Antiretroviral therapy in previously untreated adults infected with the human immunodeficiency virus type 1: established and potential determinants of virological outcome

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ABSTRACT

The aim of highly active antiretroviral therapy (HAART) for patients chronically infected with the human immunodeficiency virus type 1 is to achieve maximal and durable viral suppression. Maintaining the blood plasma HIV-1-RNA concentration (pVL) <50 copies/ml is currently considered appropriate for this goal. With the current treatment options, the percentage of previously untreated patients who achieve a pVL <50 copies/ml after one year of initial HAART is about 70%. Characteristics of the host, virus, drugs and the treatment team have been associated with the virological response to initial HAART. Adjusting the initial HAART regimen and patient management to a risk profile based on these factors is possibly helpful in improving the virological response to HAART. Adherence to a potent and well-tolerated HAART regimen is likely to be the most relevant factor for virological success. The additive value of the other factors needs to be clarified.

INTRODUCTION

The standard antiretroviral therapy (ART) first given to individuals infected with the human immunodeficiency virus type 1 (HIV-1) is highly active antiretroviral therapy (HAART). HAART is not well defined and is considered to consist of a combination of at least three selected antiretroviral drugs with good tolerability and efficacy. The primary aim of initial ART is to achieve a maximal and durable viral suppression. Maintaining the blood plasma HIV-1-RNA concentration (plasma viral load, pVL) below a detection limit of 50 copies/ml is currently recommended to achieve this goal,1-3 because it is associated with less virological failure than a level above 50 copies/ml and it may possibly prevent the emergence of drug resistance despite ongoing low-level (residual) viral replication.6-12 If virological failure to the initial HAART regimen occurs, subsequent therapy is usually less effective due to accumulation of drug-resistance-associated mutations and cross-resistance amongst antiretroviral agents within the same class and generally the subsequent therapy is also more of a burden for the patient.11,13-21 A good initial HAART regimen is therefore of great importance.

The aim of this review is to stress the importance of maximal and durable viral suppression, give an overview and update of the virological response to initial HAART and give insight into which factors have been associated with the virological response to initial HAART. Considering these factors could be of help in identifying patients with high and low risk for virological failure, and choosing an initial HAART regimen and the most appropriate moment to start therapy. To provide a better insight for physicians who are not familiar with antiretroviral therapy, a brief
historical overview and global perspective of ART is given. For this review PubMed and the Cochrane Library were searched. The search terms were “antiretroviral therapy”, “highly active antiretroviral therapy”, “HIV”, “subtype”, “clade”, “HIV type 2”, “pharmacogenetics” and “review”. A criterion for selection was those articles which involved initial HAART. Also the reference list of articles selected in this way was screened and specific articles were added by the authors if they were not identified by the search strategy.

**ANTIRETROVIRAL THERAPY IN HISTORICAL AND GLOBAL PERSPECTIVE**

In June 1981, the world first became aware of the acquired immunodeficiency syndrome (AIDS). Major scientific breakthroughs achieved during subsequent years are summarised in table 1 and in table 2 an overview is given of the antiretroviral drugs and their date of licensing by the USA Food and Drug Administration (FDA). Now, in the year 2004, HIV can still not be cured with the available HAART regimens and there is still no preventive vaccine available.

In countries where HAART could be widely applied, the HIV-1-related morbidity and mortality has decreased tremendously since its introduction in 1996 and the treatment has appeared to be cost-effective. Basis for clinical improvement is a lasting adequate virological suppression which leads to immunological recovery. However, HAART is available to only a minority of the HIV-infected population and knowledge of its efficacy is based mainly on HIV-1 subtype M (major) subtype B. According to estimates of December 2003 about 40 million adults and children throughout the world are infected with HIV, of whom less than 2 million (<5%; those living in high-income countries) have access to HAART. In the year 2000 it was estimated that HIV-1 subtype B accounted for only 12% of new HIV-1 infections.

Thus, in contrast to current advances one must be aware that HAART is scarcely available in countries with limited resources, and that in these countries other HIV-1 subtypes are more prevalent. This may have therapeutic consequences, such as susceptibility to antiretroviral drugs, response to HAART, and rate and pattern of the emergence of drug resistance.

**WHAT IS THE VIROLOGICAL RESPONSE TO CURRENT HAART?**

A HAART regimen is currently considered adequate when after three to six months a pVL of <50 copies/ml is achieved and this level of viral suppression is maintained. In case of a baseline pVL >1,000,000 copies/ml it may take longer than six months to reach the concentration of <50 copies/ml. In table 3 an overview is given of the virological response rates reported in published prospective studies in chronic ART in previously untreated HIV type 1-infected adults.

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**Table 1**

**Historical overview of antiretroviral therapy**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event Description</th>
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<tbody>
<tr>
<td>1981</td>
<td>Recognition of first AIDS cases</td>
</tr>
<tr>
<td>1983</td>
<td>Identification of HIV-1 as the cause of AIDS; description of first AIDS cases in the Netherlands</td>
</tr>
<tr>
<td>1985</td>
<td>FDA approval of first commercial blood screening test</td>
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<tr>
<td>1986</td>
<td>Identification of HIV-1</td>
</tr>
<tr>
<td>1987</td>
<td>Introduction of antiretroviral therapy: zidovudine</td>
</tr>
<tr>
<td>1994</td>
<td>Reduction of HIV-1 transmission from mother to child</td>
</tr>
<tr>
<td>1995</td>
<td>Availability of standardised (commercial) HIV-1 RNA assay, which gave better understanding of HIV-1 viral dynamics</td>
</tr>
<tr>
<td>1996</td>
<td>Release of first protease inhibitors and introduction of HAART</td>
</tr>
<tr>
<td>1997</td>
<td>Ritonavir-induced pharmacokinetic enhancement of other PIs, which made twice-daily dosing of many PIs possible; Recognition of a long-lived HIV cellular reservoir</td>
</tr>
<tr>
<td>1998</td>
<td>After induction therapy maintenance with two NRTIs or one or two PIs or one NRTI and one PI is insufficient; Recognition of strong improvement of survival in HAART era</td>
</tr>
<tr>
<td>1999</td>
<td>A high degree of drug adherence is needed to achieve a proper viral suppression; Demonstration of residual replication during HAART, which made clear that treatment with the current kind of HAART would be for life</td>
</tr>
<tr>
<td>2000</td>
<td>HAART can be relatively safely deferred until the CD4 count is nearing 200 cell/mm³</td>
</tr>
<tr>
<td>2001</td>
<td>Current guidelines to initiate HAART in HIV-1 infected adolescents and adults</td>
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</table>

AIDS = acquired immunodeficiency syndrome, FDA = USA Food and Drug Administration, HAART = highly active antiretroviral therapy, HIV = human immunodeficiency virus, NRTI = nucleoside analogue reverse transcriptase inhibitor, PI = protease inhibitor.
HIV-1-infected, previously untreated adults and adolescents. The HAART regimens mostly used and studied are those of two nucleoside-analogue reverse transcriptase inhibitors (NRTIs) with either a (boosted) protease inhibitor (PI) or non-nucleoside reverse transcriptase inhibitor (NNRTI) or a third NRTI. As will be discussed later, the latter type of regimen is nowadays considered insufficient for initial ART. Table 3 demonstrates that the studies with initial HAART are very heterogenous. This table and others show that according to an ‘intent-to-treat’ analysis between 20% and 88% of patients achieve a pVL of <50 copies/ml at 48 weeks of therapy or later with an average of 50%. This may be about 70% with once-daily-dosed regimens and regimens with a low pill burden. The ‘intent-to-treat’ analysis gives insight into the overall success of a certain HAART regimen.

It should be considered that in general clinical practice, the virological response rate to the first HAART regimen could be less than in prospective, randomised studies. Also, as the knowledge and treatment possibilities evolves and patient management and therapy have improved (tables 1 and 2) there is a historical bias in the effectiveness figures of HAART regimens. One study showed that between 1996 and 1998 the rate of virological failure after one year of therapy decreased from about 50% to about 15% in an unselected population of an open clinic, but hereafter did not decrease further. This decrease in virological failure could be related to increased experience and the introduction of boosting of PIs with low-dose ritonavir which resulted in a reduction of the dosing frequency and pill burden and an increase in plasma drug levels of PIs (tables 1 and 2).
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<th>REF</th>
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<th>BASELINE VL</th>
<th>OT</th>
<th>ITT</th>
<th>% VL &lt;50 C/ML +ACD4</th>
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<td>184</td>
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<td>CBV/EFV</td>
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<td>5.22 log</td>
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<td>2NRTIs/IDV/RTV</td>
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<td>40 (&lt;80 c)</td>
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<td>&gt;100,000</td>
<td>38 (&lt;80 c)</td>
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**Remarks:**
- VL: bDNA
- Different doses LPV-r
- Follow-up
- SQV/RTV 400/400 b.i.d.
- VL: bDNA
- VL: NASBA
- IDV/RTV 800/100 mg b.i.d.
Table 3 continued

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<th>REF</th>
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<th>FU</th>
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<th>N</th>
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<th>ITT</th>
<th>% VL &lt;50 C/ML</th>
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REF = reference. FU = follow-up period in weeks (w) or months (m). N = number of patients included. CD4 = CD4+ cell count, preferentially the median. VL = viral load = blood plasma [HIV-1 RNA] copies/ml in log10 or linear count, preferentially the median. % VL <50 c/ml = Percentage with viral load <50 c/ml with reverse transcriptase PCR from Roche Pharmaceuticals. Between brackets VL is indicated if other limit of detection is used. OT = on treatment. ITT = intention to treat. +AD4 = increase of CD4+ T-cell count from baseline. ns = not stated. *= other HIV-1 RNA assay, see remarks.

ABV = abacavir 300 mg b.i.d. AZT=3 = zidovudine 300 mg t.i.d. AZT=2 = AZT 300 mg b.i.d. AZT=200 = AZT 200 mg b.i.d. CBV = combivir (zidovudine/lamivudine 300/150 mg) b.i.d. DDI=2 = didanosine 200 or 125 mg b.i.d. DDI=3 = DDI 400 or 250 mg q.d. D د = stavudine 30 or 40 mg b.i.d. 3TC = lamivudine 150 mg b.i.d. 3TC=5 = 3TC 300 mg q.d. 2-3NRTIs = 2 or 3 nucleoside-analogue reverse transcriptase inhibitors. TZV = trizivir (zidovudine/lamivudine/abacavir 300/150/300 mg) b.i.d. EFV = efavirenz 600 mg q.d. NVP = nevirapine 200 mg b.i.d. NVP+1 = NVP 400 mg q.d. APV=200 = amprenavir 200 mg b.i.d. KLT = Kaletra (lopinavir/ritonavir 400/100 mg) b.i.d. NVP=5 = nevirapine 500 mg t.i.d. NVP=10 = NVP 150 mg t.i.d. LPV-r = lopinavir-ritonavir b.i.d. KIT = Kaletra (lopinavir/ritonavir 400/100 mg) b.i.d. NFV=3 = nelfinavir 750 mg t.i.d. NFV=2 = NFV 1250 mg b.i.d. NFV500 = NFV 500 mg t.i.d. RTV = ritonavir 600 mg b.i.d. SQV = saquinavir.
**Baseline Characteristics That Can Influence Virological Response**

In ART-naive individuals with a chronic HIV-1 infection several factors present at baseline have been associated with the virological response to HAART. These factors can be classified as being related to the host (genetic make-up, adherence), the virus (drug-resistant virus, HIV-1 subtype), the drug, the treatment team or a combination of these. Some factors have been more extensively investigated because they are more easily available, for example the CD4 count, pVL, blood plasma drug levels and patient adherence. The impact of these determinants on virological response is more clear and established. On the other hand, HIV pharmacogenetics, which can elucidate factors at baseline that are associated with proper drug concentrations, toxicity and virological response, is still in its infancy. It will, next, we will describe the factors associated with the virological response to initial HAART starting with the two most extensively investigated factors.

**Low CD4⁺ T lymphocyte cell count**

A low CD4⁺ T lymphocyte cell count (CD4 count) is usually associated with a high pVL. This makes it unclear which of these two is mostly associated with the virological response. Retrospective cohort studies have shown that patients with a baseline CD4 count <200 cells/mm³ have a worse virological response and more progression to HIV-related morbidity than patients with a higher baseline CD4 count. The question is whether this difference in response is due to a difference in biology (host-virus-drug interactions) or in behaviour, for example that patients with a low CD4 count are probably more difficult to treat (initially). Deferring initial HAART until the CD4 count is between 200 and 350 cells/mm³ is associated with a minimally increased risk of AIDS compared with starting at a CD4 count >350 cells/mm³, depending on the pVL, as the risk of AIDS is higher when the pVL is higher. As a result, since 2001 most guidelines advise adolescents and adults with a chronic HIV-1 infection to start HAART when their CD4 count is nearing 200 cells/mm³ in order to postpone possible long-term side effects of HAART, such as lipodystrophy syndrome and cardiovascular diseases.

**High blood plasma viral load**

For ART consisting of two NRTIs and either a (boosted) PI or an NNRTI, there is conflicting evidence from studies as to whether the risk of virological failure is increased or not if the pVL at baseline is high. On theoretical grounds there could be an increased risk of virological failure when the pVL is very high. The virological response after HAART is initiated in ART-naive patients biphasic with a rapid decay of the pVL in the first two weeks and a slower decay thereafter. Given that there is a constant first- and second-phase viral decay rate after initiation of HAART, more time is required to reach the level of <50 copies/ml with a higher baseline pVL, thus increasing the window for early development of drug resistance. It is estimated that per HIV-1 replication cycle one to two base-pair transcriptional errors occur. Thus, there could be an increased risk of an (early) emergence of strains with one or more drug-resistance mutations if the pVL at baseline is high, especially when drugs with a low genetic resistance barrier (drugs for which only one or two specific mutations in the reverse transcriptase or protease gene are needed to cause significant resistance), such as lamivudine, atazanavir, neflinavir and the NNRTIs, are components of a triple-drug regimen.

Adding a fourth active drug in the initial phase of therapy if the pVL is high (e.g., >50,000 copies/ml) is defendable and some guidelines do recommend this strategy. A triple-class, five-drug regimen (three NRTIs, a (boosted) PI and an NNRTI) is more potent than a two-class, three-drug regimen (two NRTIs and a PI), thus giving rise to the question as to what the optimum potency of a HAART regimen should be. However, more drugs implicates more toxicity. An alternative is to use three drugs with a high genetic resistance barrier in the initial phase.

It has now become obvious that when the baseline pVL is high, (certain) convergent regimens consisting of three NRTIs as initial therapy are virologically inferior to divergent regimens consisting of two NRTIs and either a (boosted) PI or NNRTI (table 3). Possibly this inferiority is also the case at low pVL. Some studies, such as a study with tenofovir, lamivudine and abacavir once daily as initial therapy, a study with zidovudine, lamivudine and abacavir, and a study with didanosine, lamivudine and tenofovir were even prematurely aborted because of more virological failure. In one very small study with subjects with sustained control of pVL there was more viral evolution in the lymph nodes with subsequent development of drug resistance mutations in the subjects who were treated with dual or triple NRTIs alone compared with the divergent regimen. What needs to be clarified is whether switching to a triple NRTI regimen during proper virological suppression in the absence of previous suboptimal treatment or resistance is associated with more virological failure or whether these convergent NRTI regimens can still be applied when the baseline pVL is low.

**Early virological response**

It has been demonstrated that the first phase pVL decay rate after initiation of HAART might be predictive for the potency of the regimen and the virological response at two to three months. Similarly a decrease in pVL by 1 log₁₀
at week 4 or a pVL of <500 copies/ml at week 4 or 8 of therapy has been associated with a more favourable virological response at 24 or 48 weeks of therapy.120

Primary infection with drug-resistant virus

Of great concern for virological response to initial HAART is the presence of (archived) drug-resistant virus at baseline.111,112 The prevalence of HIV-1 viruses with one or more RT and/or protease resistance-associated mutations in recently infected individuals has increased in some parts of the world to 20%.111,112,113 In Europe this is about 10%.114,115 Thus, depending on the local prevalence, initial HAART needs to be optimised based on empiricism or on genotypic resistance testing. The International AIDS Society – USA Panel recommends a baseline drug resistance test for an HIV-1 infection that was acquired less than two years previously in areas with a drug resistance prevalence of more than 5%.116

SI and NSI phenotype of the virus

In the early asymptomatic phase of HIV-1 infection nonsyncytium-inducing (NSI) (macrophage or CCR5-tropic) virus variants predominate. In the later course of the infection syncytium-inducing (SI) (T-cell or CXCR4-tropic) variants emerge. This switch in phenotype predominance coincides with a faster progression of the infection.117,118 In vitro, zidovudine preferentially inhibits NSI variants, while didanosine preferentially inhibits SI variants.119,120 For lamivudine and the protease inhibitor ritonavir an equal inhibition of NSI and SI variants was observed.121,122 For the other NRTIs the protease inhibitor ritonavir an equal inhibition of NSI and SI variants was observed.121,122 For the other NRTIs the effect on NSI and SI variants by zidovudine and didanosine is probably due to differences in intracellular phosphorylation to the active triphosphate.123,124 Zidovudine and stavudine are preferentially phosphorylated in activated cells, while didanosine, lamivudine and zalcitabine are preferentially phosphorylated in resting cells.125,126 Activated CD4+ cells express more CCR5 receptors and resting cells express more CXCR4, thus giving a rationale for the divergent inhibition of NSI and SI variants by zidovudine or stavudine and didanosine or lamivudine or zalcitabine, respectively.122,123 This difference in inhibition is probably of no importance when current HAART is applied, but may be relevant for the use of CCR5 blockers.128,129

HIV-1 subtype

Based on genetic divergence in the env, gag and pol region, HIV-1 is phylogenetically divided into an M (major), O (outlier) or N (non-M, non-O or new) subtype or clade.38,39,40 These three subtypes are further subdivided into several subtypes or clades. The O and N subtypes are rare and mainly restricted to West Africa.41 The M subtype accounts for >90% of reported HIV/AIDS cases.39 M subtypes that have been identified until now are A, B, C, D, F, G, H, J, K, AE and other recombinants, called circulating recombinant forms (CRFs).38,39,41 In Europe, the Americas, Australia and New Zealand subtype B is the most prevalent, while the non-B subtypes are mainly prevalent in the other continents. However, due to travel and migration within the Western world these differences in prevalence are changing.42,43-45

Parallel to this, the HIV-1 subtype outlier is naturally resistant to NNRTIs due to different amino acids at RT position 181.46,47 Also, HIV-2 is naturally resistant to the NNRTIs because in the wild-type virus amino acid substitutions associated with drug-resistance mutations in HIV-1 (at position 181, 188 and 190) are already present. Furthermore, there is a faster emergence of the multi-NNRTI-resistance mutation Q151M and a rapid emergence of genotypic drug resistance (D30N) to the PI nelfinavir in HIV-2.38,39,130

Clinical studies with antiretroviral therapy have predominantly been done in populations with the B subtype (table 3). Prospective studies comparing the virological response among HIV-1 subtypes are lacking. Three retrospective studies with a limited number of patients showed no difference in response to HAART between B and non-B subtypes.140-142 Thus, the impact of the different HIV-1 subtypes on the virological response to initial HAART needs to be established.

Trough concentration of PIs and NNRTIs in blood plasma and the intracellular concentration of triphosphorylated NRTIs

Retrospective and prospective studies have shown a correlation between the blood plasma (trough drug concentration between the blood plasma (trough drug concentration between the blood plasma (trough drug concentration and the intracellular concentration of triphosphorylated NRTIs and the virological response.143-147 Minimaly effective drug concentrations have been defined, and nowadays therapeutic drug monitoring, the proactive regular measurement of drug concentrations, is considered a standard during PI and NNRTI treatment in some countries.1,5,141,144-146 Likewise, a positive association was found between the intracellular concentration of triphosphorylated NRTIs and the virological response.149,150

Adherence to therapy

Proper adherence to the dosing interval and administration requirements of the drugs is one of the most important factors for success of HAART. The importance of patient adherence to HAART has been demonstrated in clinical trials.151-153 The most common reasons for suboptimal adherence are pill burden, side effects and compliance problems.154,155 Based on vaccine trials and results from animal models, the use of long-acting depot formulations for antiretrovirals is a promising area.156,157
Experience and knowledge of the treating physician

A better survival was associated with more experience in treating HIV on the part of the physician as well as better adherence to therapy by the patient.184 These two factors even outweighed the worse outcome if HAART was started at a CD4 count below 50 cells/mm³.184 Although not evaluated, the improved outcome was probably partly due to a better virological response because of a better instruction and management of the patient by the more experienced physician.

EPILOGUE

The aim of initial HAART is to achieve maximal and durable viral suppression which is currently a pVL of <50 copies/ml. With current knowledge, patient management and treatment possibilities virological success after one year of initial HAART has improved to about 70%. So, there is much room for further improvement and the challenge is how to achieve this. Adjusting therapy to a virological failure risk profile could be a useful strategy. As an example, a patient with a high pVL (e.g. >300,000 copies/ml), a low CD4 count (e.g. <100 cells/mm³) and a low socioeconomic status (e.g. poor housing) could be given a four-drug divergent regimen as initial HAART or a three-drug divergent regimen with a high genetic barrier to resistance, and such a patient should be more intensively monitored.

How the clinical relevance of the several determinants of virological response compare with each other needs to be established. However, likely adherence to a potent and well-tolerated HAART regimen is the most basic and relevant factor for virological success and the other factors probably modulate this response.

SUGGESTIONS FOR FURTHER STUDIES

What needs to be further evaluated is the importance of other factors, what are early markers for long-term virological response, whether switch to a triple NRTI regimen is virologically safe, whether once-daily-dosed regimens have a virological advantage over twice-daily-dosed regimens, how regimens with a low, middle and high genetic resistance barrier compare with each other, how the virological response in non-B subtypes compare with subtype B, and what level of virus suppression is needed to prohibit virological failure. As long as HIV cannot be cured, this last factor will really define what should be considered as HAART. However, improving adherence to therapy is likely to be the most relevant measure to achieve a durable virological success.19

Since the risk of HIV-related morbidity and mortality is
substantially increased as long as the CD4 count is below 200 cells/mm³, strategies to raise the CD4 count more rapidly above this threshold (e.g. type of HAART regimen, interleukin-2) should also be explored. Chronic hyper-activation of the immune system might be an important cause of CD4 cell loss. Considering the toxicity of HAART and the importance of a high level of adherence to HAART, it is also worthwhile to evaluate inhibition of this hyper-activation.

ACKNOWLEDGEMENT

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REFERENCES


75. Van Leth F, Andrews S, Grinsztien B, et al. Virological failure in antiretroviral therapy naive patients is only determined by extreme low values of CD4+ cells or high value of HIV-1 RNA concentration, not by choice of treatment with nevirapine or efavirenz [Abstract 550]. 11th Conference on Retroviruses and Opportunistic Infections; 2004 Feb 8-11; San Francisco, CA, USA.


78. AVANTI study group. AVANTI 2. Randomized, double-blind trial to evaluate the efficacy and safety of stavudine plus lamivudine versus zidovudine plus lamivudine plus indinavir in HIV-infected antiretroviral-naive patients. AIDS 2000;14:167-4.


104. Van Lunzen J, Zöllner B, Stellbrink HJ, et al. How hard is HAART?
Residual viral replication and evolution in lymphoid tissue during sustained control of viremia [Abstract 183]. 10th Conference on Retroviruses and Opportunistic Infections; 2003 Feb 10-14; Boston, Massachusetts, USA.
179. Sankatsing SUC, Beijnen JH, Schinkel AH, Lange JMA, Prins JM. P-glycoprotein in human immunodeficiency virus type 1 infection and therapy. Antimicrob Agents Chemother 2004; Accepted
228. Chun T-W, Engel D, Berrey MM, Shea T, Corey L, Fauci AS. Early establish-
ment of a pool of latently infected, resting CD4+ T cells during primary infection. Proc Natl Acad Sci USA 1997;94:13193-7.


