to Readers: Updated guidelines for the use of rifamycins for the treatment of tuberculosis among HIV-infected patients taking protease inhibitors or nonnucleoside reverse transcriptase inhibitors. *MMWR*; 2004;53:37. <http://www.amedeo.com/lit.php?id=11795500>
42. Muirhead GJ, Wulff MB, Fielding A, et al. Pharmacokinetic interactions between sildefanil and saquinavir/ritonavir. *Br J Clin Pharmacol* 2000; 50: 99-107. <http://www.amedeo.com/lit.php?id=9161669>
43. Ghofrani HA, Olschewski H, Seeger W, et al. Sildenafil for treatment of severe pulmonary hypertension and commencing right-heart failure. *Pneumologie*. 2002; 56: 665-72. <http://www.amedeo.com/lit.php?id=12442206>
44. Piscitelli SC, Burstein AH, Welden N, et al. The effect of garlic supplements on the pharmacokinetics of saquinavir. *Clin Infect Dis* 2002; 34: 234-5. <http://www.amedeo.com/lit.php?id=11740713>
45. Darlington MR. Hypoprothombinemia during consomitant therapy with warfarin and saquinavir [letter]. *Ann Pharmacother* 1997; 31: 647. <http://www.amedeo.com/lit.php?id=9161669>
46. Brinkman K, Huysmans F, Burger DM. Pharmacokinetic interaction between saquinavir and cyclosporine. *Ann Intern Med* 1998, 129:915-916.
47. Roter Hand Brief Saquinavir, Hoffmann La-Roche.
48. Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir alone or in combination with saquinavir, amprenavir, or lopinavir: interim analysis of B11182.51. Abstract 34, 5th Int Worksh Clin Pharmacol HIV-Ther 2004, Rome.
49. US product information on Prezista®.



50. Frohlich M, Burhenne J, Martin-Facklam M, et al. Oral contraception does not alter single dose saquinavir pharmacokinetics in women. *Br J Clin Pharmacol* 2004;57:244-52. <http://www.amedeo.com/lit.php?id=14998420>
51. Hofmann C et al. Effect of saquinavir/ritonavir on CYP-3A4 activity in healthy volunteers using midazolam as a probe. Abstract 47. 7th Int Worksh Clin Pharmacol HIV-Ther 2006, Lissabon.

## T-20 (Enfuvirtid, Fuzeon™)

No clinically significant interaction.

## Tenofovir (TDF, Viread™; component of Truvada™)

Elimination: TDF is eliminated by a combination of glomerular filtration and active renal tubular secretion. Approved dose: TDF 300 mg QD

Drugs	Interactions	Comments
<b>NRTIs</b>		
ddI [1-5]	ddI EC 250 QD + TDF 300 QD: ddI AUC equivalent to ddI 400 alone. Dose recommendation: patients $\geq$ 60 kg: ddI 250 mg patients < 60 kg: ddI 200 mg Despite dose reduction of ddI, there is probably an increased risk of lactic acidosis and pancreatitis.	<b>Unfavourable combination.</b> Virological failure [4]. Closely monitor for amylase, lipase and lactate.  ddI and TDF can be taken with a meal.
Other NRTIs [6-9]	No clinically significant interaction	
<b>NNRTIs</b>		
EFV [9]	No clinically significant interaction	
<b>PIs</b>		
ATV [11]	ATV 400 QD + TDF 300 QD: ATV $\downarrow$ 25 % ( $C_{\min}$ 40 % $\downarrow$ ) TDF $\uparrow$ 24 % [11]	ATV/r 300/100 QD: Administer with food.
ATV/r [10,12,13,27]	ATV/r 300/100 + TDF QD [10] ATV $\downarrow$ 25 % ( $C_{\min}$ 23 % $\downarrow$ , not significant) [12]	Boosted ATV-levels are 2-4-fold higher than unboosted ATV without TDF [13].
IDV [9]	No clinically significant interaction	
LPV/r [14,15,23,28]	Healthy volunteers: TDF $\uparrow$ 32 % ( $C_{\max}$ 15 % $\uparrow$ ) LPV/r: unchanged 18 heavily pre-treated patients: LPV: $C_{\min}$ 34 % $\downarrow$ , RTV: $C_{\min}$ 44 % $\downarrow$	In clinical studies, no increased appearance of renal side-effects.  TDM of LPV/r.
NFV [18]	No clinically significant interaction	

Drugs	Interactions	Comments
SQV [16,17]	No clinically significant interaction	
FPV [25,26]	No clinically significant interaction	
TPV/r [15]	TPV/r 500/100 or 750/200 BID + TDF 300 QD: TDF (depending on dose): TPF ↓ 11 % and 17 % respectively (C <sub>max</sub> 23-38 % ↓)	<b>Avoid combination</b> , clinical significance of this interaction is not firmed yet.
DRV (TMC 114) /r [24]	DRV/300/100 BID + TDF 300 QD: TDF ↑ 22 %	No dose adjustment.
<b>Co-medication</b>		
Methadone [20]	No clinically significant interaction	
O. contraceptives [19]	No clinically significant interaction	
Ribavirin [21]	No clinically significant interaction	
Rifampicin [22]	No clinically significant interaction	
<b>Nephrotoxic drugs</b>		
e.g. amphotericin B, aminoglycosides, cidofovir, foscarnet, pentamidine (i.v.), vancomycin [2]	No data, but perhaps additive nephrotoxicity.	<b>Avoid combination.</b>
e.g. acyclovir, probenecid, salicylate, tacrolimus, valaciclovir, valganciclovir	No data, but these drugs are renally eliminated as tenofovir	<b>Avoid combination</b> in patients with risk of renal failure; or monitor for kidney function weekly.

## References

1. Tseng A. www.tthhivclinic.com, General Hospital, Toronto, 2006.
2. Viread™, Gilead.
3. Clinical Pharmacology, Gold Standard Multimedia, 2004. <http://www.gsm.com>
4. Kearney BP, Damle B, Plummer A, et al. Tenofovir DF (TDF) and didanosine EC (ddl EC): investigation of pharmacokinetic (PK) drug-drug and drug-food interactions. Abstract LBPE9026, XIV Int AIDS Conf 2002, Barcelona. <http://www.aegis.com/conferences/14WAC/LbPeB9026.html>
5. Kearney BP, Isaacson E, Sayre J, et al. Didanosine and tenofovir DF drug-drug interaction: assessment of didanosine dose reduction. Abstract 533, 10th CROI 2003, Boston. <http://www.retroconference.org/2003/abstract/abstract.aspx?abstractID=181>
6. Blum MR, Begley J, Zong J, et al. Lack of a pharmacokinetic interaction between emtricitabine and tenofovir DF when coadministered to steady state healthy volunteers. Abstract A-1621, 43rd ICAAC 2003, Chicago. [http://www.thebody.com/confs/icaac2003/pdfs/A-1621\\_poster.pdf](http://www.thebody.com/confs/icaac2003/pdfs/A-1621_poster.pdf)
7. Kaul S, Bassi K, Damle B, et al. Stavudine extended release formulation and tenofovir disoproxil fumarate: lack of a pharmacokinetic drug interaction. Abstract 602, 11th CROI San Francisco, 2004. <http://www.retroconference.org/2004/cd/abstract/602.htm>
8. Kearney BP, Isaacson E, Sayre J, et al. The pharmacokinetics of abacavir, a purine nucleotide analog, are not affected by tenofovir DF. Abstract A-1615, 43rd ICAAC 2003, Chicago. [http://www.thebody.com/confs/icaac2003/pdfs/A-1615\\_poster.pdf](http://www.thebody.com/confs/icaac2003/pdfs/A-1615_poster.pdf)
9. Kearney B, Flaherty J, Wolf J, et al. Lack of clinically relevant drug-drug interactions between tenofovir DF and efavirenz, indinavir, lamivudine and lopinavir/ritonavir in healthy subjects. Abstract P171, 8th European Conference on Clinical Aspects and Treatment of HIV Infection 2001, Athens. <http://www.eacs.ws/conference/index/htm>
10. Taburet A, Piketty C, Chazallon C, et al. Interactions between atazanavir-ritonavir and tenofovir in heavily pretreated human immunodeficiency virus-infected patients. Antimicrob Agents Chemother 2004; 48:2091-6. <http://www.amedeo.com/lit.php?id=15155205>

11. Kaul S, Bassi K, Damle B, et al. Pharmacokinetic evaluation of the combination of atazanavir (ATV), enteric coated didanosine (ddl-EC), and tenofovir disoproxil fumarate (TDF) for a once-daily antiretroviral regimen. Abstract A-1616, 43rd ICAAC 2003, Chicago.  
[http://www.natap.org/2003/ICAAC/day6\\_1.htm](http://www.natap.org/2003/ICAAC/day6_1.htm)
12. Kruse G, Stocker H, Breske A et al. Trough levels of six different atazanavir regimens in HIV-infected patients. Abstract 6.6, 5th Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
13. Truvada, Gilead Sciences, September 2004.
14. Kearney BP, Mittan A, Sayre J, et al. Pharmacokinetic drug interaction and long term safety profile of tenofovir DF and lopinavir/ritonavir. Abstract A-1617, 43rd ICAAC 2003, Chicago.  
[http://www.thebody.com/confs/icaac2003/pdfs/A.1617\\_poster.pdf](http://www.thebody.com/confs/icaac2003/pdfs/A.1617_poster.pdf)
15. Roszko PJ, Curry K, Brazina B, et al. Standard doses of efavirenz (EFV), zidovudine (ZDV), tenofovir (TDF), and didanosine (ddl) may be given with tipranavir/ritonavir (TPV/r). Abstract 865, 2nd IAS Conference on HIV Pathogenesis and Treatment 2003, Paris.  
<http://www.aegis.com/conferences/2ndIASHIVPT/865.html>
16. Ananworanich J, Siangphoe U, Mahanontharit A, et al. Saquinavir Cmin before and after switching NRTI to tenofovir in patients treated with once daily saquinavir-hard gel capsule/ritonavir 1600 mg/100 mg. Abstract 4.15, 5th Int Worksh Clin Pharmacol HIV Ther 2004, Rome.  
<http://www.amedeo.com/lit.php?id=15651763>
17. Boffito M, D'Avolio A, Di Perri G, et al. Repeated pharmacokinetics of tenofovir disoproxil fumarate (TDF) in HIV-infected-adults receiving Saquinavir hard gel (SQV)/Ritonavir (RTV) 1000/100 mg BID. Abstract 4.19, 5th Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
18. Kruse G, Esser S, Stocker H, et al. Tenofovir does not impair the pharmacokinetics of nelfinavir in HIV-infected patients. Abstract A-446, 44th ICAAC 2004, Washington.
19. Kearney BP, Isaacson E, Sayre J, et al. Tenofovir DF and oral contraceptives: Lack of a pharmacokinetic drug interaction. Abstract A-1618, 43rd ICAAC 2003, Chicago.  
[http://www.thebody.com/confs/icaac2003/pdfs/A-1618\\_poster.pdf](http://www.thebody.com/confs/icaac2003/pdfs/A-1618_poster.pdf)
20. Smith P, Kearney B, Cloen D. Tenofovir DF does not affect the pharmacokinetics or pharmacodynamics of methadone. Abstract 869, 2nd IAS Conference on HIV Pathogenesis and Treatment 2003, Paris. <http://www.aegis.com/conferences/2ndIASHIVPT/865.html>
21. Kearney B, Benhamou Y, Flaherty J, et al. Lack of systemic or renal drug interactions of tenofovir DF with ribavirin or adefovir dipivoxil. Abstract 69, XV Int AIDS Conf 2004, Bangkok.
22. Droste JAH, Kearney BP, v Horssen P, et al. Lack of clinically relevant drug-drug interaction between tenofovir DF and rifampin in healthy volunteers. Abstract 4.11, 5th Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
23. Kearney BP, Mittan A, Sayre J, et al. Pharmacokinetic drug interaction and long term safety profile of tenofovir DF and lopinavir/ritonavir. Abstract A-1617, 43rd ICAAC 2003, Chicago.  
[http://www.natap.org/2003/ICAAC/day5\\_2.htm](http://www.natap.org/2003/ICAAC/day5_2.htm)
24. US Product information on Prezista.
25. Kurowski M, Walli R, Breske et al. Co-administration of tenofovir 300 mg QD with fosamprenavir / ritonavir 1400/100 mg QD or 1400/200 mg QD does not affect amprenavir pharmacokinetics. Abstract 10, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
26. Peytavin G, Rouault A, Agher R, et al. Plasma concentrations of amprenavir, ritonavir and tenofovir in HIV-infected patients treated with fosamprenavir / ritonavir (700 / 100 mg BID) and tenofovir (300 mg QD) containing regimen. Abstract 32, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
27. Agarwala S, Eley T, Villegas C, et al. Pharmacokinetic interaction between tenofovir and atazanavir co-administered with ritonavir in healthy subjects. Abstract 16, 6th Int Worksh Clin Pharmacol HIV Ther 2005, Quebec.
28. Breilh D, Rouzes A, Djabarouti S, et al. Pharmacokinetic drug interaction of lopinavir/ritonavir in combination with tenofovir in experienced HIV+ patients. Abstract A-445, 44th ICAAC 2004, Washington.

## Tipranavir (TPV/r, Aptivus™)

Approved dose: TPV/r: 500/200 mg BID taken with a meal [1,2]. Metabolism: TPV is metabolized by the isoenzyme CYP3A4 and is also a substrate of P-glycoprotein. Further, TPV is an inducer of the isoenzyme CYP3A4, of the glucuronyltransferase, and of P-glycoprotein [1,2]. By means of boosting with RTV, TPV becomes to be

an inhibitor of CYP3A4. Thus, interactions between TPV/r and drugs that are both metabolized by CYP3A4 and transported by P-glycoprotein are hardly predictable.

Substance	Interactions	Comments
<b>NRTIs</b>		
ABC [2,12]	ABC ↓ 40 %	<b>Avoid combination</b> , clinical significance of this interaction is not firmed yet.
AZT [1,2,4,12] ddI [1,2,4,12]	AZT ↓ 35 % (C <sub>max</sub> 46-61 % ↓) [4] TPV: C <sub>max</sub> 32 % ↑, C <sub>min</sub> 34 % ↓ [4]	ddI 2 h before or after taking of TPV/r.
TDF [1,2,4]	TPV/r 500/100 or 750/200 BID + TDF 300 QD [4]: TDF (depending on dose): 11 % ↓ and 17 % ↓, respectively (C <sub>max</sub> 23-38 % ↓)	<b>Avoid combination</b> , clinical significance of this interaction is not firmed yet.
<b>NNRTIs</b>		
EFV [2,4,12]	EFV ↓ 1-31 % [4] TPV ↓ (C <sub>max</sub> ↓, C <sub>min</sub> ↓)	Limited data. No dose adjustment as yet.
NVP [5]	NVP ↓ 3-24 %	Limited data. No dose adjustment as yet.
<b>PIs</b>		
APV [6]	TPV/r 500/200 + APV 600 BID: APV ↓ 44 % (C <sub>min</sub> 56 % ↓ C <sub>max</sub> 39 % ↓)	<b>Avoid combination.</b>
ATV [13]	ATV 300 QD + TPV/r 500/100 BID: ATV ↓ 68 % (C <sub>min</sub> 81 % ↓ C <sub>min</sub> TPV ↑ 75 %	<b>Avoid combination.</b>
IDV [2] LPV/r [6]	Insufficient data TPV 500 + LPV/r 400/100 BID: LPV ↓ 55 % (C <sub>min</sub> 52-70 % ↓ C <sub>max</sub> 47 % ↓)	<b>Avoid combination.</b> <b>Avoid combination.</b>
NFV [2]	No data	<b>Avoid combination.</b>
SQV [2,6]	TPV/r 500/200 + SQV 1000 BID: SQV ↓ 76 % (C <sub>min</sub> 81 % ↓, C <sub>max</sub> 70 % ↓)	<b>Avoid combination.</b>
<b>Antiarrhythmics</b>		
Amiodarone, flecainide, propafenone [2]	Theoretically: antiarrhythmics ↑, potential for severe, life-threatening arrhythmia	<b>Avoid combination.</b>
<b>Antibiotics</b>		
Clarithromycin [7]	Clarithromycin: C <sub>min</sub> 68 % ↑, active metabolite: 95 % ↓ TPV ↑ 66 % (C <sub>max</sub> 40 % ↑)	Caution with H. influenza infections, because here, the active metabolite is mainly effective.
<b>Antidepressants</b>		
Desipramine [2]	Theoretically: desipramine ↑	Close monitoring and, if necessary, dose reduction.
SSRIs: fluoxetine, paroxetine, sertraline [2]	Fluoxetine ↑, paroxetine ↑, sertraline ↑	SSRIs possess a high therapeutic range, but however, possibly dose adjustment.

Substance	Interactions	Comments
St. John's Wort	Theoretically: TPV ↓	<b>Avoid combination.</b>
<b>Antihistamines</b>		
Astemizole, terfenadine [2]	Potential for severe, life-threatening cardiac arrhythmia	<b>Avoid combination.</b>
<b>Antihypertensives</b>		
<b>Calcium channel blockers (ccb)</b> Diltiazem, felodipine verapamil [2]	Difficult to predict as ccbs are both substrates of CYP3A4 and P-glycoprotein; TPV/r inhibit CYP3A4 and induce P-glycoprotein.	Caution. Close monitoring.
<b>Antifungal drugs</b>		
Fluconazole [8]	TPV/r 500/200 BID + fluconazole 100 QD: TPV ↑ 56 % (Cmin ↑ 104 %)	Fluconazole dose of 200 mg should not be exceeded.
Itraconazole [2]	Theoretically: itraconazole ↑	Caution: dose > 200 mg are not recommended. Interactions with voriconazole hardly predictable.
Ketoconazole [2]	Theoretically: ketoconazole ↑	
Voriconazole [2]	Theoretically: voriconazole ↑↓	
<b>Antituberculosis drugs</b>		
Rifabutin [10]	TPV/r 500/200 BID + rifabutin QD (single dose): rifabutin ↑ 3-fold, active metabolite 20-fold, TPV: Cmin 16 % ↑ No data. Theoretically: TPV ↓	TPV/r + rifabutin: 150 mg 3x/week. In occurrence of side-effects, possibly further dose reduction.
Rifampicin [1]		<b>Avoid combination.</b>
<b>Ergotamines</b>		
	Theoretically: ergotamines ↑. Possibly life-threatening ergotisms.	<b>Avoid combination.</b> Theoretical alternative: triptans.
<b>Gastritis-/ Ulcer healing drugs</b>		
Antacids [2,11]	TPV/r (single dose) + Maalox®: TPV ↓ 25-29 %	Antacids: 2h before or after taking of TPV/r.
PPIs, H2-blockers	No data	Caution in combination of TPV/r and PPIs or H2-blockers.
<b>Hypnotics</b>		
Benzodiazepines, (e.g. midazolam, triazolam) [2]	Prolonged sedation	<b>Avoid combination.</b> Alternative: lorazepam, oxazepam, temazepam. Possibly dose adjustment.
<b>Hypoglycaemia</b>		
Glimepiride, glipizide, pioglitazone, repaglinide, rosiglitazone, tolbutamide [2]	No data. Theoretically: level fluctuations as TPV as well as these substances are possibly metabolized by CYP2C8, CYP2C9 and CYP3A4.	Closed monitoring for glucose levels. <b>Avoid combination:</b> pioglitazone weak inducer of CYP3A4. Alternative: rosiglitazone.
<b>Immunosuppressants</b>		
Cyclosporine, sirolimus, tacrolimus	No data. Theoretically: level fluctuations as interactions with CYP3A4 and P-glycoprotein are possible.	TDM..

Substance	Interactions	Comments
<b>Lipid-lowering drugs</b>		
Atorvastatin [2,9]	TPV/r 500/200 BID + atorvastatin 10 QD: TPV ↑ 8 %, atorvastatin ↑ 936 %	<b>Avoid combination</b> or monitoring, start with the lowest possible dose.
Lovastatin, simvastatin [2]	Myopathy, rhabdomyolysis risk ↑	<b>Avoid combination.</b> Theoretical alternative: pravastatin, fluvastatin.
<b>Neuroleptics</b>		
Pimozide, sertindole [2]	Potential for severe, life-threatening cardiac arrhythmia.	<b>Avoid combination.</b>
<b>Oral contraceptives</b>		
Ethinyl estradiol [2]	Ethinyl estradiol ↓ 50 %	Use additional contraceptive method.
<b>PDE5 inhibitors</b>		
Sildenafil, tadalafil, vardenafil [2]	Theoretically: sildenafil ↑, tadalafil ↑, vardenafil ↑	Caution. Low initial dose. Sildenafil: 25 mg every 48h. Tadalafil: 10 mg every 72h. Vardenafil: 2.5 mg every 72h.
<b>Substitution</b>		
Methadone [2]	Methadone ↓ 50 %	Monitor for withdrawal symptoms. Perhaps dose adjustment of methadone.
<b>Others [2]</b>		
Disulfiram	No data. Theoretically: TPV capsules contain alcohol and can cause reactions similar to Disulfiram.	TDM of theophylline, possibly dose adjustment.
Metronidazole		
Theophylline	Theophylline ↓	Check for INR levels.
Marcumar <sup>®</sup>	Not predictable.	

## References

1. Tseng A., General Hospital, Toronto, 2004, www.tthivclinic.com.
2. Product Information Aptivus®, Firma Boehringer Ingelheim.
3. Clinical Pharmacology, Gold Standard Multimedia, 2004, http://www.gsm.com.
4. Roszko PJ, Curry K, Brazina B, et al. Standard doses of efavirenz, zidovudine, tenofovir, and didanosine may be given with tipranavir/ritonavir. Abstract 865, 2<sup>nd</sup> IAS 2003, Paris.
5. Sabo J, MacGregor T, Lamson M, et al. Pharmacokinetics of tipranavir and nevirapine. Abstract 249, 10<sup>th</sup> Annual Canadian Conference on HIV/AIDS Research 2004, Toronto.
6. Leith J, Walmsley S, Katlama C, et al. Pharmacokinetics and safety of tipranavir/ritonavir alone or in combination with saquinavir, amprenavir, or lopinavir: interim analysis of B1182.51. Abstract 34, 5<sup>th</sup> Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
7. van Heeswijk RP, Sabo J, MacGregor TR, et al. The effect of tipranavir/ritonavir 500/200 mg BID on the pharmacokinetics of clarithromycin in healthy volunteers. Abstract A-457, 44<sup>th</sup> ICAAC 2004, Washington.
8. van Heeswijk RP, Sabo J, MacGregor TR, et al. The effect of tipranavir/ritonavir 500/200 mg BID on the pharmacokinetics of fluconazole in healthy volunteers. Abstract 20, 5<sup>th</sup> Int Worksh Clin Pharmacol HIV Ther 2004, Rome.
9. van Heeswijk RP, Sabo J, Cooper C, et al. The pharmacokinetic interactions between tipranavir/ritonavir 500/200 mg BID and atorvastatin, antacid, and CYP3A4 in healthy adult volunteers. Abstract 5.2, 5<sup>th</sup> Int Worksh Clin Pharmacol HIV Ther 2004, Rome.

10. van Heeswijk RP, Sabo J, MacGregor TR, et al. The pharmacokinetic interaction between single-dose rifabutin and steady-state tipranavir/ritonavir 500/200 mg BID in healthy volunteers. Abstract A-456, 44<sup>th</sup> ICAAC 2004, Washington.
11. Leen C. Pharmacokinetics of indinavir when co-administered with tipranavir/ritonavir. Abstract P299, 7<sup>th</sup> Int Congr Drug Ther HIV Inf 2004, Glasgow.
12. Goebel FD, Sabo JP, MacGregor TR et al. Pharmacokinetic Drug Interaction Screen of Three Doses of Tipranavir/Ritonavir (TPV/r) in HIV-Infected Patients on Stable Highly Active Antiretroviral Therapy (HAART), HIV DART. 2002, Naples.
13. Sabo JP, Elgadi M, Wruck J et al. The pharmacokinetic interaction between atazanavir/ritonavir and steady-state tipranavir/ritonavir in healthy volunteers. Abstract 41, 7<sup>th</sup> Int Worksh Clin Pharmacol HIV Ther 2005, Lissabon.





## Index

## 3

3TC .....	94, 99, 384
drug profile .....	706
interactions .....	767
resistance .....	346

## A

Abacavir .....	94, 95, 208, 385
drug profile .....	707
HSR .....	289
interactions .....	768
resistance .....	346
ABC .....	see Abacavir
Acanthamoeba sp .....	539
ACH-126,433 .....	132
Acute HIV infection .....	33
Acyclovir .....	440, 443
drug profile .....	709
Adefovir .....	133
Adherence .....	177
Adipositas .....	303
AG1549 .....	137
AG1776 .....	139
AG1859 .....	139
Agenerase .....	see Amprenavir
AIDP .....	655
AIDS .....	27
Kaposi's sarcoma .....	481
malignant lymphomas .....	491
opportunistic infections .....	395
pediatric .....	375
AK-602 .....	146
Albendazole .....	477
Allergy .....	289
Alovudin .....	133
ALT .....	274
Ambisome .....	see Amphotericin B
AMD 070 .....	146
AMD 3100 .....	149
Amisulpirid .....	675
Amitriptyline .....	671
Amoxicillin .....	452
Amphetamine .....	203
Amphotericin B . 457, 471, 473, 475, 478	
drug profile .....	709
Amprenavir .....	94, 116, 387
drug profile .....	711

resistance .....	348
Anemia .....	202, 288
Antidepressants, tricyclic .....	671
Antimony compounds .....	475
Antipsychotic agents .....	674
Aphthous ulcers .....	591
Aplaviroc .....	144
APOBEC3G .....	65
Aptivus .....	see Tipranavir
APV .....	see Amprenavir
Arrhythmias, cardiac .....	623
Arteriosclerosis .....	625
Aspergillosis .....	471
Assisted reproduction .....	690
AST .....	274
Atazanavir ... 94, 116, 122, 241, 283, 387	
drug profile .....	712
interactions .....	768
resistance .....	348
Ateviridine .....	136
Atorvastatin .....	310
Atovaquone .....	400
drug profile .....	713
Attachment inhibitors .....	141
ATV .....	see Atazanavir
Avascular necrosis .....	292
Azithromycin .....	437, 536
drug profile .....	714
AZT .....	94, 96, 384
drug profile .....	715
interactions .....	772
resistance .....	346

## B

Babesia sp .....	538
Bacillary angiomatosis .....	472
Balamuthia mandrillaris .....	539
B-cells .....	74
Bezafibrat .....	310
Bilirubin .....	274
Biperidene .....	676
BIRL 355 BS .....	136
Blips .....	164
Blood count .....	274
BMI .....	309
BMS 488,043 .....	142
BMS 806 .....	149
Boosting .....	120
Brecanavir .....	139

Burkitt's lymphoma ..... 498

## C

Caelyx ..... see Doxorubicin  
 Calanolide A ..... 136  
 Calcium channel blockers ..... 633  
 Camptothecin ..... 447  
 Candidiasis ..... 418  
 Cannabinoids ..... 157  
 Capravirine ..... 137  
 Capreomycin ..... 428  
 Carbamazepine ..... 444  
 Caspofungin ..... 419, 471  
 Castleman's disease ..... 508  
 CBV ..... see Combivir  
 CCR5 ..... 67, 143  
 CD4 receptor ..... 66  
 CD4+ T-Cells ..... 271  
 Cefpodoxim ..... 452  
 Ceftriaxon ..... 452  
 Cefuroxim ..... 452  
 Cell culture ..... 51  
 Centers for Disease Control ..... 23  
 Chancroid ..... 616  
 Chemokine receptor ..... 67  
 Chemokines ..... 68  
 Chlamydia Infection ..... 615  
 Chloroquine ..... 535  
 CHOP ..... 494  
 Ciclosporin A ..... 156  
 Cidofovir ..... 414, 447  
   drug profile ..... 717  
 CIDP ..... 657  
 Ciprofloxacin ..... 428, 460, 474, 479, 536  
 Citalopram ..... 670  
 Clarithromycin ..... 437, 452  
   drug profile ..... 718  
 Clindamycin ..... 407  
   drug profile ..... 719  
 Clomethiazole ..... 676  
 Clomipramine ..... 671  
 Clozapine ..... 675  
 CMV  
   renal insufficiency ..... 581  
   retinitis ..... 412  
 CMV encephalitis ..... 650  
 CNS lymphoma ..... 503  
 Coactinon ..... 136  
 Coccidioidomycosis ..... 474  
 Combivir  
   drug profile ..... 719  
 Condylomata acuminata ..... 617

Coreceptor antagonists ..... 143  
 Coronary heart disease ..... 619  
 Corticosteroids ..... 157  
 Cotrimoxazole ..... 400, 474  
   drug profile ..... 720  
 Crixivan ..... see Indinavir  
 Cryptococcosis ..... 456, 650  
 Cryptosporidiosis ..... 453  
 CXCR4 ..... 68, 143  
 Cycloserine ..... 426  
 Cymeven ..... see Ganciclovir  
 Cytidine analog ..... 95  
 Cytomegalovirus ..... see CMV  
 Cytotoxic T-cells ..... 78

## D

d4T ..... 94, 98, 385  
   drug profile ..... 721  
   interactions ..... 774  
   lactic acidosis ..... 291  
   prolonged release capsule ..... 131  
   replacement ..... 225  
   resistance ..... 346  
 Dapivirine ..... 137  
 Dapsone  
   drug profile ..... 722  
 Daraprim ..... see Pyrimethamine  
 Darunavir ..... 122, 138  
   drug profile ..... 722  
   interactions ..... 775  
 Daunorubicin ..... 485  
   drug profile ..... 723  
 DaunoXome ..... see Daunorubicin  
 DC-SIGN ..... 75  
 ddC ..... 94, 97  
   drug profile ..... 724  
 ddI ..... 94, 97, 385  
   drug profile ..... 725  
   interactions ..... 777  
   lactic acidosis ..... 291  
   resistance ..... 346  
 D-drugs ..... 320  
 Delavirdine ..... 94, 112, 289  
   drug profile ..... 726  
   resistance ..... 347  
 Delusions ..... 673  
 Dendritic cells ..... 74  
 Depression ..... 286, 667  
 Dermatology ..... 585  
 DEXA ..... 307  
 Dexelvucitabine ..... 133  
 DFC ..... 133

Diabetes mellitus .....	202, 302
Diarrhea .....	202, 280
Diazepam .....	676
Didanosine .....	see ddI
Diflucan .....	see Fluconazole
DILS .....	657
Dioxolanthymidine (DOT) .....	133
Discordant response .....	167
Dizziness .....	286
DLV .....	see Delavirdine
DMP-450 .....	139
Docitaxel .....	486
dOTC .....	133
Doxepin .....	671
Doxorubicin .....	485
drug profile .....	727
Doxycycline .....	535
DPC 083 .....	136
DPC 681 .....	139
DPC 684 .....	139
DPC 961 .....	136
Dronabinol .....	469
Drug interactions .....	388, 767
DSSP .....	657

## E

Ecstasy .....	203
Efavirenz .....	94, 111, 207, 385
drug profile .....	728
interactions .....	778
resistance .....	347
Effusion, pericardial .....	623
EFV .....	see Efavirenz
ELISA .....	43
Elvucitabine .....	132
Emivirine .....	136
Emtricitabine .....	94, 99, 385
drug profile .....	730
interactions .....	782
resistance .....	346
Emtriva .....	see Emtricitabine
Endocarditis .....	625
Endothelin receptor antagonists .....	634
Enfuvirtide .....	see T-20
Entry inhibitors .....	126, 140
env .....	62
Epivir .....	see 3TC
Eradication .....	174
Erypo .....	see Erythropoietin
Erythromycin .....	472, 479
Erythropoietin .....	
drug profile .....	731

Escape mutant .....	79
Ethambutol .....	426, 437
drug profile .....	731
Etravirine .....	135
Examination .....	
dermatological .....	587
general .....	517
gynecological .....	274
Exanthema, acute .....	591

## F

FABP .....	305
Famciclovir .....	444
Fanconi's syndrome .....	576
FddA .....	133
Fertility disorders .....	691
FFA .....	302
Fibric acid analogues .....	312
Filgrastim .....	see G-CSF
FLT .....	133
Fluconazole .....	419, 457, 475
drug profile .....	733
Flucytosine .....	457
Fluoxetine .....	670
Fluvastatin .....	310
Fluvoxamine .....	670
Folliculitis, acne-like .....	591
Fomivirsen .....	414
Fosamprenavir .....	94, 117, 122, 242
drug profile .....	734
resistance .....	348
Foscarnet .....	414
drug profile .....	735
Foscavir .....	see Foscarnet
FP-21399 .....	148
FPV .....	see Fosamprenavir
FSGN .....	573
FTC .....	see Emtricitabine
Fumagillin .....	477
Fundoscopy .....	274
Fusion inhibitors .....	148
Fuzeon .....	see T-20

## G

Gabapentin .....	444
gag .....	62
Ganciclovir .....	
drug profile .....	736
GB virus C .....	565
GBV-C Infection .....	565
G-CSF .....	156

drug profile .....	737
Gemfibrozil.....	310
Genetic polymorphism.....	70
Genital warts.....	592
Genotyping .....	332
GHB.....	203
Giga-HAART .....	243
Glomerulonephritis.....	571
post-infectious.....	573
Glucantime.....	475
Glucose .....	274
Glucose tolerance.....	302
GLUT-4 inhibition.....	306
GM-CSF .....	156
Gonorrhea.....	613
gp120 .....	68
Granocyte .....	see G-CSF
Growth hormone.....	310, 469
GS 4338.....	139
GS 7340.....	133
GS 9005.....	139
Guanosine analog.....	95
Guillain-Barré syndrome .....	655
GW420867X.....	136
GW5634 .....	136
GW640385X.....	139
GW8248 .....	136

## H

HAART .....	87
change.....	224, 231
dermatology .....	589
guidelines.....	184, 381
initial regimens .....	199
long-term toxicity .....	225
lymphoma .....	497
principles.....	162
recycling .....	245
renal insufficiency.....	578
side effects .....	224
start .....	184, 199
stop.....	253
Hairy leukoplakia.....	596
Hallucinations.....	673
Haloperidol.....	676
HBV.....	see Hepatitis B infection
HBV-097 .....	136
HCV.....	see Hepatitis C infection
HDL.....	302
Heart disease	
coronary .....	619
valvular .....	624

Heart failure	
congestive .....	621
Hemophilia .....	293
Hepatitis B .....	202, 554
Hepatitis C .....	202, 541
Hepatotoxicity.....	281
Herpes simplex .....	440
renal insufficiency.....	581
Herpes zoster .....	443
Histoplasmosis.....	473
HIV	
acute infection.....	33
HIV-AN .....	572
Hivid.....	see ddC
HLA B57 .....	78
HLA system.....	77
HMG-CoA reductase inhibitors .....	312
Hodgkin's disease .....	506
HPV .....	617
Hu5A8 .....	142
Hydroxyurea .....	154
Hypercholesterolemia .....	302
Hyperinsulinemia.....	303
Hyperlipidemia .....	303
Hypertension.....	202
pulmonary .....	629
Hypertriglyceridemia.....	302

## I

IDV .....	see Indinavir
Imipramine.....	671
Immune reconstitution syndrome.....	462
Immunotherapy.....	152
Indinavir.....	117, 122, 242, 283, 294, 387
boosted.....	121
drug profile .....	738
interactions.....	787
resistance.....	348
Infarction .....	see Myocardial infarction
Inosine analog.....	95
Insomnia .....	286
Insulin resistance.....	302
Integrase inhibitors .....	149
Interactions .....	see Drug interactions
Interferon .....	155, 484, 550
drug profile .....	739
Interleukin-12 .....	157
Interleukin-15 .....	158
Interleukin-2 .....	152
drug profile .....	740
Intron A.....	see Interferon
Invirase .....	see Saquinavir

Isoniazid .....	426
drug profile .....	741
Isosporiosis .....	474
Itraconazole .....	419, 471, 473, 478
drug profile .....	742

## J

JE-2147 .....	139
---------------	-----

## K

Kaletra .....	see Lopinavir
Kaposi's sarcoma .....	481
KIR receptor .....	78
Kivexa .....	94
drug profile .....	743
Klacid .....	see Clarithromycin
KNI-272 .....	139
KP-1461 .....	132
KRH-3140 .....	146
KRH-3955 .....	146
KS .....	see Kaposi's sarcoma
Kynostatin .....	139

## L

Lactic acidosis .....	98, 290, 318
Lamivudine .....	see 3TC
LDH .....	274
Leishmaniasis .....	475, 537
Lenograstim .....	see G-CSF
Leukoencephalopathy	
progressive multifocal .....	446
Leukopenia .....	288
Lexiva .....	see Fosamprenavir
Linezolid .....	426
Lipase .....	274
Lipodystrophy syndrome .....	301
Lobucavir .....	133
Lodenosine .....	133
Lopinavir <sup>94</sup> , 118, 122, 130, 205, 239,	
241, 386	
drug profile .....	744
interactions .....	791
resistance .....	348
Lorazepam .....	676
Loviride .....	136
LPV .....	see Lopinavir
LTNP .....	78
Lymphoma .....	491
cutaneous, malignant .....	594
Hodgkin's disease .....	506

plasmablastic .....	498
primary CNS .....	503
primary effusion .....	499

## M

Macrophage .....	74
Malaria .....	536
prophylaxis .....	535
Malarone .....	535
Malignant lymphoma .....	see Lymphoma
Maraviroc .....	145
Marijuana .....	203
Maturation inhibitors .....	150
Mavid .....	see Clarithromycin
MCD .....	508
Measles .....	537
Mefloquine .....	535
Mega-HAART .....	243
Megestrol acetate .....	469
Meglumin antimonate .....	475
Membrane fusion .....	71
Metformin .....	310
Micafungin .....	419
Microsporidiosis .....	476
Miltefosine .....	476
MIP-1 $\beta$ .....	68
MIP-1 $\alpha$ .....	68
Mirtazapine .....	672
Mitochondrial DNA .....	317
Mitochondrial DNA polymerase $\gamma$ .....	305
Mitochondrial myopathy .....	320
Mitochondrial toxicity .....	317
MIV-150 .....	136
MIV-210 .....	133
MKC-442 .....	136
Molluscum contagiosum .....	595
Monitoring .....	267
Mother-to-child transmission .....	53
Moxifloxacin .....	426, 452
Mozenavir .....	139
mtDNA depletion .....	305
Multicentric Castleman's disease .....	508
Murabutide .....	157
Mycobacteriosis, atypical .....	436
Mycobacterium avium complex .....	436
Mycobutin .....	see Rifabutin
Mycophenol .....	157
Mycoses, endemic .....	538
Myocardial infarction .....	202, 303, 619
Myocarditis .....	625
Myopathy .....	663

**N**

NASBA.....	52
Natural killer cell.....	75
Nausea.....	280
Necrosis, avascular.....	292
Needlestick injury.....	54
nef.....	64
Nelfinavir..... 94, 118, 130, 206, 386	
drug profile.....	745
interactions.....	797
resistance.....	348
Nephrolithiasis.....	284
Nephropathy.....	572
Indinavir.....	575
Nephrotoxicity.....	285
Neupogen.....	see G-CSF
Neuroleues.....	650
Nevirapine... 94, 110, 207, 282, 289, 386	
drug profile.....	746
interactions.....	800
resistance.....	347
NFV.....	see Nelfinavir
NFκB.....	73
Nicavir.....	132
Nightmares.....	111, 286
Nitazoxanide.....	453
NNRTI..... 94, 108	
NNRTI hypersusceptibility.....	244
Nocardiosis.....	477
Non-Hodgkin lymphoma.....	
.....	see Lymphoma
Noradrenalin reuptake inhibitor.....	672
Norvir.....	see Ritonavir see Ritonavir
NRTI.....	94, 95
Nuke backbone.....	100
Nuke sparing.....	212
NVP.....	see Nevirapine

**O**

Occupational exposure.....	54
OHL.....	596
Olanzapine.....	675
Once-daily.....	210
Opportunistic infections.....	395
Oral Hairy leukoplakia.....	596
Osteopenia.....	292
Osteoporosis.....	292
Oxymetholone.....	469

**P**

p24 antigen.....	51
PA-457.....	150
Paclitaxel.....	485
Pancreatitis.....	202, 284
Parenthood, wish for.....	687
Paromomycin.....	454
Paronychia.....	597
Paroxetine.....	670
Pathogenesis.....	61
PBS.....	72
PCP.....	see Pneumocystis pneumonia
PCR.....	52
Pediatric HIV infection.....	375
Pegasys.....	see Interferon
PegIntron.....	see Interferon
PEL.....	499
Pellet implantation.....	414
Pentacarinat.....	see Pentamidine
Pentamidine.....	400
drug profile.....	748
Pentostam.....	475
PEP.....	see Post-exposure prophylaxis
Peripheral neuropathy.....	27
Phenotyping.....	331
Phosphazide.....	132
Phosphodiesterase-5 inhibitor.....	635
Pioglitazone.....	310
Piperacillin.....	452
Plasmablastic lymphomas.....	498
PML.....	see Leukoencephalopathy
Pneumococcal polysaccharide.....	452
Pneumocystis pneumonia.....	398
renal insufficiency.....	579
Pneumonia.....	
bacterial.....	450
PCP.....	398
PNU-142721.....	136
pol.....	62
Polyneuropathy.....	202, 287, 655
Polyradiculopathy.....	655
Post-exposure prophylaxis.....	55, 697
PPARγ.....	307
Pravastatin.....	310
Pregnancy.....	357
Prevention.....	176
Prezista.....	see Darunavir
Primary effusion lymphoma.....	499
Pro-140.....	146
Pro-542.....	141
Proleukin.....	see Interleukin-2
Prostacyclin.....	633
Prostanoids.....	634

Protease inhibitor ..... 94, 115, 138  
     double PIs ..... 241  
 Proteinuria ..... 571  
 Prothionamide ..... 428  
 Proviral cDNA ..... 51  
 Pruritus ..... 596  
 Psoriasis ..... 597  
 Psychiatric disorders ..... 667  
 Psychiatric emergency ..... 676  
 Psychosis ..... 202, 673  
 Psychotherapy ..... 668  
 Pulmonary diseases ..... 639  
 Pulmonary hypertension ..... 629  
 Pyrazinamide ..... 426  
 Pyridoxine ..... 426  
 Pyrimethamine ..... 407  
     drug profile ..... 749

## Q

Quetiapin ..... 675

## R

Racivir ..... 132  
 Rash ..... 111  
 Rebetol ..... see Ribavirin  
 Reboxetine ..... 672  
 Reiter's syndrome ..... 598  
 Renal function ..... 571  
 Reproduction, assisted ..... 690  
 Rescriptor ..... see Delavirdine  
 Resistance  
     mechanism ..... 334  
     profiles ..... 336  
 Resistance testing ..... 331  
 Retrovir ..... see AZT  
 rev ..... 63  
 Reverset ..... 133  
 Reyataz ..... see Atazanavir  
 Rhodococcus equi ..... 478  
 Ribavirin ..... 550  
     drug profile ..... 750  
 Rifabutin ..... 437  
     drug profile ..... 752  
 Rifampin ..... 426, 479  
     drug profile ..... 753  
 Rilpivirine ..... 135  
 Risperidone ..... 675  
 Ritonavir ..... 94, 119, 205, 387  
     drug profile ..... 754  
 Rituximab ..... 495  
 RO033-4649 ..... 139

Roferon ..... see Interferon  
 Rosiglitazone ..... 310  
 Roxithromycin ..... 452  
 RTV ..... see Ritonavir

## S

Salmonella septicemia ..... 460  
 Salvage therapy ..... 238  
 Saquinavir ..... 94, 119, 122, 241, 387  
     boosted ..... 121  
     drug profile ..... 756  
     interactions ..... 804  
     resistance ..... 348  
 SC-52151 ..... 139  
 SC-55389A ..... 139  
 Scabies ..... 599  
 Sch-417690 ..... 145  
 SCH-C ..... 149  
 SCH-D ..... 145  
 Schizophrenia ..... 673  
 SDF-1 ..... 68  
 Seborrheic dermatitis ..... 599  
 Sempera ..... see Itraconazole  
 Sensitivity ..... 48  
 Serotonin-reuptake inhibitors ..... 669  
 Sertraline ..... 670  
 Sexually transmitted diseases ..... 538, 611  
 Shingles ..... 594  
 Side effects ..... 279  
 Skin diseases ..... 585  
 Sleep withdrawal ..... 673  
 SM-309515 ..... 139  
 Smoking ..... 303  
 SPD-754 ..... 131  
 SPD-756 ..... 133  
 Specificity ..... 48  
 Sperm washing ..... 688  
 SREBP-1c ..... 307  
 SSRI ..... 669  
 Stampidine ..... 132  
 Stavudine ..... see d4T  
 STD ..... 611  
 Stem cell transplantation ..... 499  
 Stocrin ..... see Efavirenz  
 Streptomycin ..... 426  
 Strongyloides stercoralis ..... 538  
 Substance abuse ..... 202  
 Sulfadiazine ..... 407, 478  
     drug profile ..... 757  
 Sustiva ..... see Efavirenz  
 Syphilis ..... 600, 611

## T

T-1249 .....	149
T-20 .....	68, 94, 127, 293, 387
drug profile .....	758
resistance .....	349
T-649 .....	148
TAK-220 .....	149
TAK-652 .....	146
TAK-779 .....	149
TAR .....	73
tat 63 .....	
TDF .....	see Tenofovir
TDM .....	see Therapeutic drug monitoring
Telzir .....	see Fosamprenavir
Tenofovir .....	94, 100, 209, 385
drug profile .....	759
interactions .....	809
nephrotoxicity .....	576
resistance .....	346
switch .....	227
Test performance .....	47
Testing .....	41
Testosterone .....	469
T <sub>H</sub> 1 cell .....	75, 80
Thalidomide .....	477
THC .....	469
Therapeutic drug monitoring .....	275
Therapy .....	see HAART
Tinea .....	593
Tipranavir .....	120, 122
drug profile .....	761
interactions .....	811
Tissue plasminogen activator .....	303
TMC 114 .....	138
TMC 120 .....	137
TMC 125 .....	135
TMC 126 .....	139
TMC 278 .....	135
TNF $\alpha$ .....	73
TNX 355 .....	142
Toxoplasmosis .....	406, 650
renal insufficiency .....	580
TR-290999 .....	148
TR-291144 .....	148
Transmission .....	
mother-to-child .....	53
perinatal .....	375
resistant strains .....	335
Traveling .....	533
Treatment .....	see HAART
costs .....	175
failure .....	162, 228
success .....	162

Treatment interruptions .....	253
Tricyclic antidepressants .....	671
TRIM5 $\alpha$ .....	71
Triple nuke .....	208
Trizivir .....	96
drug profile .....	762
Truvada .....	94
drug profile .....	763
Trypanosoma cruzi .....	479, 538
Tuberculosis .....	422, 537
TZV .....	see Trizivir

## U

UK-201844 .....	150
UK-427,857 .....	145
Ulcus molle .....	see Chancoid
Ultreon .....	see Azithromycin
Uridine .....	323

## V

Vaccinations .....	519
children .....	520
Valacyclovir .....	444
Valcyte .....	see Valganciclovir
Valganciclovir .....	413
drug profile .....	764
Vancomycin .....	479
Vasculitic neuropathy .....	657
Vasculitis .....	625
Venlafaxine .....	672
Vfend .....	see Voriconazole
Vicriviroc .....	145
Videx .....	see ddI
vif .....	64
Viracept .....	see Nelfinavir
Viral load .....	36, 42, 52, 162, 184, 225, 253, 267
Viramune .....	see Nevirapin
Viread .....	see Tenofovir
Vistide .....	see Cidofovir
Vitrasert .....	414
VLDL .....	303
Vomiting .....	280
Voriconazole .....	471
drug profile .....	765
vpr .....	64
vpu .....	64
VX-385 .....	139
VZV .....	see Herpes zoster
renal insufficiency .....	581
VZV encephalitis .....	650



**W**

Wasting syndrome ..... 468  
 Wellvone.....see Atovaquone  
 Western blot..... 45

**X**

Xerosis..... 601

**Z**

Zalcitabin ..... see ddC  
 Zeffix ..... see 3TC  
 Zerit ..... see d4T  
 Ziagen ..... see Abacavir  
 Zidovudin..... see AZT  
 Ziprasidone ..... 676  
 Zithromax ..... see Azithromycin  
 Zovirax..... see Acyclovir



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When should HAART be started? How can a failing drug regimen be improved? Which drugs are to be expected over the next years? What are the options for patients with lipodystrophy syndrome? How risky are interruptions of treatment?

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