Highly active antiretroviral therapy for HIV-1 infection: patients’ quality of life and treatment adherence
Nieuwkerk, P.T.

Citation for published version (APA):
Nieuwkerk, P. T. (2006). Highly active antiretroviral therapy for HIV-1 infection: patients' quality of life and treatment adherence

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
Chapter 1

General introduction
General introduction

In the mid-1990’s, the advent of potent combination antiretroviral regimens and advances in the understanding of human immunodeficiency virus type 1 (HIV-1) pathogenesis dramatically changed the management of chronic HIV-1 infection in the Western world. Advances in the treatment of HIV-1 comprised the development of more numerous and more potent inhibitors of viral replication. Two new classes of such antiretroviral drugs were introduced, i.e., the protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs) [1-4]. Furthermore, new nucleoside-analogue reverse transcriptase inhibitors (NRTIs) became available, i.e., lamivudine (3TC) and stavudine (d4T), in addition to the already approved zidovudine (AZT), didanosine (ddl) and zalcitabine (ddC). It was shown that triple combination therapy comprising of one PI and two NRTIs or comprising of one nNRTI plus two NRTIs resulted in potent and durable suppression of plasma HIV RNA concentrations, significant increases in CD4+ T-cell counts, and consequently, a large reduction in the risk of disease progression and mortality [3-7]. Such triple combination therapies are referred to as highly active antiretroviral therapy (HAART) and were introduced on a large scale in clinical practice in the Netherlands as of July 1996.

Simultaneous developments comprised the introduction of assays to quantify the concentration of HIV RNA copies in blood plasma or serum. The value of quantitative plasma HIV RNA concentrations to predict HIV disease progression and mortality was demonstrated, in addition to the importance of CD4+ T-cell counts [8, 9]. Reductions in plasma viral load were found to correlate with increases in CD4+ T-cell counts and AIDS-free survival. The use of viral load testing was also applied to the assessment of response to therapy [10]. The ability to quantify HIV RNA concentrations in plasma enabled research on the replication kinetics of HIV-1 in vivo, revealing a persistent and high replication rate of HIV-1 both during symptomatic- and asymptomatic infection [11, 12]. It was recognized that the high replication rate of HIV-1 and the high mutation rate per replication cycle would lead to a rapid appearance of drug resistant virus, if HIV replication would continue during antiretroviral therapy [13, 14]. Ongoing viral replication during antiviral triple therapy may be due to suboptimal patient adherence to therapy [15]. Given the existence of extensive cross-resistance within the three classes of antiretroviral drugs, patients are left with only a limited number of options for treatment switches once drug resistance has developed. Before the advent of HAART, antiretroviral treatment was predominantly administered to patients with symptomatic HIV infection or AIDS. Recognition of the highly dynamic nature of HIV-1 replication and the availability of HAART prompted consideration of an aggressive, earlier approach to antiretroviral treatment [16]. Mathematical models suggested that HAART could completely block the ability of the virus to replicate and infect new cells, and it was estimated that eradication of HIV could be achieved after two to four years of treatment, thereby adding an argument in favor of early treatment [17].
These developments and insights were quickly translated into new guidelines for the treatment of HIV infection [18, 19]. The goal of antiretroviral therapy became to decrease plasma HIV RNA concentrations to below the lower limit of detection of available assays as long as possible. A combination of three antiretroviral drugs from two separate classes, which would inhibit different steps in the life cycle of HIV, was recommended in treatment guidelines to obtain a durable suppression of viral replication thereby lowering the risk of the development of drug resistance. The development of drug resistance is considered the “Achilles heel” of HAART and the crucial role of adherence to therapy was recognized. Initiation of HAART was recommended for persons with a symptomatic HIV infection or AIDS. HAART initiation was also recommended for persons with an asymptomatic HIV infection with less than 500 CD4+ T-cells/μL or with plasma HIV RNA concentrations greater than 10,000 copies/mL by the Dutch 1996 guidelines for anti-HIV treatment as well as by other international guidelines [18]. Since HAART became standard-of-care in the Western world, the decrease of HIV-1 related morbidity and mortality has been impressive [4, 20, 21]. The focus of care for HIV-infected patients in Western countries shifted from treating opportunistic diseases and in-hospital care to providing antiretroviral treatment and monitoring HIV-infection in an outpatient setting.

In the years following the advent of HAART, limitations of HAART became more evident. It became clear that adverse effects occur frequently and are a major reason for discontinuation or modification of HAART in many patients [22-25]. In addition to short-term adverse effects, prolonged use of HAART was also found to be associated with metabolic abnormalities and an altered bodyfat distribution, which is known as the lipodystrophy syndrome [26, 27]. Moreover, exposure to HAART is associated with an increased risk of myocardial infarction [28]. Another limitation of HAART is the need for high levels of adherence to therapy to prevent resistance. Studies of single PI-containing regimens suggested that less than 95% pill-taking adherence is associated with an increased risk of virologic treatment failure [29]. However, it was also shown that many patients are unable to maintain such high levels of adherence to HAART over a prolonged period of time. HAART was found to result in higher virologic failure rates in clinical practice than in the well-controlled setting of clinical trials [22, 30]. This may be due, in part, by a difference in adherence to treatment between both settings. It also became clear that HAART does not fully halt viral replication and therefore eradication of HIV from an infected person using currently available HAART regimens is not feasible within a reasonable period of time [31, 32]. Therefore, antiretroviral therapy must probably be continued indefinitely.

Most patients infected with HIV are concerned not only about the duration of their survival, but also with their quality of life. Quality of life is generally considered to encompass patients’ physical-, psychological- and social functioning, which can be affected by both the disease and treatment [33]. Before the advent of HAART, it was shown that HIV disease
progression is accompanied with deterioration in quality of life [34, 35]. Therefore, it could be expected that delay of disease progression induced by HAART will be accompanied with improvement in quality of life. However, HAART could also have a negative effect on quality of life. The HAART regimens that became available in 1996 were far from convenient to patients. The daily pill burden of the first HAART regimens was usually large, and required rigid time schedules and for some drugs dietary restrictions. The adverse effects associated with most HAART regimens could also diminish quality of life. In symptomatic HIV infection or AIDS, these potential negative effects of HAART on quality of life are likely outweighed by clinical benefit of HAART. However, in asymptomatic HIV infection, the potential negative impact of HAART on quality of life is not offset by an immediate and appreciable clinical benefit [36]. There was major concern about the extent to which patients would be able to adhere to their HAART regimens. Complexity of treatment and occurrence of adverse effects influence adherence negatively [37]. In addition, non-adherence is generally more prevalent when illness is chronic and the treatment recommendations are largely prophylactic. In studies conducted in various clinical settings, typical adherence rates are about 50% for long term medication regimens [38]. However, for HAART regimens it was anticipated that almost perfect adherence would be required to prevent drug resistance. The first HAART regimens generally comprised of a single PI combined with two NRTIs. For these regimens, adherence is especially critical because of the relatively short plasma elimination half-lives of PIs and the fact that plasma concentrations of several PIs are influenced by the intake of food. Only sufficiently high plasma concentrations of PIs are able to fully suppress viral replication, which is a necessity to prevent emergence of resistant virus [1, 39, 40].

In 1996, the study “Quality of life and treatment compliance in HIV infected patients undergoing anti-HIV treatment” was launched. This study was set up alongside three randomized clinical trials and a cohort study. The National Study Protocol Anti-HIV treatment (NATIVE study) was a standard triple therapy protocol in which patients were randomly allocated to zidovudine/lamivudine, stavudine/didanosine or stavudine/ lamivudine, supplemented with additional treatment of choice comprising one or two PIs. The Prometheus study was a protocol aimed at providing patients with a more convenient treatment option than standard triple therapy [41]. The concept of starting with a simple, potent regimen, which could be intensified if necessary, was compared to starting with more drugs from the beginning. The Amsterdam Duration of Antiretroviral Medication (ADAM) study was an induction-maintenance protocol that was also aimed at providing patients with a more simplified antiretroviral regimen than standard triple therapy [42]. In the ADAM study, patients were randomly assigned to two-drug maintenance therapy or prolonged four-drug induction therapy after 26- or 50 weeks of induction therapy. The National Health Insurance Council provided a grant for a study on the implications of the new antiretroviral treatment for the course of HIV disease, public health and health
care as well as the costs and benefits. This led to the set up of the Antiretroviral Therapy Evaluation NetherAnds (ATHENA) cohort [43]. The study on quality of life and adherence was conducted within the ATHENA 600-group, a subset of 600 participants from the entire ATHENA population in which scientific research was performed.

The general objectives of this thesis are to investigate the effect of HAART on patients’ quality of life and to investigate to what extent patients are able to adhere to their HAART regimens. Results from the study on quality of life in the Prometheus study are presented in Chapter 2. In this study, we compared the impact on quality of life of treatment with ritonavir/saquinavir versus ritonavir/saquinavir/stavudine in asymptomatic- and symptomatic HIV-infected patients who did or did not receive antiretroviral therapy before entry into the study.

Results from the study on quality of life in the ADAM study are presented in Chapter 3. In this study, we compared quality of life in maintenance therapy versus prolonged induction therapy. In Chapter 4, we compared changes in long-term quality of life between patients enrolled in the NATIVE study, the Prometheus study and in the ADAM study. We also compared quality of life between patients who continued and discontinued their antiretroviral regimen.

Adaptation to changing health presents a challenge to measuring change in quality of life. Previous studies have shown that different methods for measuring change yield different results, but it is unclear which method provides a more valid measurement of change. We investigated which of three commonly used methods for measuring change in QoL yielded strongest associations with clinical measures of change in health status. These results are presented in Chapter 5.

Chapter 6 presents the results of the study on treatment adherence in the Prometheus study. We investigated changes in adherence over time, associations between adherence and treatment related symptoms, and between adherence and antiretroviral efficacy. Chapter 7 presents the results of the study on treatment adherence in the ATHENA cohort. We investigated the extent to which patients were able to adhere to their HAART regimen, the association between adherence and plasma concentrations of protease inhibitors or nevirapine, and between adherence and virologic treatment response. Adherence to HAART is essential for plasma HIV 1 RNA suppression. Self-report is the most frequently used measure of adherence to HAART, but its validity is controversial. Studies on the relation between self-reported adherence and virologic treatment response have shown inconsistent results. We investigated whether this variability between studies about the effect of self-reported adherence on virologic treatment response could be attributed to study design features. Results from this study are presented in Chapter 8.

In patients with a chronic asymptomatic HIV-1 infection and >200 CD4+ T-cells/μL, the optimal timing of HAART initiation is unclear. It involves a trade-off between a potentially reduced risk of mortality, when started earlier in the course of infection, and an earlier
exposure to pill burden and potential toxicities. Results of a study on patients' preferences for the timing of HAART initiation are presented in Chapter 9. In the general discussion (Chapter 10), recent developments and future directions of research on quality of life and treatment adherence in the context of antiretroviral therapy for HIV-1 infection are discussed.
References


