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

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Summary

This thesis describes studies on the initiation of antiretroviral therapy that have been performed in the general practice, against a background of fast moving developments in the field of HIV treatment.

Part I of chapter I (introduction) summarises the main developments in the field of HIV research. Improved treatment options, a growing insight into the HIV pathogenesis and the development of new techniques to detect and quantitate plasma HIV RNA have led to multiple revisions of the treatment recommendations in the past years. In the early years of the epidemic a restrictive policy with regard to treatment initiation was justified, considering the limited effect on the disease prognosis of the drugs available at that time. As from 1996, however, the recommendation is to start with the most potent combination of drugs in a very early stage of the infection.

In part II of this chapter, several aspects of treatment decision-making between doctors and patients are discussed. From a study of the literature it follows that, apart from medical factors, patients' views with regard to the illness and its treatment, their health perceptions, the doctor-patient interaction, and experience of the physician with the disease may play a role in the decision-making on treatment.

Epidemiologic data on the Dutch HIV/AIDS epidemic and background information on the organisation of HIV/AIDS care in the Netherlands are provided in part III, the objectives and design of the research described in this thesis in part IV of this chapter.

In chapter II the results of a pilot study conducted in 14 Amsterdam practices (of which 13 participated in the HIV Intervention Study later on) are presented.

By the end of 1994, 511 HIV-infected patients were registered in these practices. Information on CD4+ cell count and disease stage was available for 355 patients, of whom 201 met the criteria for treatment. Of these 201 patients 108 (54%) received therapy, 55 (28%) were never treated, and 38 (19) had discontinued treatment. Of the 67 patients who had started after publication of the treatment guidelines in 1991, 56 (84%) had started later than was recommended at that time; forty (60%) had been symptomatic with a CD4+ cell count < 200 x 10^6/l. The results of this pilot study show that in 1994 a considerable proportion of patients was not receiving therapy in accordance with the treatment guidelines.

In chapter III the changing attitude towards antiretroviral treatment within a group of 21 GPs who participated in the HIV Intervention Study until the end of the follow-up period is described.
In 1995, only half of the GPs had a positive attitude towards treatment of patients who qualified for therapy according to the prevailing recommendations: 12 (57%) were positive about treatment of asymptomatic patients with a CD4+ cell count ≤ 300 x 10^6/l, and 11 (52%) about treatment of symptomatic patients with a CD4+ cell count ≤ 400 x 10^6/l. At that same time, the 14 heterosexual GPs in the study were significantly more positive about treatment as compared to the seven homosexual GPs who participated.

Two years later however, mainly as a result of the positive news about triple therapy following the Vancouver AIDS conference in 1996, the proportions of GPs with a positive attitude had increased from 57 to 81% and from 52 to 95%, respectively. This positive change in attitude was most marked in the homosexual GPs, and differences between homo- and heterosexual GPs were no longer significant.

No association was found between the experience of the GPs with HIV and their attitude towards therapy. The median number of cumulative HIV-infected patients registered in the practices at baseline has been used as cut-off level in order to distinguish between high and low level experience; this was set at 20 patients. It may be that differences in attitude become apparent when a lower limit is used.

As from August 1996, treatment was recommended for all patients with CD4+ cell counts < 500 x 10^6/l. At the end of 1996/beginning of 1997, however, only nine of the GPs (48%) reported having a positive attitude towards treatment of patients with a CD4+ cell count > 300 x 10^6/l. Side effects, medicalization and strict dosing schedules were most frequently mentioned as disadvantages of treatment.

The role of the patient in the decision-making with regard to treatment initiation was studied in a group of 43 patients (86% homosexual, 70% high level of education) who had met the criteria for treatment for the first time during the HIV Intervention Study (chapter IV).

At baseline all patients to a greater or lesser extent expressed a preference to participate in treatment decision-making. The majority had a high preference for autonomy: according to 24 (56%) of the patients decisions should be made either mainly by the patient, or by the patient alone. According to the GPs, 33 of the 38 patients (87%) who were analysable at this point had also actually participated in the initial decisions on therapy that had been made once they had met the criteria for treatment. In the majority of cases treatment was initially rejected. Twenty-four of the 43 patients started with therapy after all; of the 16 patients with analysable data on this part of the study, 12 (76%) reported to have participated in the final decision to start.

Time to initiation of treatment has been estimated by using the Kaplan-Meier method. Of the 16 patients who had met the treatment criteria before August 1996, 15 (94%) had started within 12 months, whereas of the 27 patients who had met the treatment criteria in the period between August 1996 and January 1997 only nine (33%) had (p < 0.001). As a direct consequence of a revision of the treatment recommendations in August 1996,
the patients in the first group had a significantly lower CD4+ cell count as compared to
the patients in the second group (240 versus 455 x 10^6/l).

The results in this chapter demonstrate that the patients played an important role in
the decisions that were made on treatment. In addition, the data show that initiation of
therapy was delayed considerably, particularly in the group of patients with relatively
high CD4+ cell counts who had met the revised criteria for treatment.

In chapter V the results of a multivariate analysis of factors possibly associated with the
initiation of treatment are presented. The data again refer to the group of
(predominantly) homosexual men who had met the criteria for treatment during the HIV
Intervention Study. In this analysis patients who became eligible in the period between
January and April 1997 were also included; the study population in the present chapter
therefore consists of 49 patients instead of the 43 patients described in chapter V.

Sixteen patients met the treatment criteria before August 1996, and 33 in the period
between August 1996 and April 1997. The outcome variable in the analysis was ‘started
treatment by September 1997’. Apart from various sociodemographic patient
characteristics, some other possibly explanatory variables included several
psychological characteristics, which had been assessed in the last questionnaire
completed before the date the patients became eligible for therapy.

As a result of a revision of the treatment recommendations in August 1996, the CD4+
cell count had to be treated as a design confounder with forced adjustment in the
regression analysis. Nevertheless, the patients’ disease stage at the time of meeting the
treatment criteria was included in the analysis. Three variables appeared to be
independently and significantly associated with the initiation of treatment in the
multivariate Cox regression analysis; one in a positive, and two in a negative way.

The patients’ perception of their health, not their actual disease stage, appeared
predictive of treatment initiation: patients with a score lower than or equal to the median
score of the study population on the ‘general health’ scale of the Medical Outcomes
Study (MOS) HIV health status survey were more likely to start treatment than patients
with a score above the median.

Patients who, prior to the date of eligibility, had indicated to have received sufficient
information on HIV from their GP were less likely to start than patients who thought
they had not been sufficiently informed. This seems a rather odd finding, as it suggests
that it may be better to keep patients uninformed. Yet in view of the earlier mentioned
reservedness of the GPs in this study with regard to (early) treatment this result becomes
less contradictory, for the information on treatment may have been ‘coloured’ in a
negative way at that time.

The patient’s attitude towards treatment before meeting the treatment criteria,
however, proved the strongest predictor of future treatment initiation. Patients with a
negative attitude towards therapy were 5.9 times less likely to start than patients with a neutral or positive attitude towards treatment (90% CI 16.4 - 2.2).

From the results presented in this chapter follows the importance of exploring the patients’ views on their health and on the disease and its treatment in an early stage of the infection.

Of the total group of 94 study participants 43 started treatment during the HIV Intervention Study. Thirty-seven of these patients completed a questionnaire after an average six months of therapy; results of this questionnaire are discussed in chapter VI.

The median CD4+ cell count at start of treatment was $203 \times 10^6/\text{l}$, and 86% of the patients were symptomatic or had AIDS when treatment was initiated. Thirteen patients (35%) indicated that the decision to start had been primarily their own, 15 (41%) reported that the decision had been made by patient and physician together and in nine cases (24%) the decision had been made primarily by the physician. At the time of the questionnaire all patients but one were still on therapy; the majority ($n=25$) received a combination of three drugs including a protease inhibitor. Twenty-four (96%) of the patients on triple therapy were positive or very positive about their treatment because of its positive effect on their CD4+ cell count, their viral load, and/or their clinical condition; side effects did not seem to play an important role. At the start of the study only one-third of these patients had been positive about their treatment.

It is likely that active patient participation in treatment decisions, advanced disease stage, results of treatment and time all contributed to their positive attitude. Although the weight of each individual factor could not be determined, the patients’ high level of satisfaction with antiretroviral treatment is promising in view of the disadvantages involved with triple therapy. A positive attitude towards therapy has been found to be positively associated with adherence, and since strict adherence is a prerequisite for the success of the current regimens, future research on this issue seems warranted.

The results in chapter V and VII suggest that, despite the option of triple therapy, treatment frequently was started at a late stage of the disease. The observations that were made in the HIV Intervention Study on this issue were confirmed by the results of a larger study within the outpatient HIV clinics of three Amsterdam hospitals; which are presented in chapter VII.

The data of this study in secondary care relate to all 146 therapy-inexperienced patients who were referred to one of the outpatient HIV clinics in the period between April and October 1996, and to a sample of fifty therapy-inexperienced patients who were referred to these clinics in the same period one year later.

Besides the fact that in 1997 the proportion of homo/bisexual man was lower than in the year before (62% versus 40%; $p = 0.01$), there were no statistically significant
differences between patients who had been referred in 1996 and patients who had been referred in 1997. Half of the patients were symptomatic or had AIDS with a median CD4+ cell count of $130 \times 10^6/\text{l}$ and a viral load well above 10,000 copies/ml when presenting at the HIV clinic for the first time. Only 22% of the patients were asymptomatic with a CD4+ cell count $> 400 \times 10^5/\text{l}$. Patients who fulfilled the criteria for treatment started therapy after an average (median) two months.

The fact that the median time between the date at which patients had tested positive for HIV and the date at which they had presented at the clinic was only three months suggests that the advanced disease stage of the patients when consulting the AIDS specialist was not just the result of a delay in the referral, but also the result of a delay in HIV-testing.
The median CD4 cell count at start of treatment was 201 x 10^3/l, and 80% of the HIV-positive-VIH patients were symptomatic or had AIDS when treatment was initiated. Thirteen patients (39.4%) reported that the decision to start had been primarily their own, 15 (47.0%) reported that the decision had been made by patients and physician together and in some cases (24.4%) the decision had been made primarily by the physician. At the time of the questionnaire all patients had been on therapy for at least 6 months. Twenty-four (96%) of the patients felt triple therapy were positive or very positive about their treatment because of its positive effect on their CD4 cell count, their viral load, and/or their clinical symptoms. Some patients did not feel it was an important role. At the end of the study only one third of those patients still were positive about their treatment.

The study and active patient participation in making decisions, advanced disease stages results of treatment and time all contributed to their positive attitude. Although the weight of each individual factor could not be determined, the patients' high level of involvement with management of their disease is promising in view of the auto-antibody involved with triple therapy. A positive attitude towards therapy has been found to be (positively) associated with adherence, and since lower adherence is a prerequisite for the success of the current regimens, future research on this issue seems warranted.

The results of Kaplan-Meier and chi square test, despite the option of triple therapy, treatment regimens and stage of disease stage of the disease. The observations that were made in the HIV intervention study on this issue were confirmed by the results of a larger study with a prospective HIV clinics of these 4 Canadian hospitals, which are reported in chapter VII.

The data of this study in secondary care relate to all 146 therapy-inexperienced patients enrolled during the same period at the HIV clinics in the period between April and October 1990, and in a cohort of HIV therapy-experienced patients who were enrolled in those clinics for a period of at least 1 year.4

Besides the fact that in 1991 the proportion of atopical reactions was lower than in the year before 1990 (p=0.015) there were no statistically significant