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

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Psychological factors predict the initiation of antiretroviral therapy

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Summary

The objective of the study was to determine which characteristics of HIV-infected patients are associated with the initiation of therapy when qualifying for antiretroviral treatment.

From March 1995 until April 1997, 94 therapy-inexperienced HIV-infected patients and their GPs were followed with regard to decision-making on treatment. Data were collected at baseline and every six months thereafter. Medical information was recorded after each consultation. Patients' final treatment status was assessed in September 1997. This paper reports on 49 patients who met the treatment criteria for the first time during the study. Treatment was indicated for 16 patients before August 1996, and for 33 from August 1996 onwards.

The outcome variable was 'time to start of therapy'. Possible explanatory variables included various demographic, medical and psychological characteristics, of which some were assessed at baseline and the remainder referred to the last patient questionnaire preceding the date of eligibility. Relationships with the outcome variable were assessed using the Cox regression model. As a result of a revision of the treatment criteria in August 1996, the CD4+ cell count had to be treated as a design confounder, with forced adjustment in the regression analysis.

The study population consisted of 44 male (41 homosexual) and five female patients: 28 were symptomatic or had AIDS, and 21 were asymptomatic. In the multivariate analysis, three variables were independently and significantly associated with treatment initiation: a negative attitude towards therapy and satisfaction with the information on treatment provided by the GP were negatively related to the initiation of therapy;
a reduced state of ‘general health’ as perceived by the patient was positively related.

Conclusions: This study demonstrates the importance of exploring patients’ health perceptions and views on treatment before they qualify for therapy. Patient-tailored information may be needed to help HIV-infected patients accept current aggressive regimens.

Introduction

Over the years, international recommendations for the treatment of HIV infection have changed substantially. A better insight into the HIV pathogenesis and more effective drugs have resulted in a more aggressive policy with respect to the moment of treatment initiation. To date, therapy is recommended for any HIV-infected person with a plasma HIV-1 RNA level (viral load) greater than 5000 to 10,000 copies/ml who is committed to complex, long-term therapy.¹

The widespread implementation of triple therapy has led to a decreased AIDS-related morbidity and mortality.² ³ This does not mean that treatment decision-making in HIV infection has become less complicated. Many patients who are eligible for therapy according to current treatment criteria, may not yet have developed clinical symptoms. Life-long treatment with complex regimens that frequently cause considerable side effects⁴ ⁶ is thus likely to discourage patients from deciding in favour of the treatment recommendations.

Numerous studies have been performed into adherence to antiretroviral therapy.⁷ ¹⁴ To the best of our knowledge, studies into factors that in an early stage can predict future initiation of therapy when patients meet the criteria for treatment have not been performed before. For physicians, however, knowledge on these characteristics seems useful, as it may facilitate the decision-making process on the initiation of treatment. For patients who are less likely to start, more tailored support from the beginning may possibly lead to the acceptance of therapy when qualifying for treatment.

Between 1995 and 1997 we prospectively followed a sample of initially untreated HIV-infected patients and their general practitioners (GPs) with regard to decision-making on antiretroviral therapy (HIV Intervention Study). This paper reports on a subgroup of patients, who became eligible for treatment during the study. The aim of the present analysis was to determine in a multivariate model which patient characteristics measured before meeting the treatment criteria were associated with the initiation of therapy when qualifying for therapy.
Methods

Design of the HIV Intervention Study
All Amsterdam GPs with five or more untreated HIV-infected patients in their practice were asked to participate. In order to increase recruitment, GPs from outside Amsterdam were also asked to participate. Patients were eligible for participation if they had never received antiretroviral treatment ('naive'), and if they were able and willing to complete an extensive (Dutch) questionnaire every six months. Enrolment of consecutive patients by the GPs took place from March until September 1995. A total of 94 patients were included after informed consent had been obtained: 85 patients by 19 GPs in Amsterdam and the remainder by six GPs elsewhere (three urban, three suburban).

At baseline and at every six months throughout the study, both the patients and their GPs completed a semi-structured questionnaire on issues likely to be related to treatment decision-making. Registration forms were filled in by the GPs after each consultation. On these forms information on (amongst others) the patient's disease stage (using the expanded European AIDS case definition) and CD4+ cell count was recorded. Data were collected until the initiation of antiretroviral therapy or, for patients who did not start therapy, until April 1997. Patients' final treatment status was assessed in September 1997.

Criteria used to assess eligibility for antiretroviral therapy
Developments in the field of HIV treatment have led to changes in treatment recommendations during the study. As a result, assessment of eligibility for treatment in the patients that are discussed in the present paper was based on two different sets of criteria. Up until August 1996, the Dutch recommendations of 1991 were used (indicating to start treatment in asymptomatic patients at a CD4+ cell count \( \leq 300/\text{mm}^3 \), and in symptomatic patients at a CD4+ cell count \( \leq 400/\text{mm}^3 \)). From the 1st of August 1996 onwards, patients were considered eligible if they were symptomatic or had a CD4+ cell count below 500 cells/\( \text{mm}^3 \). Until the end of the study, the HIV-RNA test could not be routinely performed in the general practice and viral load could thus not be used to identify patients' eligibility in this study.

In the case of patients who qualified for treatment based on their CD4+ cell count, the date of eligibility was considered to be the date of this CD4+ cell test. However, if a patient had a CD4+ cell count of 450/\( \text{mm}^3 \) before the 1st of August 1996 this patient was considered eligible for therapy as from the 1st of August 1996 (revised criteria). For patients who were eligible because of symptoms, the date of the first consultation with the GP at which the patient appeared to be symptomatic was considered the date of eligibility. Based on these rules, 49 of the 94 patients met the criteria for therapy during the study (16 before, and 33 after August 1996) and formed the study population in this paper.
Dependent and explanatory variables

The variable of interest in the present study was 'started with therapy by September 1997'. Apart from the patients' medical condition, possible explanatory variables included various sociodemographic and psychological characteristics some of which had been assessed at baseline, and the remainder in the last questionnaire completed by the patients preceding the date of eligibility. The mean time between completion of the patient questionnaire and the date of eligibility for treatment was 89 days (range 0-335 days).

The following sociodemographic characteristics of the patients were assessed at baseline: age, gender, level of education (consisting of five categories; primary school = 1, university = 5), practice location (Amsterdam, other), HIV transmission mode (homosexual/bisexual contact, injecting drug use, heterosexual exposure, other), and date of first positive HIV-test result. At the start of the study we also assessed the sexual preference and level of HIV-related experience of the GPs the patients were registered with. At the start of the study, the median number of cumulative HIV-infected patients registered in the practices that participated in the HIV Intervention Study was twenty. We used this median number to distinguish between GPs with a low and GPs with a high level of HIV-related experience. The patient's employment status was assessed using the final questionnaire. Information on the type of care received by the patient (GP alone, or GP and AIDS specialist) is related to the consultation with the GP at which the patient was found to qualify for treatment for the first time.

The baseline questionnaire of the patients contained a question measuring 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.\(^{19}\)

The Dutch version of an HIV health status questionnaire, which uses thirty items of the Medical Outcomes Study (MOS) Instrument\(^{20}\), was part of all patient questionnaires throughout the study. This validated questionnaire measures various aspects of health and comprises the following subscales: overall health, physical functioning, role functioning, social functioning, cognitive functioning, pain, mental health, energy/fatigue, health distress, quality of life, and change in health. Results of the last questionnaire preceding the date of eligibility were used in the present analysis. According to the instructions, multi-item scales were scored by adding up the item responses after reversing the item scores where necessary so that high scores indicated better health. Mean scores were conventionally transformed linearly to a scale from 0 (poorest health) to 100 (best health). Missing values in the larger scales (four or five items) were imputed according to the MOS-HIV rules for missing items.

Data on patients' attitudes towards antiretroviral treatment ('very positive' to 'very negative' on a five-point scale), their intention to start therapy in the future, and their use of alternative treatment for their HIV infection were also derived from this last questionnaire.
We constructed a scale to measure (every six months) to what extent patients actively collected information on the disease and its treatment. As possible information sources we considered three well-known magazines for HIV-infected patients, the Dutch association for HIV-infected persons ("HIV-vereniging"), and the informative web site 'HIV Net'. In addition, patients were asked to indicate whether, in their opinion, they had been provided with sufficient HIV-related information by their GP. Again, we used the data of the last questionnaire for the present study.

Analysis
Missing data (CD4+ cell counts, health status scales), which never involved more than three cases, were randomly imputed based on the unconditional distribution of the known values. For each scale of the health status questionnaire the median score was used as cut-off value. The outcome variable in the analysis was time to start of therapy. Prior to the analysis all possible explanatory variables were dichotomised.

Relationships of the various variables with the outcome variable were assessed using the Cox regression model. Because different criteria were used to assess patients' eligibility for therapy before and after August 1996, the median CD4+ cell counts of these two groups showed a clear difference, as shown in Table 1. For this reason, the CD4+ cell count was considered to be an at onset confounder and forced into all regressions. After the CD4+ cell count had been entered into the model, all other variables were conventionally tested one by one for their association with the outcome variable in order to select candidate variables for the multivariate Cox regression.

Table 1. Disease stage and CD4+ cell count when meeting the treatment criteria of patients who were given an indication for therapy before August 1996, and of patients who were given an indication from August 1996 onwards.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Before August 1996 (n=16)</th>
<th>From August 1996 onwards (n=33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>5</td>
<td>16</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>Median CD4 (cells/mm$^3$)</td>
<td>240</td>
<td>450</td>
</tr>
</tbody>
</table>

Before August 1996 patients qualified for treatment when asymptomatic and having CD4+ cells $\leq$ 300/mm$^3$ or when symptomatic and having CD4+ cells $\leq$ 400/mm$^3$. From August 1996 onwards all symptomatic patients and patients with CD4+ cells $< 500/mm^3$ met the treatment criteria.
Table 2. Baseline characteristics, and characteristics as indicated in the last questionnaire completed before the moment patients became indicated for antiretroviral treatment. Results are shown for the total population and after classification of patients by treatment status at the end of the study.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All n=49</th>
<th>Started n=26</th>
<th>Not started n=23</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age [range]</td>
<td>35 [24-55]</td>
<td>34.5</td>
<td>39</td>
</tr>
<tr>
<td>Male sex</td>
<td>44</td>
<td>24</td>
<td>20</td>
</tr>
<tr>
<td>Residency Amsterdam</td>
<td>45</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>High education level</td>
<td>35</td>
<td>17</td>
<td>18</td>
</tr>
<tr>
<td>Employed</td>
<td>30</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Homosexual transmission mode</td>
<td>41</td>
<td>22</td>
<td>19</td>
</tr>
<tr>
<td>First positive HIV test &gt; 5 yrs ago</td>
<td>28</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Registered within practice with high HIV case load</td>
<td>39</td>
<td>21</td>
<td>18</td>
</tr>
<tr>
<td>Registered with homosexual GP</td>
<td>28</td>
<td>15</td>
<td>13</td>
</tr>
<tr>
<td>Consulting an AIDS specialist</td>
<td>23</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

| Symptomatic/AIDS when meeting treatment criteria | 28 | 17 | 11 |

Health status (proportion with score ≤ cut-off value)

| Overall health (cut off: 65) | 26 | 18 | 8 *a |
| Social functioning (cut off: 80) | 27 | 17 | 10 |
| Cognitive functioning (cut off: 775) | 25 | 15 | 10 |
| Pain (cut off: 89) | 26 | 18 | 8 |
| Mental health (cut off: 76) | 27 | 17 | 10 |
| Energy/fatigue (cut off: 65) | 27 | 17 | 10 |
| Health distress (cut off: 80) | 25 | 15 | 0 |
| Quality of life (cut off: 75) | 40 | 24 | 16 |

Views regarding antiretroviral treatment

| Having a negative attitude towards treatment | 16 | 5 | 11 *b |
| Intending to start with treatment in the future | 41 | 24 | 17 *a |
| Using alternative therapy | 16 | 12 | 4 |

HIV-related information

| Not actively seeking information (= 0 sources) | 24 | 12 | 12 |
| Satisfied with amount of information provided by GP | 39 | 17 | 22 *b |

Preference for autonomy

| Preferring to make decisions on treatment (mainly) alone | 28 | 11 | 16 *a |

1Variables that were found to be associated with treatment initiation in the univariate analysis when considering the CD4+ cell count as confounder. a p ≤ 0.1; b p ≤ 0.05. 1 All scales range from 0 to 100, with 100 reflecting optimal health. For each item the median score of the total group is the cut-off value. In case of Physical Functioning and Role Functioning the analysis could not be performed, as the median score was 100.
Given the exploratory character of the study and the small sample size the level of significance was set at 0.10. Significant variables from the univariate analysis were tested for correlation using a correlation matrix; in case two predictor variables were intercorrelated, the strongest predictor was included in the subsequent multivariate analysis. The step-wise forward procedure was used to build up the model. The assumption of proportional hazards was tested.

Results

Patient characteristics

The study population was formed by 44 male (41 homosexual) and five female patients. Table 2 shows the baseline characteristics, and characteristics of the patients preceding the moment they became eligible for therapy. Results are shown for the total group of 49 patients and, after classification, of patients by treatment status at the end of the study.

The median age of the 49 patients was 35 years (range 24 to 55), 45 (92%) were living in the country's capital Amsterdam, 35 (71%) had a high level of education (category 4 or 5 on a scale from 1 to 5) and 30 (61%) were employed. The majority of the patients (80%) were registered with a practice with a high HIV caseload, as defined by a cumulative number of twenty or more HIV-infected patients at start of the study. Of all patients, 24 (49%) were registered with three GPs (seven, eight, and nine patients, respectively), two of whom were practising together. The remaining 25 patients were seen by 13 GPs in 12 practices. Twenty-eight patients (57%) had a homosexual GP, 23 (47%) consulted an AIDS specialist in addition to the GP. The median time between the date of the first positive HIV test and the date of eligibility for therapy was 5.6 years; 28 patients (57%) were symptomatic or had been diagnosed as having AIDS, and 21 (43%) were asymptomatic when meeting the treatment criteria.

In the last questionnaire preceding the moment of becoming eligible for therapy, the patients in general scored high on the health status scales. Median scores on the subscales ranged from 65 for ‘overall health’ and ‘energy/fatigue’ to 100 for ‘physical functioning’ and ‘role functioning’.

Only 12 patients (25%) felt positive about antiretroviral treatment, 21 (43%) reported feeling neither positive nor negative, and 16 (32%) felt negative. Forty-one patients (84%), however, indicated that they intended to start therapy in the future. Alternative treatment for HIV infection was used by 33% of the patients.

Nearly half of the total number of patients (24 of 49) had never consulted any of the information sources mentioned in the questionnaire, 17 (35%) had consulted one or two, and eight (16%) three or four sources. According to 39 patients (80%) the HIV-related
information provided by their GP was sufficient, the remainder would have liked to have received more information.

At the start of the study, 28 patients (57%) reported a high preference for autonomy. In their opinion decisions on treatment ideally should be made mainly by the patient, or by the patient alone. The remaining patients had a preference for shared decision-making or thought decisions should be made mainly by the doctor, while taking the patient’s opinion into account.

By September 1997, 26 patients had started, and 23 had (not yet) started treatment. The median time between the date of eligibility and the study endpoint (i.e. date of starting therapy or September 1st, 1997 if not started) was ten months (range 1 to 21). Median CD4+ cell counts of the starters and non-starters were 295 and 450/mm³, respectively (p = 0.003), but for reasons that have been explained earlier the CD4+ cell count in our analysis was treated as design variable with a consequent forced adjustment in the regression analysis.

Patient characteristics associated with the initiation of treatment

As indicated in Table 2, five psychological characteristics of the patients were found to be associated with initiation of treatment in the univariate analysis: the patient’s attitude towards treatment, intention to start with treatment in the future, satisfaction with the amount of HIV-related information provided by the GP, preference for autonomy in treatment decision-making, and score on the ‘overall health’ scale.

Although the patient’s attitude towards treatment and intention to start were only moderately correlated (correlation coefficient -.4) we decided not to include the last variable in the multivariate analysis, as in light of the relatively small number of events we wanted to keep the number of predictor variables as low as possible.

In the multivariate regression analysis, three variables were significantly and independently associated with treatment initiation (Table 3). Patients with a negative attitude towards antiretroviral therapy were almost six times (1/0.1669 = 5.9; CI = 16.4-2.2) less likely to start therapy during the study as compared to patients whose attitude was neutral or positive. Compared to patients who reported not to have received enough HIV-related information from their GP, patients who had indicated the information from the GP to be sufficient were three times (1/0.3246 = 3.1; CI = 6.6-1.4) less likely to start therapy. Patients with a median score lower or equal than 65 on the ‘overall health’ scale, finally, were 2.6 times more likely to start as compared to patients with a score above 65 (CI = 1.2-5.4). In the multivariate analysis, patients’ preference for autonomy in treatment decision-making was not found to be significantly associated with treatment initiation.
Table 3. Final Cox regression model, showing the variables that were independently associated with treatment initiation in the multivariate analysis.

<table>
<thead>
<tr>
<th>Variables included</th>
<th>HR</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4+ cell count*</td>
<td>0.9942</td>
<td>0.9916-0.9969</td>
</tr>
<tr>
<td>Negative attitude towards antiretroviral treatment</td>
<td>0.1669</td>
<td>0.0610-0.4570</td>
</tr>
<tr>
<td>Satisfied with the amount of information provided by the GP</td>
<td>0.3246</td>
<td>0.1516-0.6947</td>
</tr>
<tr>
<td>Overall health score ≤ 65</td>
<td>2.5687</td>
<td>1.2303-5.3638</td>
</tr>
</tbody>
</table>

HR = hazard ratio

The CD4+ cell count was considered to be an at-onset confounder and therefore forced into the regression.

Discussion

This paper describes the results of an analysis of factors possibly associated with the initiation of antiretroviral treatment, as part of a larger exploratory study of treatment decision-making in HIV infection in a sample of predominantly male homosexual patients. We aimed to determine which patient characteristics, measured before they had met the treatment criteria, were associated with the initiation of therapy once they had qualified for therapy.

Due to the revision of the treatment criteria, which occurred during our study, patients who had met the criteria before August 1996 had a significantly lower CD4+ cell count as compared to patients who had met the criteria later on. The CD4+ cell count was therefore adjusted in the analysis.

In the multivariate Cox regression analysis, three psychological patient characteristics were found to be significantly and independently associated with treatment initiation. Patients' attitudes towards therapy emerged as the strongest predicting variable, in that a negative attitude towards therapy prevented patients from starting once they were eligible for therapy. Although the variable consisted only of one question and did not differentiate between for instance patients' beliefs about safety, efficacy, or personal benefit, we think this result corresponds with the results of numerous other studies in which patients' views about treatment were found to be an important factor in the acceptance of, and/or the adherence to treatment recommendations.8-13,21-23

We feel that it is important to re-emphasise at this point that in our study the attitude towards treatment was measured before patients met the treatment criteria. This finding stresses the importance of exploring the patient's attitude towards therapy in an early stage. The doctor has to be aware of the reasons for a possible negative attitude towards
therapy, in order to be able to influence the decision-making by his/her patients. Apart from general information on the various treatment options, some patients at this point in time may for instance require information on toxicity profiles or side effects, others on dosing schemes, and some may need to understand the main principles of the HIV pathogenesis in order to be able to perceive early aggressive treatment as necessary to maintain good health.

The observation that patients who had reported to have received sufficient information from the GP were less likely to start seems contradictory to what one would expect, as it suggests that it is better to keep patients uninformed. However, in view of earlier results that were obtained within the HIV Intervention Study, which showed that within the group of GPs who participated the attitude towards early treatment was still not explicitly positive in 1997, this finding becomes understandable: the information provided by the GPs may have been ‘coloured’ in a negative way. The fact that more information on disease and treatment does not necessarily result in decisions in accordance with treatment recommendations has also been described by others.

In previous research, a history of prior opportunistic infection was found to be associated with compliance to antiretroviral therapy. As we assumed that patients with disease symptoms or AIDS - and hence a higher illness severity- would perceive a greater benefit of treatment, we expected to find an association between the patients’ disease stage and the initiation of therapy in our study.

Very interestingly though, the patients’ perception of their health status (‘overall health score’), not their actual disease stage, emerged as a factor associated with treatment initiation. It should be remarked that the overall health scale consisted of only one item, in which the patients were asked to rate their health in general on a five-point scale, ranging from excellent to poor. The importance of inquiring after a patient’s health perceptions follows from this finding. Particularly in the case of patients who reported to feel well, and who were thus less likely to start therapy as compared to patients who reported an inferior general health, the severity of their illness in absence of adequate treatment may need to be emphasised.

The study has several limitations. The sample was relatively small and the results should therefore be interpreted with caution. In a larger population more variables may be found to be associated with treatment initiation. The (unforeseen) developments in the field of HIV treatment, which resulted in the modification of the treatment recommendations, complicated our study considerably. As has been said before, we had to adjust the CD4+ cell count in the analysis. Furthermore, variables that we measured in relation to the 1991 treatment recommendations, which were operative at the start of the study, appeared to be of no use in the present analyses: possible explanatory variables, such as the attitude of the GPs towards antiretroviral treatment, could not be taken into account. The study population was quite homogeneous, and therefore we cannot draw reliable conclusions on, for instance, the influence of the level of HIV-
related experience of the GP on treatment initiation. Further research will be necessary to test the generalizability of our findings within the different groups at risk for HIV.

In conclusion: in this exploratory study, psychological characteristics of patients before meeting the treatment criteria were found to be significantly and independently associated with the initiation of therapy once qualifying for therapy. Our results therefore stress the importance of exploring patients’ health perceptions and views with regard to treatment in an early stage. Provision of ‘patient-tailored information’ will be needed before patients who have proven to be less likely to start will be willing to accept ‘patient-tailored treatment’ in an early stage of the infection.

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References


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