Initiation of antiretroviral treatment for HIV infection. Studies in the general practice

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IV

High level of patient participation in the decision-making on antiretroviral treatment for HIV infection

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Summary

The main objective was to gain an insight into the role of HIV-infected patients in the decision-making on antiretroviral treatment once, according to international consensus recommendations, the criteria for treatment were met. Furthermore we assessed the time to start of therapy when patients qualified for treatment.

As part of an observational study in general practices, 43 patients (predominantly homosexual, living in Amsterdam, and well-educated) who met the criteria for treatment for the first time in the period between March 1995 and January 1997 were intensively studied. We assessed patients' preference for participation at baseline, their actual involvement (according to the GP) in the decision-making on therapy once the criteria for treatment were met, and the perceived participation in the decision-making as reported retrospectively by patients who started treatment. Time to start of therapy was estimated by using the Kaplan-Meier method.

As a consequence of a revision of the guidelines, the 16 patients who met the criteria before August 1996 had a lower median CD4+ cell count ($p < 0.0001$) as compared to the 27 patients who met the criteria after this date. The patients in general displayed a high preference for participation at baseline, and were actively involved in the decision-making on therapy once the treatment criteria were met. In most cases it was initially decided not to start therapy (yet). Of the patients who started therapy, three quarters reported to have been involved in the decision to start. In the group of patients who met the treatment criteria before August 1996 the median time to start of treatment was seven months, whereas only 25% of the patients who met the criteria after this date
started therapy within seven months \( (p < 0.001) \). Within this last group in particular the patients with a high desire for autonomy were the ones in whom the initiation of therapy had been delayed \( (p < 0.01) \).

In conclusion: The patients in this study played an important role in the decision-making on their antiretroviral treatment, and the initiation of therapy was delayed considerably.

**Introduction**

Guidelines for the treatment of HIV have changed considerably over the years. In the earlier years of the epidemic, when treatment options were limited, it was justified to delay the initiation of therapy and to wait for the development of HIV-related symptoms or a marked decrease in the number of CD4+ cells. Better insights into the HIV pathogenesis, improved ways of monitoring and the availability of more potent drugs resulted in a new therapeutic strategy in 1996. According to the latest guidelines, triple drug treatment ideally should be recommended in a very early stage of the infection.

Current antiretroviral combination therapy has resulted in a reduced morbidity and mortality, but also has many shortcomings. Most of the recommended regimens, which probably have to be taken for life, still have rigid, complex dosing schedules and considerable toxicity. Adherence to the prescribed regimen has to be maximal to prevent the development of drug resistance. Despite the benefits of current treatments, the decision to start has thus remained a difficult one.

Approximately 50% of the AIDS patients registered in the Netherlands live in Amsterdam and only a limited number of general practitioners (GPs) in Amsterdam has attracted the majority of the patients. Although the actual initiation of treatment should occur in specialist care, the initial discussions and decisions on therapy which may lead to referral for treatment take place during the interaction between the patient and the GP in a considerable number of patients.

The HIV Intervention Study was designed to gain an insight into the way in which decisions on antiretroviral treatment in the general practice are made. In this observational study, 94 initially untreated HIV-infected patients and their GPs were followed for two years with regard to decision-making on treatment initiation.

This paper presents results on a subgroup of patients, who became eligible for treatment during the study according to the prevailing treatment recommendations. The main objective of the current substudy was to gain an insight into the role of HIV-infected patients in the decision-making on antiretroviral treatment once the criteria for treatment were met. Furthermore, we assessed the time to start of therapy when patients qualified for treatment.
Methods

Design HIV Intervention Study

Enrolment of patients and GPs in the HIV Intervention Study occurred as follows. All Amsterdam GPs with five or more untreated HIV-infected patients in their practice were asked to participate in the study. In the second instance, in order to increase recruitment, GPs from outside Amsterdam were also approached. Ultimately, 21 GPs in Amsterdam and six in other parts of the country participated. Patients were eligible if they had never received antiretroviral treatment, and were able and willing to complete multiple (Dutch) questionnaires. In the Amsterdam practices 85 patients were included, which was approximately 30% of the total number of untreated patients in these practices. Because of the high workload some GPs were only willing to include a very small number of their untreated patients. Study participants had less frequently been infected by intravenous drug use (5% vs. 13%; 95 CI of the difference 0.02 to 0.14), but were comparable to the total group of untreated patients in these practices with regard to HIV disease stage and median CD4+ cell count. Nine patients were included by GPs outside Amsterdam, so in total 94 patients participated in this study. GPs and patients were followed from March 1995 until April 1997.

At baseline and at every six months throughout the study, both the patients and their GPs completed a semi-structured questionnaire on a range of factors likely to be associated with treatment decision-making. Visit registration forms were filled in by the GPs after each patient’s visit. On these forms information on (amongst others) the patient’s disease stage (using the expanded European AIDS case definition\textsuperscript{13}) and CD4+ cell count was recorded. Data were collected until the initiation of antiretroviral therapy or, for those patients who had not started therapy, until April 1997.

Criteria used to assess eligibility for antiretroviral treatment

The present paper reports results on a subgroup of patients who, during the HIV Intervention Study, became eligible for antiretroviral treatment according to the Dutch treatment recommendations. Two different criteria were used to assess patients’ eligibility for therapy: Until August 1996 asymptomatic patients with a CD4+ cell count $< 300$ cells/mm$^3$ and symptomatic patients with a CD4+ cell count $< 400$ cells/mm$^3$ qualified for treatment.\textsuperscript{14} Following international recommendations\textsuperscript{4}, the Dutch treatment policy was revised in August 1996. From that moment on treatment was recommended for all symptomatic patients, irrespective of CD4+ cell count, for patients with a CD4+ cell count below 500 cells/mm$^3$, and for patients with a viral load greater than 10,000 copies/ml.\textsuperscript{15,16} Until the end of the study, however, HIV-RNA could not routinely be performed in the general practice and viral load could thus not be used to identify patients’ eligibility for therapy. Therefore, from August 1996 onwards, we considered patients eligible if they were symptomatic or had a CD4+ cell count below 500 cells/mm$^3$. 

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As we were interested in the decision-making between GP and patient, we considered the date of the first consultation with the GP at which the patient met the treatment criteria as the date of eligibility in this paper, not the date of the CD4+ test. In order to guarantee a follow-up on the decision-making of at least three months, only patients who met the treatment criteria before January 1997 were included in the present analysis.

**Measurements**

The results presented in this paper refer to data that were collected at three different time points during the HIV Intervention Study.

*Baseline.* At baseline we measured the patient’s preference for participation in (general) treatment decision-making under ‘ideal’ circumstances. Preferences were rated on a five-point scale ranging from the physician assuming full responsibility for decision-making to the patient assuming this role.  

*First discussion about treatment with the GP after meeting the treatment criteria.* Results on the initial decision-making on therapy refer to the first consultation with the GP during which therapy was discussed. The GP was asked to indicate (amongst others) who had initiated the subject of therapy, which decision had been made, and who had made the decision.

*Six months after the initiation of therapy.* Patients’ final treatment status was assessed in September 1997. Patients who started treatment during the study (i.e. before April 1997) were asked to complete an “After Start” questionnaire six months after the initiation of therapy. With this questionnaire patients’ perceived participation in the decision to start was measured.

**Analysis**

Analyses were performed using SPSS for Windows 6.1.3 (SPSS inc., Illinois, USA). Median values were compared using the non-parametric median test, proportions using the $\chi^2$ test. In case the expected number in any of the four cells was lower than 5, the Fisher’s exact test (two-tailed) was used.

Time from meeting the treatment criteria to initiation of therapy was estimated with the Kaplan-Meier method. Patients were stratified according to the period in which they had become indicated for treatment (before or after the 1st of August 1996). Within these two periods, patients were further stratified according to their preference for participation at baseline (high or low preference for autonomy).
Results

Study population

During the follow-up period of the HIV Intervention Study, 45 of the 94 patients became indicated for treatment. Two had already started treatment before they visited the GP and were excluded; the 43 remaining patients formed the study population. As can be observed from Table 1, patients were predominantly male, homosexual, and well-educated. Thirty-four of the 43 patients (79%) were registered in five Amsterdam practices with a high HIV caseload (i.e. cumulative number of patients at start of the study > 20). The remaining nine patients were registered in seven practices with a low HIV caseload (four in Amsterdam, three outside Amsterdam). Approximately 50% of the patients were also seeing a specialist for their HIV infection at the time they became eligible for treatment.

Sixteen patients (37%) became indicated for treatment before the 1st of August 1996, and 27 after this date. As a direct consequence of a revision of the treatment recommendations patients in the first group had a lower median CD4+ cell count at the time they met the treatment criteria than patients in the second group (240 vs. 455; p < 0.0001). The two groups did not differ significantly with regard to the proportion of symptomatic/AIDS patients or the HIV caseload of the practices.

Patients' preference for participation in treatment decision-making at baseline

At baseline, all 43 patients to a greater or lesser extent had expressed the preference to participate in treatment decision-making. Seven (16%) thought decisions should be made by the patient alone, and 17 (40%) mainly by the patient. These 24 patients will from now on be referred to as having a high preference for autonomy. Twelve patients (28%) preferred decisions to be made by patient and doctor together, and seven (16%) preferred decisions to be made mainly by the GP. These 19 patients were considered to have a low preference for autonomy.

No significant relationships were observed between the patients' participation preference and either the HIV caseload of the practice they were registered with, or their disease stage when meeting the treatment criteria. Besides, there was no significant difference between patients who met the criteria before August 1996, and patients who became eligible after this date with regard to their preference for participation at baseline.
Table 1. Patient characteristics (n=43)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>40 (93)</td>
</tr>
<tr>
<td>Mean age in years</td>
<td>37.8 [24-26]</td>
</tr>
<tr>
<td>High education level</td>
<td>30 (70)</td>
</tr>
<tr>
<td>Registered with GP in Amsterdam</td>
<td>40 (93)</td>
</tr>
<tr>
<td>Consulting AIDS specialist</td>
<td>21 (49)</td>
</tr>
<tr>
<td>HIV transmission mode</td>
<td></td>
</tr>
<tr>
<td>homosexual</td>
<td>37 (86)</td>
</tr>
<tr>
<td>heterosexual</td>
<td>2 (5)</td>
</tr>
<tr>
<td>intravenous drug use</td>
<td>2 (5)</td>
</tr>
<tr>
<td>other</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Mean time (yrs) since 1st positive HIV test [range]</td>
<td>5.8 years [0-15.7]</td>
</tr>
<tr>
<td>Indication for treatment¹</td>
<td></td>
</tr>
<tr>
<td>I. before August 1996</td>
<td>17 (40)</td>
</tr>
<tr>
<td>II. as of August 1996</td>
<td>26 (60)</td>
</tr>
<tr>
<td>Disease stage symptomatic/AIDS</td>
<td></td>
</tr>
<tr>
<td>Indication for treatment before August 1996</td>
<td>11/17</td>
</tr>
<tr>
<td>Indication for treatment as of August 1996</td>
<td>14/26</td>
</tr>
<tr>
<td>Median CD4+ cell count [range]</td>
<td></td>
</tr>
<tr>
<td>Indication for treatment before August 1996</td>
<td>240</td>
</tr>
<tr>
<td>Indication for treatment as of August 1996</td>
<td>460</td>
</tr>
</tbody>
</table>

¹Until August 1996 asymptomatic patients with a CD4+ cell count ≤300, and symptomatic patients with a CD4+ cell count ≤ 400/mm³ qualified for treatment. From August 1996 onwards patients were given an indication for therapy when symptomatic or when having a CD4+ cell count < 500/mm³.

Patient participation in the initial decision on therapy that was made after meeting the treatment criteria

In the case of 42 of the 43 patients the issue of treatment was discussed with the GP once the criteria for treatment were met. One patient started with therapy in specialist care without having discussed treatment with his GP in the meantime. In forty patients the first discussion about treatment resulted in a decision: in nine cases it was decided not to start, in 22 it was decided to postpone the start of therapy, and in the remaining nine cases it was decided to start. Table 2 shows the extent to which, according to their GPs, the patients initiated the discussion about therapy and participated in the decision-making. In cases where it was decided not to start, the discussion about treatment had
been initiated predominantly by the GPs (seven out of nine). In cases where it was
decided to start, the discussion had been initiated predominantly by the patients (six out
of nine). When it was decided to postpone the start of treatment, approximately equal
numbers of patients and GPs had initiated the discussion.

Information concerning the person who had made the initial decision on treatment
was available for 38 cases. In 33 of these cases (87%) the patients participated in the
decision-making, either by deciding alone or by making a joint decision with the GP. In
eight of the nine cases where it was decided not to start, the decision was made by the
patient alone. Reasons for not wanting to start therapy were perceived lack of benefit,
fear of side effects and a negative attitude towards treatment in general. In the 22 cases
where the initiation of treatment was postponed and in the nine cases where it was
decided to start, the proportions of patients who decided alone and patients who decided
together with the GP were approximately equal. The initiation of treatment was
postponed because a (re)assessment of the CD4+ cell count or viral load was desired,
because therapy was not considered necessary yet, or because more time was needed to
make a final decision.

Patients who met the treatment criteria before August 1996 and patients who had
been given an indication for treatment later on during the study did not differ
significantly with regard to either the kind of decisions that were made or the level of
patient participation; the groups were therefore combined in Table 2. There was also no
statistically significant relationship found between the HIV caseload of the general
practitioner and these variables.

Table 2. The extent to which the patients initiated the discussion about ART and to which they
participated in the decision-making are shown for the initial decisions that were made after the
patients had come to meet the treatment criteria.

<table>
<thead>
<tr>
<th>Characteristics of the decision-making</th>
<th>n</th>
<th>Not to start</th>
<th>Initial decision</th>
<th>To postpone</th>
<th>To start</th>
</tr>
</thead>
<tbody>
<tr>
<td>Person who initiated discussion on ART*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt</td>
<td>17</td>
<td>2</td>
<td>9</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Pt + GP</td>
<td>4</td>
<td></td>
<td>3</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>19</td>
<td>7</td>
<td>10</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Person who made decision on ART*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pt</td>
<td>19</td>
<td>8</td>
<td>7</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Pt + GP</td>
<td>14</td>
<td>1</td>
<td>10</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>GP</td>
<td>5</td>
<td></td>
<td>3</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

ART denotes antiretroviral treatment. In the case of 42 patients treatment was discussed with the GP;
in 40 this discussion led to a decision, and in the case of 38 patients information on the person who
made this decision was available.
Patients' perceived participation in the decision to start

By September 1997, 24 of the 43 patients (67%) were receiving therapy. Sixteen completed the 'After Start' questionnaire; five did not receive this survey, as treatment was initiated after April 1997 (end of follow-up period), and three did not respond. Twelve of these 16 patients (76%) stated that they had participated in the final decision to start, either by deciding alone, or by making the decision together with the GP or specialist (data not shown).

Time to initiation of therapy

Figure 1 shows the estimated Kaplan-Meier curves of time to initiation of therapy for the 16 patients who met the treatment criteria before August 1996, and for the 27 patients who had been given an indication for treatment after the 1st of August 1996.

![Figure 1. Estimated Kaplan-Meier curves of time to initiation of therapy for patients who had been given an indication for treatment between March 1995 and August 1996 (—) and for patients who had been given an indication between August 1996 and January 1997 (— — —).]
In the first group the median time to initiation of treatment was seven months (95% CI 1.2 - 12.8). In the second group the curve did not drop below 0.5 and the median time to initiation of treatment could therefore not be estimated. In this group only 25% of the patients had started within seven months since the moment they met the treatment criteria. After 12 months, 15 of the 16 patients in the first group (94%), and nine of the 27 patients in the second group (33%) had started treatment (log rank test p = 0.0002).

Within the group of 27 patients who had been given an indication for treatment after the 1st of August 1996, further stratification according to patients’ preference for participation at baseline resulted in significant differences (figure 2). Of the 11 patients with a low preference for autonomy 50% had started within six months, and 64% within a year. Of the 16 patients with a high preference for autonomy, only two had started by September 1997: one after seven, and one after 11 months (p = 0.0045).

Figure 2. Estimated Kaplan-Meier curves of time to initiation of therapy for patients who had been given an indication for treatment between August 1996 and January 1997 by participation preference at baseline. — = low preference for autonomy; ---- = high preference for autonomy.
Discussion

As part of an exploratory study in the general practice we aimed to gain an insight into the degree to which HIV-infected patients participate in the decision-making on their antiretroviral treatment. This paper presents results on a group of patients who became eligible for treatment during the study, based on the Dutch treatment recommendations.

At baseline, all patients (to a greater or lesser extent) had expressed the preference to be involved in the decision-making. Once they met the criteria for treatment, the great majority of these patients were found to have played an active role in the decision-making on therapy. According to their GPs, the patients were either the principal initiators of, or actively participated in the initial decisions on therapy that were made. Of the patients who started treatment during the study, three quarters reported having participated in the decision to start, either by deciding alone or by making the decision together with their GP or specialist.

From these results we conclude that the (predominantly) homosexual patients described in this paper did play an important role in the decision-making on treatment. The active participation of the patients in our study may be explained by the fact that they were relatively young and well-educated. Prior research in cancer patients has identified a younger age and a high education level as factors positively associated with both preference for participation in treatment decision-making and actual participation.18-22 Our results are in agreement with those of Catalan et al, who also reported a high preference for information and participation in decision-making of gay HIV-infected patients.23 In their study, however, symptomatic patients tended to have a lower preference for autonomy than asymptomatic patients, a finding which could not be confirmed by our study.

In the majority of cases, the initial decision was either not to start or to postpone initiation of treatment. In cases where it was decided not to start therapy, patients generally did not initiate the discussion about treatment themselves. From this we conclude that they were inclined not to start in an early stage, and as a result saw no need to bring up the subject themselves.

The main reasons for rejecting therapy were fear of side effects and perceived inefficacy or low benefit of treatment. Postponement of treatment appeared to be the decision most often shared between GP and patient. The most frequently given reasons for postponing treatment were the wish for an additional CD4+ or viral load assessment and the fact that therapy was not considered necessary yet.

By September 1997, fifty-six percent of the 43 patients had started treatment after all. The patients who started were not just the patients who received specialist care at the time of meeting the treatment criteria: approximately half of the starters were only visiting their GP when therapy was indicated for them. Of the 16 patients who met the treatment criteria before the 1st of August 1996, 50% percent had started within seven months, whereas of the 27 patients who had become eligible after this date only 25%
had. This difference was statistically significant. In the second group particularly the patients with a high preference for autonomy were the ones who were less likely to start.

On the one hand, these findings were not surprising given the significantly lower median CD4+ cell count in the group of patients who had become before August 1996, which was a direct consequence of the revision of the criteria. On the other hand, the delay observed in the second group can be considered interesting in light of the availability of potent triple therapy at that time, and the increasing conviction that treatment should preferably be initiated before destruction of the immune system has occurred.\textsuperscript{2,24,25}

In the population that we studied, the recommendations for antiretroviral treatment clearly were not very strictly followed. Growing consensus that early treatment initiation is associated with virologic, immunologic and clinical benefits has resulted in an even further sharpening of the treatment criteria.\textsuperscript{5} Patients may only be willing to accept, and even more importantly to adhere to the latest recommendations if the (perceived) benefit of early aggressive treatment outweighs the disadvantages. The discussion about this issue, however, is beyond the scope of this paper. Multivariate analysis of the factors that were associated with the initiation of treatment in our study is currently being performed; results of this analysis will be described in another paper.

We realise that this investigation had several limitations. As a result of the small sample size differences between groups seldom reached statistical significance and causal factors could not be reliably studied. The fact that the patients participated on a voluntary basis may to some extent have influenced the results; patients who agreed to participate in the study may have had a higher preference for participation in the decision-making than patients who were not willing to participate. The extent to which patients and GPs were familiar with the fact that the patient met the treatment criteria at the time of the consultation during which treatment was discussed, was not established. It can be assumed that the GPs, of whom the majority was experienced in HIV care, were informed about the recommendations. The patients, however, may not yet have had this knowledge at this point. The results of this study, finally, may not be generalizable to the general HIV-infected population but reflect the situation in Amsterdam fairly well. Our findings may function as points for attention for future research.

In conclusion: we observed a high level of patient participation in the decision-making on antiretroviral treatment. We furthermore observed a delay in the initiation of therapy, particularly in the group of patients with relatively high CD4+ cell numbers who met the treatment criteria after August 1996. Research into patient characteristics associated with the initiation of treatment seems warranted in this light.
Acknowledgement


We want to thank dr. Charles Boucher for his helpful comments.

References


