Initiation of antiretroviral treatment for HIV infection. Studies in the general practice
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When do HIV-infected persons start with antiretroviral therapy?

A retrospective analysis of patients’ monitoring and treatment status in general practice, as compared with the 1991 Dutch HIV treatment guidelines

M. Reedijk, J. Mohrs, L. Wigersma

Summary

In a sample of Amsterdam general practices, we aimed to compare the monitoring and treatment status of HIV-infected patients to the 1991 Dutch consensus guidelines for antiretroviral treatment of HIV infection. This guideline advised to start therapy at a CD4+ cell count ≤ 300 x 10^6/l in asymptomatic patients, or a CD4+ cell count ≤ 400 x 10^6/l in symptomatic patients.

In 1994, data were collected from the records of all 511 HIV-infected patients registered in 14 Amsterdam general practices (twenty doctors). The main outcome measures were the antiretroviral treatment status of all patients who were eligible for treatment, and the disease stage and CD4+ cell count at the onset of therapy in patients who started treatment following publication of the 1991 guidelines.

For 472 patients, data were available on CD4+ cell measurement status and disease stage. For 15.9% of patients, CD4+ cells had never been measured; most of them were asymptomatic. In 84.1% of patients, CD4+ cells had been measured. Of the 8.9% of patients whose results were not known to GPs, 93% were treated by a specialist and 76% were symptomatic. Of the remaining 355 (75.2%) patients whose CD4+ cell count and disease status were known, 201 (56.7%) met the guideline criteria for treatment. Of these, 53.7% received treatment, 27.4% were never treated and 18.9% had discontinued treatment. Of 67 patients who started treatment following publication of the guidelines,
36.2% of asymptomatic patients and 92.8% of symptomatic patients started later than the guidelines advised.

Conclusion: in the population studied, we found a discrepancy between the 1991 treatment guidelines and the actual situation. In a substantial proportion of eligible patients, antiretroviral treatment was either not administered at all, or at a (very) late disease stage. This can only be attributed to physicians’ and/or patients’ attitudes towards antiretroviral treatment. Other studies confirm that a number of psychological factors may influence treatment decisions. The new combination treatment of HIV infection requires an early start and compliance with the guidelines. The degree to which doctors and patients are willing and able to comply with the guidelines is an important factor to be taken into account, both in research and in the development of guidelines.

Introduction

In the Netherlands, many persons with an asymptomatic HIV infection only visit their GP; they do not receive specialist care. For antiretroviral treatment, HIV-infected persons have to be referred to the AIDS specialist, as GPs are not allowed to initiate antiretroviral therapy. Patients who receive care from an AIDS specialist may also see their GP for HIV-related matters, depending on the relationship they have with their GP and the GP’s knowledge of HIV.

In Amsterdam, where 50% of the country’s cases of HIV and AIDS have occurred, almost 60% of all HIV patients are registered with 11% of the GPs (unpublished data). Experience shows that in these ‘expert’ practices, HIV patients receive care shared between the GP and the AIDS specialist, although there are no supporting research data available.

In 1991, the Dutch AIDS specialists developed the first consensus guidelines for antiretroviral treatment of HIV-infected persons, which were published in the country’s leading journal of medicine, the Nederlands Tijdschrift voor Geneeskunde.1 Neither other medical professionals, nor patients were involved in this process, and apart from publication no effort was undertaken to implement the guidelines. Based on the information available at that time, it was recommended to start zidovudine (200 mg, 3 times daily) in asymptomatic HIV-infected persons at a peripheral blood CD4+ cell count of ≤ 300 x 10^6/l, and in persons with clinical symptoms of HIV infection at a higher CD4+ cell count, ≤ 400 x 10^6/l.

Reasons for referral to an AIDS specialist by the GP could be the patient’s wish for (early) antiretroviral treatment, a decrease in CD4+ cell counts, the development of HIV-related symptoms, or a combination of these.

It is obvious that important decisions regarding interventions in HIV-infected persons are made in the general practice. The degree of adherence to treatment guidelines, both in the general practice and in clinical practice, is unknown. It is likely to depend, among
other factors, on the attitude of physicians and patients towards monitoring and treatment. Consequently, a proportion of HIV-infected persons who are eligible for antiretroviral therapy may not receive it. The new combination treatments require strict adherence to monitoring and treatment recommendations. Therefore it is important to investigate whether treatment guidelines are followed in daily practice, and to study the factors which influence considerations and decisions of patients and doctors with respect to CD4+ cell monitoring and the initiation (or deferral) and degree of sustainment of antiretroviral therapy for HIV infection.

In order to assess these factors, a prospective study (the HIV Intervention Study) was started in 1995. Prior to this study, the monitoring and treatment status of patients who were eligible for antiretroviral therapy was compared with the recommendations of the 1991 consensus guidelines.

Methods

Twenty GPs in 14 practices in Amsterdam who were going to participate in the HIV Intervention Study, collected data from the records of their HIV-infected patients. The selection of GPs and patients was as follows. It was our intention to select GPs with five or more untreated HIV-positive patients for the HIV Intervention Study, in order to secure a minimum level of interest and involvement. As we did not know how many GPs would meet this criterion, we notified all 400 Amsterdam GPs about the study and asked them if they were interested in participating. Sixty GPs responded, the majority of whom did not meet this criterion. Twenty GPs with five or more patients agreed to participate. For the present study they were asked to collect data on the treatment status from the records of all their living HIV-infected patients. Data collection took three months (Oct.-Dec. 1994). For staging of HIV infection we distinguished two categories: (i) asymptomatic HIV infection, including acute HIV infection and persistent generalised lymphadenopathy, and (ii) symptomatic HIV infection and AIDS. The study was performed on an anonymous basis.

Results

Study population

At the time of data collection, 511 HIV-infected patients were on the lists of the participating GPs (91% male, 9% female; 80% homosexual men, 11% IVDU). The number of patients per practice differed greatly; three practices, each contributing more than ninety patients, accounted for 60% of all patients. Four practices had twenty to forty patients, and seven had less than twenty.
Disease stages and CD4+ cell monitoring

Of 472/511 (92.4%) patients, analysable data were available. In 75/472 (15.9%) patients the CD4+ cell count had never been measured. Of these patients, 58 (77.3%) were asymptomatic and 17 (22.7%) symptomatic; 72 (96%) were treated only by their GP. Of 42/472 (8.9%) patients the CD4+ cell count result was not available to the GPs; 39 (92.9%) of them were treated exclusively by an AIDS specialist. In 355/472 (75.2%) patients the CD4+ cell count and the disease stage were known to the GP.

Antiretroviral therapy

Of the 355/472 (75.2%) patients whose CD4+ cell count and disease stage were known, 103 (29%) were in GP care only, and 252 (71%) were (also) treated by a specialist. In total 201/355 (56.7%) met the 1991 consensus guideline criteria for antiretroviral treatment. Of these patients, 108 (53.7%) received treatment, 55 (27.4%) had never been treated, and 38 patients (18.9%) had their treatment discontinued. Of the patients who had never been treated, 62% were in specialist care; of those who had been treated, over 90% were in specialist care.

Table 1 shows the disease stage and CD4+ cell counts at the start of antiretroviral therapy for patients who were eligible for treatment and started therapy after publication of the consensus guidelines in 1991. Of asymptomatic patients, 4/11 (36.2%) started therapy at CD4+ cell counts below 200 x 10^6/l, and 2/11 (18.1%) at CD4+ cell counts below 100 x 10^6/l. Of symptomatic/AIDS patients, 52/56 (92.8%) started therapy at CD4+ cell counts below 300 x 10^6/l, and 40/56 (71.4%) at CD4+ cell counts below 200 x 10^6/l.

Discussion

This is the first study in the Netherlands in which the monitoring and treatment status of HIV-infected patients eligible for antiretroviral therapy has been compared with treatment recommendations. The representativeness of the data for the situation in the Netherlands cannot be assessed. As the 14 general practices that were studied had well over 50% of the caseload of HIV/AIDS in Amsterdam at the time of data collection, the data probably reflect the situation in Amsterdam fairly well.

A recent study in Amsterdam has confirmed this distribution pattern among general practices. Fifty-eight per cent of HIV patients are registered with 29 GPs (11%) who have 11 or more HIV patients on their list. Another 11% of GPs have between six and ten HIV patients, 57% of GPs have five or fewer, and 21% have no HIV patients on their list. As the great majority of the patients in this study were registered with GPs in
Table 1. Disease stage and CD4+ cell counts (x 10⁹/l) at the start of antiretroviral therapy in patients who were eligible for treatment and who started therapy after publication of the consensus guideline (n=67)

<table>
<thead>
<tr>
<th>Criteria</th>
<th>No (%) of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Asymptomatic and</strong></td>
<td></td>
</tr>
<tr>
<td>CD4+ &lt; 100</td>
<td>2 (18.1)</td>
</tr>
<tr>
<td>CD4+ 100-200</td>
<td>2 (18.1)</td>
</tr>
<tr>
<td>CD4+ 200-300</td>
<td>7 (63.7)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>11 (100)</td>
</tr>
<tr>
<td><strong>Symptomatic/AIDS and</strong></td>
<td></td>
</tr>
<tr>
<td>CD4+ &lt; 100</td>
<td>26 (46.4)</td>
</tr>
<tr>
<td>CD4+ 100-200</td>
<td>14 (25.0)</td>
</tr>
<tr>
<td>CD4+ 200-300</td>
<td>12 (21.4)</td>
</tr>
<tr>
<td>CD4+ 300-400</td>
<td>4 (7.1)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td>56 (100)</td>
</tr>
</tbody>
</table>

the first group, it can be assumed that their GP had sufficient experience and knowledge of HIV.

For a small minority of patients, the CD4+ cell count had never been measured. Most of them were asymptomatic and nearly all of them were cared for solely by the GP. Of all assessable patients who were eligible for treatment according to the recommendations, more than a quarter had never been treated - 60% of whom were solely in GP care - and almost a fifth had discontinued treatment. Patients who discontinued treatment most probably did so because of problems with compliance, ineffectiveness of treatment or side effects. A considerable proportion of patients eligible for treatment who started antiretroviral therapy following publication of the consensus guidelines did so at a (very) late stage of infection. It is unlikely that the GPs in our sample were less aware of the monitoring and treatment recommendations than the AIDS specialists, but there nevertheless was a difference in monitoring and treatment status between patients who received only GP care and patients who were also treated by a specialist.

Data on the onset or delay of antiretroviral treatment in HIV-infected patients who died between 1992 and the time of assessment were, for several reasons, not available. Although such data would have completed the picture, they would not have changed our finding that the monitoring and treatment status of HIV-infected patients substantially differed from the recommendations in the 1991 consensus guidelines for antiretroviral treatment.

The question of the degree to which provider and/or patient-related factors have contributed to these findings could not be addressed in this retrospective study. However, from previous research it follows that both physicians’ and patients’ attitudes
and opinions towards CD4+ monitoring and antiretroviral treatment can be causal factors. The fact that neither patients nor other health care professionals were involved in the development and implementation of the consensus guidelines may be another factor.

Facts as well as opinions influence attitudes towards antiretroviral treatment in different ways and with different effects. At the moment of data collection, there was uncertainty about the moment at which antiretroviral treatment should be started, the agent(s) with which to start, and their effectiveness. After publication of the Concorde study results in 1993, treatment of asymptomatic patients with zidovudine became questionable. Two studies showed a negative effect of Concorde on the prescription of zidovudine. As a result of this controversy, patients as well as physicians may well have chosen to delay antiretroviral treatment.

For the majority of the patients in a study of Nannis et al., psychological factors like hope and perceptions of personal control were more important than medical factors in the initiation and/or maintenance of zidovudine therapy. The role of health beliefs has been stressed by several authors. Patients’ health beliefs and their relation to (zidovudine) treatment seem to play a role in treatment decisions, and attitudes and beliefs about zidovudine are considered as predictors of zidovudine compliance.

As reasons for rejection or delay of antiretroviral treatment by HIV-infected patients Siegel et al. reported: distrust in the ‘medical establishment’, anticipated toxicity and side effects of the available treatments, stigmatisation, stress and anxiety associated with monitoring, fear of being disqualified from future trials, and unwillingness to risk being assigned to a placebo study arm in a clinical trial.

An anticipated decrease in quality of life as well as the confrontation with one’s HIV status when taking antiretrovirals may also be reasons to reject treatment, especially for asymptomatic HIV-infected persons. Stall et al. identified the quality of the doctor-patient relationship as an important factor in the adherence of HIV-infected patients to prophylaxis for opportunistic infections. It is likely that doctor-patient interaction influences decisions regarding antiretroviral therapy as well. The reasons for starting antiretroviral therapy late or not at all cannot be inferred from the present study. The HIV Intervention Study will provide an insight into provider- and patient-related factors, both in general and in specialist care, which determine decision-making regarding monitoring and treatment in HIV infection.

In view of the current combination treatment of HIV infection, the findings of both the study reported here and the prospective HIV Intervention Study are important. The new treatment strategy is to administer triple combination therapy in an early stage of HIV disease. In order to prevent the development of viral resistance, strict adherence to the treatment regimen is highly important. The success of this rather aggressive approach will not only depend on proven effectiveness, but probably even more on the degree to which doctors and patients are willing and able to sustain and support treatment.
Considering the fact that the majority of HIV patients are registered with GPs with a high HIV caseload and hence a lot of expertise in the field, it is very important that GPs as well as patients are involved in the development of strategies to improve treatment compliance, which should be based on research data on factors which influence adherence to treatment.

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