Patients’ preferences regarding the timing of highly active antiretroviral therapy initiation for chronic asymptomatic HIV-1 infection

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Objective: In patients with a chronic asymptomatic HIV-1 infection and >200 CD4⁺ T-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 patients’ preferences for immediate HAART initiation relative to delaying HAART for 1 year.

Methods: Consecutive patients were asked for their preference during an interview. A hypothetical difference in 3-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.

Results: About 30% of patients preferred HAART initiation even if the mortality risk would be equal for both options. Almost 25% always preferred delaying HAART even if this would result in a 10% greater mortality risk. Most treatment guidelines recommend delaying HAART >350 CD4⁺ T-cells/µl. However, at a risk difference between starting and delaying HAART that corresponds with this CD4⁺ T-cell count, about 50% would prefer to start HAART immediately. Most guidelines recommend starting HAART below 200 CD4⁺ T-cells/µl. However, at a risk difference between both options corresponding with this CD4⁺ T-cell count, about 40% preferred delaying HAART.

Conclusions: We found large variation in patients’ preferences. Some patients were more inclined to initiate HAART earlier than the recommended guidelines, whereas others were more inclined to delay HAART. These findings emphasize the need for shared decision-making when deciding on the most optimal timing of HAART initiation in chronic asymptomatic HIV-1 infection.

Introduction

The clinical benefit of highly active antiretroviral therapy (HAART), as determined in randomized controlled trials, has been established among patients with advanced or symptomatic disease [1,2]. For less immunodeficient individuals (that is, asymptomatic individuals with CD4⁺ T-cell counts >200/µl), there are no data from randomized controlled studies to determine the level of immunodeficiency that HAART is associated with clinical benefit. Observational cohort studies have shown an increased risk of mortality when antiretroviral therapy is initiated in patients with CD4⁺ T-cell counts <200/µl compared with initiation at higher levels [3,4]. The CD4⁺ T-cell count >200/µl at which to initiate therapy remains unclear, as evidence is inconsistent [3–7].

Various professional societies and governmental entities have provided guidelines for the initiation of HAART [8–10]. Such guidelines aim to determine the optimal threshold at which benefits of initiating HAART outweigh the disadvantages. Arguments
favouring the initiation of HAART earlier in the course of HIV infection consist of preserving immune function, earlier control of viral replication, prolonging disease-free survival, protecting cognitive function and a possible reduction of the risk for HIV transmission. In recent years, increased recognition of long-term adverse effects of HAART and difficulties with adherence to therapy have outweighed the arguments in favour of very early treatment. Consequently, guidelines have shifted the threshold for HAART initiation to a later stage of immune suppression. However, the precise CD4+ T-cell count threshold at which HAART initiation is recommended in asymptomatic patients with CD4+ T-cell counts above 200/μl vary between guidelines and undergo regular revision.

Previous studies have shown that judging the advantages and disadvantages of treatment may differ between patients and healthcare professionals [11]. Therefore, physicians should explicitly and actively seek a patient’s preference [12]. Most guidelines recognize that individual factors, such as a patient’s preference, should be taken into account when deciding on the optimal timing of HAART initiation. Our objective was to investigate patients’ preferences regarding the timing of HAART initiation for asymptomatic chronic HIV infection.

Materials and methods

Patients

For our study, we approached consecutive HIV-negative patients, who were treated for a sexually transmitted disease (STD), at the outpatient STD clinic of the Academic Medical Center (AMC) in Amsterdam between March and April 2004. We considered these patients to be at risk for acquiring HIV and, therefore, potential candidates to decide when to initiate HAART. Between July and September 2004, we also approached consecutive HIV-positive patients, who were currently treated or had previously been treated with HAART, at the HIV outpatient clinic of the AMC. To be eligible, patients had to be over 18-years old, and able to understand verbal and written Dutch. The study was approved by the Ethics Committee of the AMC. All patients signed written informed consent.

Preference assessment

We used interviews to investigate patients’ preferences. Patients were asked if they were willing to participate immediately after their consultation at the outpatient clinic. Patients did not know beforehand that they would be asked to participate in this study.

STD patients received verbal and written information about HIV infection prior to the interview. Both groups were asked to imagine having an asymptomatic HIV infection with no prior antiretroviral therapy experience and with this in mind, they were asked to pick from the following options: immediate initiation of HAART or delaying HAART initiation for 1 year. The two options were presented as vignettes, which included a description of the pill burden, possible short and long-term toxicities, and the resulting consequences for daily living (Box 1). We described a typical HAART regimen in terms of pill burden and potential toxicities. HIV counselling nurses, physicians specialized in HIV and a member of the Dutch HIV patient association were consulted while designing the vignettes.

We presented a hypothetical difference in the 3-year mortality risk between both options, ranging from 0 to 10%. Patients were first asked which option they would prefer if delay of HAART initiation would result in a 10% higher mortality risk. If the patient preferred HAART initiation, the difference in mortality risk was lowered to 5% and patients were again asked for their preference. If patients now preferred delaying HAART initiation, the difference in mortality risk was increased to 7%. For each patient, we sought to obtain the mortality risk at which they would switch from delaying HAART initiation to immediate initiation of HAART (in other words, the initiation threshold), by using this ping-pong technique [11]. In addition, we asked patients for the reason behind their preference. Similar probability trade-off techniques have successfully been used in previous studies [11,13–15].

Patients’ preferences versus treatment guidelines

Currently, most treatment guidelines would recommend HAART initiation <200 CD4+ T cells/μl and delaying of HAART >350 CD4+ T cells/μl. As no data directly comparing the immediate initiation of HAART with delaying HAART for 1 year were available for these CD4+ T-cell counts, we used data available from two cohort studies to estimate the corresponding risk differences. Prognostic information about the 3-year mortality risk after starting HAART among antiretroviral-naive patients, with a Centers for Disease Control and Prevention (CDC) disease stage A, was derived from the Antiretroviral Cohort Collaboration. We excluded patients in whom intravenous drug use was the HIV transmission route [4,16]. Prognostic information about the 1-year mortality risk without HAART was derived from the Amsterdam Cohort Studies among homosexual males and combined with the 2-year mortality risk after starting HAART obtained from the Antiretroviral Cohort Collaboration [17]. Both databases provide mortality risks stratified by CD4+ T-cell count. We thus estimated the 3-year mortality risk difference between immediate HAART...
initiation and delaying HAART for 1 year at 200 and 350 CD4+ T-cells/µl to be approximately 3% and 1%, respectively. We subsequently determined the percentage of patients who preferred delaying HAART at a risk difference that would correspond with 350 CD4+ T cells/µl and the percentage of patients that preferred starting HAART at a risk difference that would correspond with 200 CD4+ T cells/µl.

Factors potentially influencing initiation thresholds
We explored whether patients’ characteristics like age, gender and whether or not patients had children influenced initiation thresholds. We also explored the influence of patients’ facility with basic probability and numerical concepts, that is, numeracy, using three previously validated questions [18]. In HIV-infected patients, we explored the influence of CD4+ T-cell count, plasma HIV RNA concentrations and CDC disease stage at the time of their actual HAART initiation, as well as time since HAART initiation. This information was extracted from medical charts. Additionally, we asked patients if they were currently bothered by symptoms, which they attributed to HAART, on a four-point scale consisting of ‘not at all’, ‘a little’, quite a bit’ and ‘very much’. Continuous variables were dichotomized at the median. Numeracy was dichotomized into no correct responses to the three questions versus at least one correct response. We dichotomized CDC disease stage into CDC A versus CDC B or C. Symptom bother was dichotomized into ‘not at all’ versus ‘a little bit’ to ‘very much’.

Data analysis
We determined, a priori, to recruit a total of 90 patients into the study of which 40 were STD patients and 50 were HIV patients. In similar studies, such a sample size was sufficient to characterize patients’ preferences [13,14]. The percentage of patients that would prefer initiating HAART over delaying HAART was determined at specified hypothetical differences in 3-year mortality risks between both options. We investigated if the percentage of patients with initiation thresholds above the median differed between STD patients and HIV patients using a χ² test. Additionally, we explored whether percentages of patients with initiation thresholds above the median differed between the potentially influencing factors, using χ² or Fishers’ exact tests, as appropriate. P-values <0.05 were considered to indicate statistical significance. Analyses were performed using the SPSS software for Windows version 11 (SPSS Inc., Chicago, IL, USA).

Results
A total of 69 STD patients were invited to the study; of these, 40 patients (58%) agreed to participate (at-risk group). Additionally, a total of 96 HIV patients; of these, 50 patients (52%) agreed to participate. The main reason for not participating was time constraints, as patients were not aware they would be approached for a study before their consultation. Patients’ characteristics are shown in Table 1.

One patient in the at-risk group and one patient in the HIV group were unable to express an initiation threshold. The percentage of remaining patients in the at-risk group and HIV group who would prefer HAART initiation at specified hypothetical differences in the 3-year mortality risk between HAART initiation and delay of HAART are shown in Figure 1. The median (interquartile range) initiation threshold was 1% (0–9.8%). We found no statistically significant difference in the percentage of patients with an initiation threshold above the median between
the at-risk group and the HIV group (54% versus 43\%, \(P=0.39\)).

About 30\% (26/88) of all patients would prefer HAART initiation even if mortality risks would be equal for both options. Most of these patients mentioned that they wanted to do anything they could against HIV, and as a result, would initiate HAART. Others believed in treatment benefits that did not translate into an immediate difference in mortality risk, but expected these benefits to appear in the future. Almost half (41/88) of all patients switched their preference to HAART initiation when any further delay of HAART would result in a higher mortality risk. Almost 24\% (21/88) of patients always opted for delaying HAART even if this would result in a 10\% greater mortality risk.

We estimated that the 3-year mortality risk difference between starting and delaying HAART at a CD4\(^+\) T-cell count of 350/\(\mu\)l would be approximately 1\%. Most guidelines would recommend delaying HAART initiation. We found that about 50\% (46/88) of patients would prefer to start HAART at this risk difference. We estimated the 3-year mortality risk difference between starting and delaying HAART at a CD4\(^+\) T-cell count of 200/\(\mu\)l would be approximately 3\%. Most guidelines would recommend the initiation of HAART. We found that about 40\% (38/88) of the patients would prefer to delay HAART initiation at this risk difference.

A significantly lower percentage of patients who provided incorrect responses to all three numeracy questions had initiation thresholds above the median, thus indicating a preference for earlier HAART initiation as compared with patients with at least one correct response (26\% versus 54\%, \(P=0.041\)). A significantly higher percentage of patients who had been on HAART for more than 5.5 years had initiation thresholds above the median, indicating a preference for later initiation, as compared with patients who had been on HAART for less than 5.5 years (58\% versus 28\%, \(P=0.045\)). We found no statistically significant differences between males and females (53\% versus 33\%, \(P=0.15\)); patients who are older or younger than 40.5 years (54\% versus 42\%, \(P=0.39\)); patients with or without children (49\% versus 40\%, \(P=0.58\)); patients with more or less than 165 CD4\(^+\) T-cells/\(\mu\)l at actual HAART initiation (36\% versus 46\%, \(P=0.76\)); patients with more or less than 4.96 HIV RNA log\(_{10}\) copies/ml at actual HAART initiation (29\% versus 50\%, \(P=0.22\)); patients at CDC disease stage A versus B/C at actual HAART initiation (48\% versus 38\%, \(P=0.57\)); or patients not reporting symptom bother versus those reporting symptom bother attributed to HAART (48\% versus 39\%, \(P=0.71\)).

Discussion

We found substantial variability in patient preferences regarding the moment of HAART initiation. Some patients were more inclined to initiate HAART earlier than the recommended treatment guidelines, whereas other patients were more inclined to delay HAART.

### Table 1. Patients’ characteristics

<table>
<thead>
<tr>
<th></th>
<th>At-risk group (n=40)</th>
<th>HIV group (n=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (sd)</td>
<td>35 (12)</td>
<td>46 (10)</td>
</tr>
<tr>
<td>Males</td>
<td>58%</td>
<td>86%</td>
</tr>
<tr>
<td>Possess a college degree</td>
<td>53%</td>
<td>29%</td>
</tr>
<tr>
<td>Unable to provide correct responses to three numeracy questions</td>
<td>20%</td>
<td>24%</td>
</tr>
<tr>
<td>CD4(^+) T cells/ml, median [IQR]*</td>
<td>–</td>
<td>165 [45–270]</td>
</tr>
<tr>
<td>Plasma HIV RNA log(_{10}) copies/ml, median [IQR]*</td>
<td>–</td>
<td>4.96 [4.51–5.38]</td>
</tr>
<tr>
<td>Antiretroviral naive*</td>
<td>–</td>
<td>70%</td>
</tr>
<tr>
<td>CDC-A*</td>
<td>–</td>
<td>50%</td>
</tr>
<tr>
<td>Years on HAART, median [IQR]</td>
<td>–</td>
<td>5.5 [2.7–7.8]</td>
</tr>
<tr>
<td>Years since first positive HIV test, median [IQR]</td>
<td>–</td>
<td>7.2 [3.6–12.8]</td>
</tr>
<tr>
<td>Extent to which patients are bothered by symptoms which they attribute to HAART</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not at all</td>
<td>–</td>
<td>55%</td>
</tr>
<tr>
<td>A little</td>
<td>–</td>
<td>33%</td>
</tr>
<tr>
<td>Quite a bit</td>
<td>–</td>
<td>8%</td>
</tr>
<tr>
<td>Very much</td>
<td>–</td>
<td>4%</td>
</tr>
</tbody>
</table>

\*At time of actual highly active antiretroviral therapy (HAART) initiation. CDC, Centers for Disease Control and Prevention; IQR, interquartile range; sd, standard deviation.
The question as to when to start HAART during the course of chronic HIV infection is an issue of ongoing debate. To date, no definitive evidence from randomized controlled trials exists on the optimal timing of HAART initiation in asymptomatic chronic infection. Even if definitive evidence would demonstrate a survival benefit of earlier HAART initiation, patients might still be willing to trade-off an increased risk of mortality with the perceived benefits of delaying HAART. We observed that almost 25% of patients opted to delay HAART even if this would lead to a substantially increased risk of mortality. This is consistent with other reports, of appreciable numbers, of HIV-infected patients voluntarily deciding not to access HAART despite their awareness of the risks associated with delaying HAART [19,20]. About 30% of our patients would prefer HAART initiation even if mortality risks would be equal for both options. Some of these patients believed in the benefits of early HAART initiation that would only appear in the future. This belief may be plausible in light of the relatively recent advent of HAART, and the uncertain, sometimes conflicting evidence about the clinical benefit of earlier versus later HAART initiation. Other patients mentioned a wish to do everything they could against HIV infection. The finding that some patients are willing to receive treatment even in the face of no stated benefit has also been observed by others, and has been linked with a persistent belief in treatment benefits coupled with negative emotions and a perceived necessity to take action [21]. Although it is generally acknowledged that patients’ preferences should be incorporated into medical decision making [22], clearly treatment should only be initiated when there is evidence of clinical benefit.

Our study has several limitations. We did not investigate patients facing the actual decision of HAART initiation. As we provided patients with hypothetical ranges of mortality risks, this would not necessarily represent their actual risk – we felt it would be inappropriate to burden patients facing the actual decision. In addition, we aimed to avoid interfering with information provided by regular healthcare providers. The selection of patients who had recently been at risk for acquiring HIV infection seemed to be the best alternative, as these patients could have been confronted with the decision when to initiate HAART. Additionally, we chose to investigate a group of HIV-infected patients...
who were currently or previously treated with HAART. As these patients may have actually experienced the burden and benefit of HAART, we considered their preferences also highly relevant. However, the a posteriori preferences of these patients could be affected by a post-decision justification bias [23]. Nevertheless, we found no difference in preferences between the group at-risk of acquiring HIV infection and the group who actually contracted HIV infection. Remarkably, the extent to which patients were bothered by symptoms, which they attributed to HAART, did not influence initiation thresholds. This finding was unexpected as previous studies have shown that side effects of HAART may have a clear impact on treatment continuation and adherence [24,25].

Patients could choose between immediate HAART initiation and delaying HAART for 1 year. This fixed time period of a year was picked for feasibility reasons: a shorter time delay than 1 year would be a less meaningful choice to patients, whereas a longer time period of deferring therapy would represent an unrealistic choice. In reality, the duration of deferring HAART until initiation of therapy will vary across patients and will be guided by periodical clinical and laboratory examination.

Patients were presented with a description of a typical or average HAART regimen based on the availability of about 20 antiretroviral agents, which can be combined into dozens of recommended regimens. The results of our study may therefore not be representative for regimens that substantially differ from our standard description. As HAART regimens continue to become simpler and less toxic, the pendulum could swing back towards recommending earlier initiation of HAART. Nonetheless, patient preferences will still be important.

We chose to describe the consequences of an immediate versus delayed HAART initiation in terms of mortality risk instead of using the combined endpoint of disease progression and mortality. Considering the variety of AIDS-defining events, the use of the combined endpoint would have produced an increased change of confusion. It would have been difficult to find out whether the patient focused on mortality, a severe AIDS-related disease or a milder AIDS-related condition. Expressing the prognosis in the risk of mortality is unambiguous. Thereby, we considered disease progression and mortality as too divergent to combine in a single endpoint for our preference assessment.

We chose the range of 0–10% increased risk for delaying of HAART versus starting HAART, as we estimated that the actual risk difference between both options at 200 and 350 CD4+ T-cells/µl would be within this range. We considered increasing the range even further, especially in patients for whom a 10% increase in risk did not change their decision. However, as we wanted to limit both the cognitive burden as well as the duration of the interview, we decided not to assess preferences beyond a 10% increased risk.

We used data from two different cohorts to estimate the risk difference between starting and delaying HAART for 1 year at 200 and 350 CD4+ T cells/µl. Preferably, such information should be derived from a single study; unfortunately this was not available. Combining information from two cohorts seemed to be the best alternative to provide an approximation of the risk differences involved. If future studies provide higher or lower risk differences, the percentage of patients with a preference for initiating HAART could still be derived from Figure 1 as long as the risk difference did not exceed 10%.

Quantitative information about risks, similar to those provided during our preference assessment, may be meaningful only to patients who have some understanding of probability concepts. Patients who were unable to provide correct responses to the numeracy questions had lower initiation thresholds, thus indicating a preference for earlier HAART initiation than patients with correct responses. Patient education may be an approach to influence patients’ preferences as only well-informed patients will be able to make truly informed decisions about HAART initiation.

Our analysis relating potentially influencing factors to initiation thresholds had only limited statistical power and should therefore be considered explorative. A final limitation of the study is that we do not know whether the preferences of patients who consented to participate in our study are representative for those who were unable or unwilling to participate.

Our study has several implications. To date, there is no evidence from a randomized clinical trial on the optimal timing of starting HAART among asymptomatic patients with more than 200 CD4+ T cells/µl. We observed considerable and unpredictable variability in patients’ preferences regarding the timing of HAART initiation that, in many instances, would not coincide with recommendations from current treatment guidelines. We believe that the individual preferences of HIV-infected patients are important and should be taken into account when weighing up the risks and benefits of treatment, and deciding when to initiate treatment. The inter-individual differences in treatment preferences emphasizes that there is a necessity for shared decision-making when deciding on the most optimal timing of HAART initiation in patients with a chronic asymptomatic HIV infection.

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