Highly active antiretroviral therapy for HIV-1 infection: patients' quality of life and treatment adherence

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Citation for published version (APA):
Nieuwkerk, P. T. (2006). Highly active antiretroviral therapy for HIV-1 infection: patients' quality of life and treatment adherence
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Chapter 1 presents the background and general objectives of this thesis. The advent of highly active antiretroviral therapy (HAART) for HIV-1 infection has resulted in a dramatic decline in HIV-related morbidity and mortality in the Western world. For many patients however, consistent use of HAART is difficult to sustain. The daily pill burden of the first HAART regimens was usually large and required rigid time schedules and for some drugs dietary restrictions. Additionally, HAART regimens are associated with significant short-and long-term adverse effects. Strict adherence to HAART is crucial because of the risk of drug resistance development. The pill burden associated with most HAART regimens and adverse effects could diminish patients' quality of life. Conversely, the delay of disease progression induced by HAART could be accompanied with improvement in quality of life. In symptomatic HIV infection or AIDS, the potential negative effects of HAART on quality of life are likely outweighed by clinical benefit. 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. 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.

Chapter 2 compares the impact on patients' quality of life of treatment with ritonavir/ saquinavir versus ritonavir/saquinavir/stavudine (Prometheus study) in asymptomatic and symptomatic HIV infected patients who did or did not receive antiretroviral therapy before entry into the study. Quality of life improved significantly in both treatment groups over 48 weeks, despite an increase in reported symptoms. Quality of life improved more in symptomatic patients than in asymptomatic patients, and more in patients without prior antiretroviral therapy than in patients with prior antiretroviral therapy.

Chapter 3 presents the study on quality of life (ADAM study) in which patients were randomly assigned to prolonged induction therapy with four antiretroviral agents or maintenance therapy with two antiretroviral agents after 26 weeks of induction therapy. Clinical findings from the ADAM study revealed that maintenance therapy after 26 weeks of induction therapy resulted in inferior suppression of viral replication. Quality of life declined more during maintenance therapy than during prolonged induction therapy. Quality of life was associated with suppression of viral replication. Patients with suboptimal suppression of viral replication (predominantly patients assigned to maintenance therapy) had more decline in quality of life than patients with suppression of viral replication in plasma to below detectable concentrations. Possibly, the negative effects of inferior viral suppression on quality of life were greater than the added burden of the four-drug regimen.

In Chapter 4 the changes in long-term (96 weeks) quality of life are compared among patients enrolled in a standard triple therapy protocol (NATIVE study), patients enrolled in a protocol in which treatment was intensified in case of insufficient viral suppression (Prometheus study), and patients enrolled in an induction-maintenance therapy protocol
(ADAM study). Additionally, changes in quality of life were compared between patients who continued and discontinued their antiretroviral regimen. We found no difference in changes in quality of life over time between the triple therapy protocol and the treatment intensification protocol, with patients generally showing improvements in their quality of life over time. Changes in quality of life were significantly different among patients enrolled in the induction-maintenance protocol compared to the other two protocols. Quality of life generally remained unchanged or declined among patients in the induction-maintenance protocol. Patients who discontinued study medication due to insufficient efficacy, toxicities or at their own request showed less favourable changes in quality of life than patients who did not discontinue their regimen. The highest proportion of discontinuations was within the induction-maintenance protocol.

Chapter 5 focusses on the measurement of change in quality of life. Adaptation to changing health presents a challenge to measuring change in quality of life. A method that aims to take this adaptation into account when measuring change in quality of life is the use of a retrospective baseline measurement in addition to a follow-up measurement. Previous studies comparing results of the retrospective baseline measurement method with two other commonly used methods for measuring change in quality of life, namely the comparison of a prospective baseline measurement with a follow-up measurement and transition questions, have shown that different methods for measuring change yield different changes in quality of life. It is unclear which method provides a more valid measurement of change in quality of life. Therefore, we investigated which method for measuring change in quality of life yielded strongest associations with four objective measures of change in health status, namely CD4⁺ cell count, plasma HIV RNA concentration, body mass index, and haemoglobin concentration. The retrospective baseline measurement method yielded strongest associations with the objective measures of change in health status. This finding suggests that methods for measuring change in quality of life that take adaptation to changing health into account may be more valid measures of change in quality of life than measures that do not take adaptation to changing health into account.

Chapter 6 presents results of the study on treatment adherence in the Prometheus study. Treatment adherence was assessed using a self report questionnaire administered at 12, 24, 36 and 48 weeks after the start of treatment. The percentages of patients reporting skipping medication at separate time-points ranged from 12 to 15%. The percentage of patients reporting deviation from time schedule at separate time-points ranged from 32 to 35%. Patients reporting abdominal pain, nausea, vomiting, a tingling feeling around the mouth or tongue, or taste disturbances were more likely to report being non-adherent than patients not reporting these symptoms. Skipping medication significantly predicted HIV RNA concentrations in serum.

Results of the study on treatment adherence in the ATHENA cohort are presented in Chapter 7. We determined the percentage of patients who reported taking all antiretroviral medication on time and according to dietary instructions in the past week. Only about
half of all patients took all antiretroviral medication in accordance with time and dietary prescriptions in the preceding week. Deviation from the antiretroviral regimen was associated with decreased drug exposure. Among those patients receiving HAART for at least 24 weeks, deviation from the antiretroviral regimen was also associated with a decreased likelihood of having suppressed plasma HIV RNA loads.

The subject of Chapter 8 is the measurement of treatment adherence using self-report. Self-report is the most frequently used measure of adherence to HAART, but its validity is controversial. Support for the validity of a self-report adherence measurement is provided if an association is found between higher levels of adherence and lower plasma HIV-1 RNA concentrations. Such an association is biologically plausible and has been demonstrated using more objective measures of adherence, although factors other than adherence may influence plasma HIV RNA concentrations as well. Studies on the relation between self-reported adherence to HAART and plasma HIV RNA concentrations have shown inconsistent results, with some studies finding fairly strong associations and others finding no association at all. The reason for this inconsistency in results is unclear. We investigated if this variability between studies in the effect of self-reported adherence on virologic treatment response could be attributed to study design features. This was investigated through meta-analysis of published articles in which treatment adherence was assessed using self-report and in which information was provided about the relation between adherence and plasma HIV RNA concentrations. Overall, we observed that self-reported adherence was significantly related with plasma HIV RNA concentrations. This implies that self-report measures of adherence can distinguish between clinically meaningful patterns of medication taking behavior. Distinct study characteristics were significantly associated with the relation between adherence and virologic treatment response.

Chapter 9 presents a study on patients' preferences regarding the timing of HAART initiation. In patients with a chronic asymptomatic HIV-1 infection and more than 200 CD4-cells/µL, the optimal timing of highly active antiretroviral therapy (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. We investigated patient preferences for immediate HAART initiation relative to delaying HAART for one year during a structured interview. A hypothetical difference in three-year mortality risk between both options was systematically varied between 0% and 10% to determine the threshold at which preference would switch to HAART initiation. We found large variation in patient preferences. About 30% of all patients would prefer HAART initiation even if mortality risks would be equal for both options. Almost 25% always opted for delaying HAART even if this would result in a 10% greater mortality risk. These findings emphasize there is ample room for shared decision-making when deciding on the most optimal timing of HAART initiation in chronic asymptomatic HIV-1 infection.
Chapter 10 is the general discussion of this thesis. In this chapter, recent developments in the treatment of HIV infection are described that are relevant for patients' quality of life and treatment adherence. Considerations for future research are discussed.