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

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Positive attitude towards antiretroviral therapy after six months of treatment in a sample of Dutch HIV-infected people

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Summary

The objective of the study was to assess the attitude towards antiretroviral treatment after six months of therapy and the extent to which patients had participated in the decision to start with treatment.

As part of a Dutch study into decision-making regarding interventions in HIV infection in the general practice, 37 HIV-infected patients (81% homosexual, 89% living in Amsterdam) who started therapy in the period between 1995 and 1997 completed a questionnaire after on average six months of therapy.

At start of therapy the mean CD4+ cell count was 203 x 10^6/l; 14% of the patients was asymptomatic, 54% symptomatic and 32% already had AIDS. In 35% of the cases the decision to start had been made predominantly by the patient and in 41% by patient and doctor together. Thirty-six patients (97%) were still on treatment when completing the questionnaire. Of the 25 (69%) who were receiving so called ‘triple therapy’, 96% felt positive about their treatment.

In conclusion: the vast majority of patients were positive about their treatment after six months of antiretroviral therapy, which in most cases consisted of triple therapy. It is likely that active patient participation in treatment decisions, advanced disease stage, results of treatment and the factor time each contributed to their positive attitude.
Introduction

In 1995, the combination of two nucleoside reverse transcriptase inhibitors (NRTIs; zidovudine with didanosine or zalcitabine) was found to be superior to zidovudine monotherapy in delaying disease progression in patients infected with HIV. Unfortunately the effect was temporary; the combinations were not powerful enough to completely block viral replication and drug-resistant strains appeared rapidly.

Real progress was booked in 1996, when protease inhibitors were found to be capable of causing a sustained suppression of viral replication to undetectable HIV-RNA (viral load) levels when used in combination with two NRTIs. This was announced during the World AIDS Conference in Vancouver and soon thereafter this so-called ‘triple therapy’ internationally became the standard in the treatment of HIV infection.

The initial euphoria over the new treatment options gradually made place for realism and even scepticism, as it became clear that treatment with a triple-drug regimen can be very difficult for patients. The protease inhibitors all show considerable toxicity and drug interactions. The complicated dosing regimens, which often interfere with a patient’s daily life, have to be followed strictly. These factors may well have a negative influence on adherence to treatment and may thus result in the emergence of resistant virus and ultimately in therapy failure.

A positive relation between patients’ attitudes towards treatment and treatment adherence has been established in case of anti-HIV monotherapy. Also, patient participation in treatment decision-making in general has been found to be a predictor for future treatment adherence. It is important to assess whether both relations also exist with regard to the more complicated triple-therapy regimens.

In this paper we describe a sample of patients who started with antiretroviral therapy between 1995 and 1997. Results will be presented on CD4+ cell counts and disease stages at start of therapy, patients’ participation in the decision to start, and patients’ attitudes towards treatment after six months of therapy.

Methods

The patients described in this paper were part of a cohort of initially untreated persons with HIV who participated in a descriptive, prospective study into antiretroviral treatment decision-making in the general practice, the HIV Intervention Study. Of all Amsterdam GPs with ≥ five therapy-naïve HIV patients in their practice who were asked to participate, 21 entered the HIV Intervention Study. In the second instance six GPs from outside Amsterdam were included as well. These 27 GPs included 94 patients, who were then studied from March 1995 until April 1997 or until the initiation of therapy before April 1997.
At study entry and during follow-up data were collected on (amongst others) CD4+ cell count, disease stage\textsuperscript{19}, type of care (GP and/or specialist), and attitude towards therapy. Patients who started therapy during the study received a semi-structured questionnaire six months after the initiation of treatment. They were asked when they had actually started, which drug(s) they had started with, whose decision it had been to start, and to what extent they had been satisfied or dissatisfied with the decision to start (5-point scale). If their therapy had changed in the meantime, information was collected on their present treatment. Finally, the attitude towards antiretroviral therapy after six months of treatment was assessed ('very positive' to 'very negative') on a 5-point scale. The patients were requested to further explain their answer.

Results on CD4+ cell count and disease stage at start of therapy were based on information recorded by the GP during the last consultation of the patient preceding treatment initiation, unless a more recent CD4+ cell count was provided by the patient in the final questionnaire.

Three periods were distinguished with regard to the moment treatment was initiated. In period I, from March 1995 until January 1996, the benefit of two NRTIs compared to one was established. In period II (January 1996 until August 1996) the new NRTI lamivudine (3TC) became available and the first patients received triple therapy with a protease inhibitor in clinical trials. In period III, from August 1996 onwards, triple therapy was the standard treatment.

**Statistical analysis**

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS for Windows, version 6.1.3.). Differences in proportions were assessed by using the $\chi^2$ test, differences in means by using the analysis of variance (ANOVA) procedure.

**Results**

**Treatment status of patients who participated in the HIV Intervention Study**

Forty-three of the 94 patients started therapy and forty were still untreated at the end of the follow-up period. Of the remaining 11 patients, three died during follow-up, five were excluded because they were lost to follow-up and three withdrew from the study.

In Table 1, baseline characteristics of patients who started are compared with those of patients who did not start during the study. At study entry starters had significantly lower CD4+ cell counts, were more often symptomatic and were more often seen by an AIDS specialist. The attitude towards treatment did not differ significantly. Of the forty patients who did not start during the study, 85% fulfilled the treatment criteria at the end
of the follow-up period; they were symptomatic and/or had a CD4+ cell count < 500 x 10^6/l. Of the 43 patients who started, six did not return the final questionnaire, despite two reminders. According to their GPs these non-responders were all still on therapy six months after treatment initiation. The population presented in this paper is constituted of the 37 patients who completed the questionnaire.

Table 1. Baseline characteristics of patients who did, and patients who did not start with antiretroviral treatment during the HIV Intervention Study

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Starters^1</th>
<th>Non-starters</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=43 (%)</td>
<td>n=40 (%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>38 (88)</td>
<td>35 (88)</td>
<td>NS</td>
</tr>
<tr>
<td>Female</td>
<td>5 (12)</td>
<td>13 (13)</td>
<td></td>
</tr>
<tr>
<td>Age in years (mean)</td>
<td>36</td>
<td>37</td>
<td>NS</td>
</tr>
<tr>
<td>HIV transmission</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>homosexual contact</td>
<td>35 (81)</td>
<td>34 (85)</td>
<td></td>
</tr>
<tr>
<td>heterosexual contact</td>
<td>4 (9)</td>
<td>5 (13)</td>
<td>NS</td>
</tr>
<tr>
<td>intravenous drug use</td>
<td>2 (5)</td>
<td>1 (3)</td>
<td></td>
</tr>
<tr>
<td>other</td>
<td>2 (5)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Time in months since positive HIV test (mean)</td>
<td>59</td>
<td>58</td>
<td>NS</td>
</tr>
<tr>
<td>CD4+ cell count (x10^6/l)</td>
<td>398 ±184</td>
<td>537 ±176</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>(160-990)</td>
<td>(280-960)</td>
<td></td>
</tr>
<tr>
<td>Disease stage</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>asymptomatic</td>
<td>20 (47)</td>
<td>34 (85)</td>
<td>0.0006</td>
</tr>
<tr>
<td>symptomatic/AIDS</td>
<td>23 (54)</td>
<td>6 (15)</td>
<td></td>
</tr>
<tr>
<td>Attitude towards treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>positive/very positive</td>
<td>10 (23)</td>
<td>6 (15)</td>
<td></td>
</tr>
<tr>
<td>neutral/negative/very negative/??</td>
<td>33 (77)</td>
<td>34 (85)</td>
<td>NS</td>
</tr>
<tr>
<td>Type of care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GP only</td>
<td>25 (58)</td>
<td>34 (85)</td>
<td>0.01</td>
</tr>
<tr>
<td>Specialist</td>
<td>18 (42)</td>
<td>6 (15)</td>
<td></td>
</tr>
</tbody>
</table>

^1Of the 43 patients who started, six did not return the final questionnaire. The population presented in this paper is constituted of the 37 patients who completed the questionnaire.
Characteristics of the study population at initiation of treatment

The study population consisted of 33 male (91% homosexual) and four female patients. The female patients had acquired HIV through heterosexual contacts. When therapy was initiated, five patients (14%) were asymptomatic, and 32 (86%) were symptomatic or had AIDS. The mean CD4+ cell count at the start of treatment was $203 \times 10^6$ (SD 120, range 10-570). Only 19% of the patients had a CD4+ cell count above $300 \times 10^6$. The median number of months during which patients had received therapy when completing the questionnaire was six (range 4-14).

The decision to start treatment

Thirteen of the 37 patients (35%) indicated that the decision to start had been primarily their own. In the case of 15 patients (41%) the decision had been made by patient and physician together (with GP: 14%, with specialist: 27%) and in 9 cases (24%) the decision had been made primarily by the physician (GP: 8%, specialist: 16%).

At the start of treatment, 22 patients (60%) had felt satisfied or very satisfied with the decision to start, 12 patients (32%) had felt neither satisfied nor dissatisfied, and three (8%) had felt dissatisfied or very dissatisfied. Medicalisation, fear of adverse events and doubts/uncertainty whether the treatment would be successful or not, were mentioned as reasons for dissatisfaction.

Attitude towards therapy after six months of treatment

Table 2 shows the attitude of the patients towards treatment at the time they completed the questionnaire. The patients are classified according to the number of drugs they were receiving, and whether their therapy had undergone a modification.

Two patients had a negative attitude towards treatment; one had already stopped because of side effects, the other (who received quadruple therapy) simply did not like medication of any kind. Two patients were neither positive nor negative: one because he preferred triple therapy, which at that time was not available yet, the other because of difficulties with the large number of pills. All four patients who did not have a positive attitude towards therapy after six months had been symptomatic at the start of treatment and had a CD4+ cell count $\leq 350 \times 10^6$ (mean CD4+ cell count $167 \times 10^6$). Three of them had taken the initiative to start; in the fourth patient the decision to start had been primarily the doctor’s.

Of the 33 patients with a positive to very positive attitude towards treatment after six months, 76% had participated in the decision to start, and 85% had been symptomatic or had AIDS with a mean CD4+ cell count of $207 \times 10^6$ when treatment was initiated. In 22 of these 33 cases, favourable results of the therapy had led to their positive attitude:
CD4+ cell numbers had increased, viral loads had decreased, clinical symptoms had diminished or were resolved, and/or their general well-being had improved. Four of these patients did experience side effects of the medication, but were positive nevertheless.

Table 2. Attitude towards antiretroviral therapy in relation to the number of drugs the patient was receiving when completing the questionnaire. Percentages are given in parentheses.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>(very) positive</th>
<th>not positive/not negative</th>
<th>(very) negative</th>
</tr>
</thead>
<tbody>
<tr>
<td>no drugs (stopped)</td>
<td>1</td>
<td>2 (100)</td>
<td></td>
<td>1 (100)</td>
</tr>
<tr>
<td>Still 1 NRTI</td>
<td>2</td>
<td>2 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Still 2 NRTIs</td>
<td>8</td>
<td>7 (89)</td>
<td></td>
<td>1 (11)</td>
</tr>
<tr>
<td>Still 2 NRTIs +1 PI</td>
<td>20</td>
<td>19 (95)</td>
<td></td>
<td>1 (5)</td>
</tr>
<tr>
<td>Currently 2 NRTIs + 1 PI</td>
<td>5</td>
<td>5 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently 2 NRTIs + 2PIs</td>
<td>1</td>
<td></td>
<td></td>
<td>1 (100)</td>
</tr>
<tr>
<td>Total</td>
<td>37</td>
<td>33 (89)</td>
<td>2 (5)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

1 NRTI = nucleoside reverse transcriptase inhibitor; PI = protease inhibitor

Two patients were positive about their treatment because they did not/no longer experience side effects and one because the side effects were not as bad as he had expected. Three patients were positive because they now had a new perspective for the future. The remaining five patients gave varying reasons for feeling positive about treatment.

Because of the very small numbers of asymptomatic patients (n=5) and of patients with a non-positive attitude towards treatment after six months (n=4) in our sample, statistical testing for differences in the extent to which patients participated, the CD4+ cell count and the disease stage between patients with a positive attitude and patients with a non-positive attitude after six months of therapy could not be performed in a reliable way.
Discussion

Some interesting observations were made in this study among the 37 HIV-infected patients who started antiretroviral treatment between 1995 and 1997. As could be expected, their mean CD4+ cell count was significantly lower and their disease stage significantly more advanced at baseline compared to non-starters. Despite this fact, there was no significant difference in attitude towards therapy at baseline.

Although the majority of the patients who started with therapy initially did not have a positive attitude towards treatment and 40% still had mixed feelings after the decision to start had been made, 90% of them had a positive attitude towards treatment after six months of therapy. In the group receiving triple therapy, the proportion of patients with a positive attitude was even higher (96%), which is promising in view of the side effects and complicated dosing schedule of triple therapy. In only one patient treatment - with two drugs - was discontinued, because of side effects.

It is likely that the deteriorating medical condition of the patients was one of the principal determinants of the more positive attitude towards treatment at start of therapy as compared to baseline. A positive correlation between HIV disease stage and patients’ attitudes towards, and adherence to, a single-drug regimen has been described before by several authors.\(^{20,21}\) Obviously, the positive results of treatment further increased the patients’ satisfaction with treatment, despite side effects and other disadvantages; these did not seem to play an important role.

Most patients (76%) had actively participated in the decision to start treatment. Their positive attitude towards treatment and the very low discontinuation rate after six months of therapy suggest that the degree of patient participation is another important factor in determining patients’ attitudes towards antiretroviral therapy.

A fourth factor is time. Earlier results of the HIV Intervention Study had shown that after becoming eligible for antiretroviral therapy during the study, only 59% of eligible patients had actually started within a year (M. Reedijk et al, submitted for publication). Patients obviously had to get used to the idea of starting therapy. The factors time and disease progression are thus likely to be closely interlinked.

Our data do not permit statistically sound conclusions on the relationship between disease stage or degree of participation in treatment decisions, and attitude towards antiretroviral treatment. A controlled study with comparable groups is required to determine whether significant relationships exist.

In conclusion: in the population we studied, the vast majority of patients were positive about their treatment after six months of antiretroviral therapy, which in most cases consisted of triple therapy. It is likely that active patient participation in treatment decisions, advanced disease stage, results of treatment, and time each contributed to their positive attitude. Although the weight of each separate factor could not be determined, the high level of satisfaction with antiretroviral treatment is promising in view of the disadvantages of triple therapy. Considering the importance of this finding
for adherence to treatment, we think every effort should be made by physicians to ensure that patients are ready for antiretroviral treatment when they start. These efforts include: initiation of the discussion about antiretroviral therapy in the earliest possible stage, and assurance of maximum patient participation in the decision-making process.

Acknowledgement


References


19. Ancelle-Park R. Expanded European AIDS case definition. Lancet 1993; 341:441