Highly active antiretroviral therapy for HIV-1 infection: patients' quality of life and treatment adherence
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Chapter 10

General discussion
General discussion

In July 2006, it was ten years ago that HAART became available for use in standard clinical care in the Netherlands. Since the introduction of HAART, significant further improvements in therapy have been made. HAART regimens are now more effective, easier to take, and often better tolerated than the first HAART regimens that became available. Still patients must take lifetime therapy with potential treatment related side effects to prevent progression of HIV infection. Consequently, quality of life and treatment adherence will remain relevant in the treatment of HIV infection. The topics addressed in this thesis comprised the impact of antiretroviral therapy on quality of life, the measurement of change in quality of life, adherence to antiretroviral therapy, the measurement of adherence, and patient preferences for the timing of HAART initiation. In this discussion section I will describe recent developments regarding these topics, and areas where future research on quality of life and adherence might be relevant. Finally, I will address the composition of the study population described in this thesis and the current composition of the HIV-1 infected population in the Netherlands.

Impact of antiretroviral therapy on quality of life

Since the studies on quality of life and adherence described in this thesis were conducted, many advances in antiretroviral therapy have been made. These advances comprise multiple new antiretroviral drugs within existing classes. Moreover, new combinations of ritonavir with various protease inhibitors have been introduced, enabling reduction in dose and dosing frequency, fixed-dose combinations, and once-daily regimens. These advances in antiretroviral therapy have resulted in regimens that have increased efficacy, are often less toxicity, have a lower pill burden, and have easier dosing schedules than the first HAART regimens [1-5]. Nevertheless, HAART regimens are still associated with adverse effects that may diminish quality of life and may negatively impact patients' willingness and ability to adhere to their antiretroviral regimen [6]. Most treatment switches currently occur because of treatment related adverse effects [7, 8]. To date, suppression of HIV is possible in the vast majority of patients with a wide variety of regimens. However, each of these effective HAART regimens may differ in their associated limitations, such as differences in side effect profiles and differences in convenience of regimens [9]. This leads to questions such as how regimens with comparable efficacy but different side effect profiles should be weighed against each other, and how potency should be weighed against tolerability and convenience. Future studies comparing between different HAART regimens should continue to include quality of life and treatment adherence as outcome measures in addition to clinical and virological endpoints, as this will help to answer questions concerning these trade-offs.
Measurement of change in quality of life

An important area of quality of life research is to investigate the impact of illness or treatment on patients' quality of life. However, the measurement of self-reported quality of life is complicated by the fact that patients tend to adapt to their changing health, and thereby change the reference value by which they evaluate their quality of life. Prospective serial measurements of quality of life over time may therefore not necessarily capture patients' change in health status. Distinguishing between differences in self ratings due to actual health differences and differences due to varying reference values by which patients evaluate their self-rated health is a key challenge in interpreting self-reported measures of health. Standard methods for measuring quality of life do not distinguish changes or differences in health from changes or differences in reference values between patients and within patients over time. Therefore, expanding our understanding and the measurement of self-rated health remains therefore a challenge [10-12]. In a study described in this thesis we used the thenth test method when attempting to assess change in reference values. However, more sophisticated methods such as structured equation modeling have also been used to assess change in reference values [13, 14]. Using structural equation modeling to assess change in reference values does not require the administration of an additional measure, i.e., the thenth test, and is not subject to recall bias.

Adherence to therapy

Although current HAART regimens are far more convenient than the early regimens, adherence to therapy remains relevant for the treatment of HIV infection. Adherence rates to self-administered therapies for chronic medical conditions are typically as low as 50% [15]. Studies among HIV infected patients using electronic medication monitoring to measure adherence to HAART have revealed that adherence rates average 70% [16-20]. Although these adherence rates compare favorably to those achieved in other chronic medical conditions, the minimal required adherence threshold below which the effectiveness of treatment is significantly reduced is higher for HAART regimens than for therapies prescribed for most other chronic conditions. For single protease inhibitor regimens this minimal adherence threshold is reported to be as high as 90% to 95% [16, 17, 19]. However, recent evidence suggests that successful virologic outcome may be achieved with adherence within the 80% to 96% range [21]. More potent regimens, especially ritonavir-boosted PI-based or NNRTI-based regimens have not been thoroughly studied and may lead to better viral suppression at lower levels of adherence [22-24]. To date, studies on the relationship between adherence and virologic success of treatment are also limited by their relatively short follow-up periods. Consequently, the relationship of adherence to HAART and long-term virologic control has not yet been established.

The development of once daily regimens can be expected to improve adherence [25]. However, the consequences of missed doses for once daily regimens may be more serious than for twice-daily regimens. Missing a once daily dose of HAART may result in a long
period of drug exposure that is inadequate to maintain viral suppression. In two large randomized trials, once daily regimens resulted in better virologic outcome compared with twice daily regimens [26, 27]. It is sometimes difficult to determine, however, whether the benefits seen with once daily HAART result from increased potency of the regimens studied, better adherence, or both. In one of the two trials, a better treatment adherence was observed in the once daily arm compared with the twice daily arm [26]. However, in the other trial no difference in adherence between treatment arms was observed [27].

As many patients may be unable to achieve sufficiently high levels of adherence, interventions to improve adherence have been designed in the past years. To date, the literature on adherence enhancing interventions among patients on HAART is limited. A recent systematic review containing 24 studies concluded that adherence interventions seemed to be moderately successful in improving adherence among patients with known or anticipated adherence problems, but minimally successful among unselected patients [28]. The number of studies was too small to draw conclusions about whether there were certain types of interventions that were more effective than other types. Clearly, there is ample room for the development and evaluation of interventions aimed at improving or maintaining patient adherence to HAART.

**Measurement of adherence**

For our studies on treatment adherence described in this thesis, we chose self-report as method for measuring adherence to HAART. To date, self-report is the most widely measure of adherence to HAART. Advantages of self-report comprise low costs, ease of administration, and its applicability in a variety of clinical and research settings. Disadvantages of self-report include its susceptibility to recall bias and social desirability bias. Self-report measures typically overestimate adherence compared with other methods. Various other measures of adherence to HAART have been used such as, pill count, electronic medication monitoring, measurement of plasma drug concentrations and prescription refill monitoring. Generally, electronic medication monitoring predicts the largest proportion of variation in virologic treatment outcome if compared with other adherence measures, but not in all studies [29-31]. However, the use of electronic monitoring may be hampered by high costs, labour intensity, low patient acceptability, and the fact that electronic monitoring may serve as an adherence intervention in itself. A study comparing various adherence measures in their ability to predict virologic treatment response found that a combination of several measures leads to significantly better predictions than each separate measure [32]. Others have found that although different measures of adherence may correlate with virologic response, they may not necessarily correlate with each other [32]. It is therefore suggested that different adherence measures capture different aspects of adherence, although the underlying construct of adherence is common across various measures. Furthermore, each measure of adherence has specific limitations. The appropriateness of adherence measures for different settings may
depend upon the required level of sensitivity of the adherence measurement, the extent to which various adherence measures are acceptable to the target study population, literacy of the target study population, and practical considerations such as costs and ease of administration. Self-report will likely remain an important tool for measuring adherence to HAART. Future studies should investigate strategies to minimise social desirability and recall bias when asking questions about adherence.

Initiation of antiretroviral therapy

In the beginning of 1997, when the first patients enrolled in our studies on quality of life and adherence, guidelines recommended to start HAART in asymptomatic patients with chronic HIV infection who had less than 500 CD4+ T-cells/μL or plasma HIV RNA above 10,000 copies/mL. Arguments in favor of initiating HAART earlier in the course of HIV infection comprise preservation of immune function, earlier control of viral replication, and prolongation of disease free survival. In recent years, increased recognition of long term adverse effects of HAART and difficulties with adherence to therapy have outweighed arguments in favor of very early treatment. Consequently, treatment guidelines have shifted the threshold for initiation of HAART to a later stage [33]. To date, the optimal timing of HAART initiation is unclear among patients with a chronic asymptomatic HIV-1 infection and more than 200 CD4+ T-cells/μL. As HAART regimens continue to become simpler and less toxic, the pendulum could swing back towards recommending earlier initiation of HAART. Recent findings have suggested that starting HAART earlier, i.e., at a higher CD4+ T-cell count, reduces the incidence of common treatment-related toxicities compared with starting HAART later at a lower CD4+ T-cell count [34]. Incorporating quality of life as an outcome-measure in future studies assessing the relative advantages and disadvantages of earlier versus later initiation of HAART, would allow determining the extent to which positive effects of HAART on quality of life, such as delay of disease progression, outweigh negative effects, such pill burden and toxicities. Patient preferences are also relevant. Some patients may decide that an increased risk of adverse effects or disease progression is worth delaying treatment, and may choose to take this risk to gain some perceived or anticipated benefit.

Study population

Participants in the studies described in this thesis comprise predominantly Dutch males who acquired HIV infection through homosexual contact. This largely reflects the composition of the HIV infected population in the Netherlands that started HAART at the time patients enrolled into the studies on quality of life and adherence described in this thesis, i.e., from January 1997 to December 2000. During the last years, the HIV infected population in the Netherlands has evolved from a population dominated by the classical risk group of homosexual men to a population of which heterosexuals and immigrants from parts of the world where HIV-infection is prevalent form a substantial part [35]. Most
immigrants are from sub Saharan Africa and the former Dutch colonies in the Americas. Two recent studies revealed that HAART is less successful in suppressing plasma HIV RNA to below 50 copies/mL in immigrants compared with native Dutch patients [36, 37]. Supposedly, this was due to a difference in adherence between both groups of patients. Another recent study revealed a poor quality of life including HIV stigma concerns and high levels of depression among HIV infected immigrants [38]. Depression is a well-established risk factor for lower levels of treatment adherence [39]. To date, our knowledge about quality of life and the relationship between quality of life and treatment adherence among HIV infected immigrants is limited. Clearly, this relation deserves further investigation.


24. Bangsberg DR, Weiser S, Guzman D, et al. 95% adherence is not necessary for viral suppression to less than 400 copies/mL in the majority of individuals on NNRTI regimens. In: Program and abstracts of the 12th conference on retroviruses and opportunistic infections; February 22-25, 2005; Boston. Abstract 616.


