In the years that have passed since the onset of the HIV/AIDS epidemic in 1981, important developments in the field of HIV research and treatment have occurred. Whereas initially treatment only had a modest effect on the disease prognosis, and infection with HIV in most patients was lethal within a few years, from 1996 on the HIV infection has increasingly become a manageable chronic condition due to effective treatment combinations. From being mainly palliative, treatment has become close to curative.

However, despite better treatment options the decision when to start therapy has remained complex. The benefits of treatment still have to be weighed against the disadvantages, which are numerous. The success rate of treatment is still nowhere near 100% and uncertainty concerning long-term toxicity and efficacy still exists.

In the Netherlands, practically all HIV-infected patients are registered with a general practitioner (GP), who can be regarded as the ‘gatekeeper’ of the Dutch health care system. Most GPs play a role in HIV prevention, testing and counselling. In particular GPs who are more experienced in HIV care may also play a role in the decision-making on antiretroviral therapy.

This thesis describes studies on the initiation of antiretroviral treatment that have been performed in the general practice, against the background of the fast-moving developments in the field of HIV research and of patient- and provider-related factors that may influence decisions on treatment. Part I of this introductory chapter summarises the main developments in the field of HIV research that have led to the current treatment strategy, and part II gives an overview of the relevant literature on (HIV) treatment decision-making. 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. And in part IV of the introduction, the aims and design of the research performed are discussed.
Changing views on HIV pathogenesis: improved ways of monitoring viral activity

Infection with HIV leads to the progressive destruction of CD4+ T lymphocytes (CD4+ cells), which play a role in the generation and maintenance of immune responses. In the absence of treatment, several stages can be distinguished in the natural history of the disease: 1) the acute infection, which may present itself with influenza- or mononucleosis-like symptoms; 2) an asymptomatic interval, which has been denoted as the period of ‘clinical latency’; and 3) a period of symptomatic HIV disease and AIDS. For adults in developed countries, the median time to the development of AIDS after initial infection is about nine to eleven years. Over the years several classification systems for the staging of the HIV infection have been developed, and in Europe the ‘Expanded European AIDS case definition’ has been used since 1993.

The pace at which immunodeficiency develops is associated with the rate of decline in CD4+ cells. This rate of CD4+ cell decline varies from person to person and is not constant throughout all stages of the infection; acceleration in the rate of decline means disease progression. Because of its strong association with HIV disease, the CD4+ cell count was for many years the primary marker used for the monitoring of patients.

Until 1993 it was common belief that there was no active viral replication during the asymptomatic stage of the infection, as no virus could be cultured from the peripheral blood during the period of clinical latency. Methods for monitoring viral replication, however, initially were poor. The development of better techniques to detect and quantitate virus in clinical specimens resulted in an increasing understanding of the HIV pathogenesis and has had important implications in the design of therapeutic strategies.

In early-stage disease, HIV was found to be active and progressive in lymphoid tissue, and latently infected lymphocytes and macrophages throughout the lymphoid system were found to constitute an enormous intracellular reservoir, from the early to late stages of infection. From studies into the viral dynamics of HIV a very high viral replication rate and turnover of the HIV virion became evident. During incomplete therapy, without suppression of viral replication below detectable levels, the continuing accumulation of mutations was shown to result in the outgrowth of a drug-resistant virus population which stressed the importance of using the most potent regimen. In addition, plasma HIV RNA levels (‘viraemia’ or ‘viral load’) were found to reflect the extent of virus replication throughout the body, and, very importantly, the relationship between viraemia and clinical outcome was established. A single plasma HIV RNA measurement obtained shortly after the initial infection appeared to be a more powerful predictor of disease progression than the number of CD4+ cells. Thus the value of
viral load monitoring was soon increasingly recognised: in clinical practice as a tool for assessing the need for therapy or changes in therapy, and in clinical trials for assessing the potency of a drug (combination).\textsuperscript{13-15}

Changing treatment options

Within a period of twelve years the number of drugs approved for the treatment of HIV infections has increased from one to thirteen. According to their site of action and chemical structure, antiretroviral agents can be grouped into three classes: nucleoside and non-nucleoside inhibitors of the viral enzyme reverse transcriptase (NRTIs and NNRTIs), and inhibitors of the enzyme protease. It is beyond the scope of this thesis to discuss all compounds in detail; only major developments are summarised here.

Monotherapy

The first compound found to inhibit HIV replication was the NRTI zidovudine (AZT). This drug was licensed in 1987 when a significant reduction in mortality and morbidity was observed in patients with AIDS or AIDS-related complex after two to six months of treatment.\textsuperscript{16} AZT was also found to delay disease progression in mildly symptomatic patients and in asymptomatic patients, to reduce vertical transmission and to prevent HIV neurologic disease, including AIDS dementia complex.\textsuperscript{17-20}

The Concorde study, however, showed that the effect of AZT was only temporary; there was no difference in survival between asymptomatic patients who had started immediately and patients who had deferred therapy until the onset of HIV-related symptoms. Besides, no effect of treatment on the overall progression of the disease was found.\textsuperscript{21} Preliminary findings of Concorde were announced in 1993.\textsuperscript{22} Meanwhile, two other NRTIs had been developed: didanosine (ddI), and zalcitabine (ddC). When used as initial monotherapy in an advanced stage of the infection, these compounds were found to be inferior to AZT; yet in patients who had been treated with AZT for at least 16 weeks, switching to ddI was found to be more beneficial than continued AZT treatment.\textsuperscript{21-25}

Dual combination therapy

The benefit of combination therapy over monotherapy has been established in many studies, but the ACTG 175 trial conducted in the U.S. and the European/Australian Delta trial were the largest trials to prove that initial treatment with a combination of AZT plus either ddC or ddI was superior to treatment with AZT alone. Preliminary results on the Delta trial were published in September 1995, and from that moment on AZT monotherapy was considered suboptimal.\textsuperscript{26} In that same year, the NRTIs lamivudine (3TC) and stavudine (d4T) and the NNRTI nevirapine became available for use in combination therapy.\textsuperscript{27-32}
Although dual combination therapy had shown to be superior to monotherapy in delaying disease progression, the long-term prognosis remained poor due to persistent viraemia. More potent drugs were needed to achieve a more complete virus suppression.

**Triple combination therapy**

The major breakthrough in the field of HIV treatment was caused by a new class of drugs, which inhibit the enzyme HIV protease. The first protease inhibitor tested in vivo was saquinavir. The combination of saquinavir plus AZT and ddC was found to be superior to the combination of saquinavir plus AZT or ddC plus AZT, which resulted in the approval of saquinavir in the United States in December 1995. At the same time, preliminary data on the pharmacokinetics, safety and efficacy of ritonavir, a second protease inhibitor, were published, and during a conference in January 1996 it was announced that ritonavir had been capable of reducing mortality by about 50% in advanced AIDS patients. During that same conference very promising preliminary results on a third protease inhibitor, indinavir, were presented. In patients who had previously been given antiretroviral therapy, treatment with this drug in combination with AZT and 3TC was found to result in undetectable plasma HIV RNA levels in most patients.

During the XI International Conference on AIDS in Vancouver (July 1996) updated results on these trials were presented. In the ritonavir study, a significant decrease in mortality in patients who were randomised to the protease inhibitor continued to be seen; in the indinavir study, 80% of the patients on triple therapy continued to sustain undetectable levels of plasma viraemia after 36 weeks of therapy. Short-term results of other trials with a combination of three drugs were equally impressive. Both the new protease inhibitor nelfinavir and the NNRTI nevirapine were able to suppress viral replication to undetectable plasma levels when used in combination with AZT plus 3TC, and AZT plus ddl, respectively. After the Vancouver conference, viral load-driven triple therapy became available in most Western countries, including the Netherlands.

In Europe, death rates among HIV-infected patients have been falling since September 1995, which coincided with the introduction of dual combination therapy. At the beginning of 1998, death rates were only one-fifth of those in 1995. The lowest mortality rates, however, were observed among patients who started a triple-drug regimen that included a protease inhibitor. These findings were consistent with those of a study in the U.S., in which more intensive antiretroviral therapies were found to have resulted in a declining morbidity and mortality rate among patients with an advanced HIV-1 infection.
Changing treatment recommendations

Recommendations for the initiation of antiretroviral therapy in adult HIV-infected patients have been revised several times over the past years (Table 1).

Table 1. National and international recommendations for the initiation of antiretroviral treatment in adult HIV-infected patients.

<table>
<thead>
<tr>
<th>Year</th>
<th>Organisation</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1991</td>
<td>Dutch AIDS specialists</td>
<td>asymptomatic patients: start AZT at CD4+ ≤ 300 \times 10^6/l &lt;br&gt; symptomatic patients: start AZT at CD4+ ≤ 400 \times 10^6/l</td>
</tr>
<tr>
<td>1993</td>
<td>NIAD</td>
<td>asymptomatic patients: start AZT at CD4+ &lt; 200 \times 10^6/l &lt;br&gt; symptomatic patients: start AZT at CD4+ &lt; 500 \times 10^6/l</td>
</tr>
<tr>
<td>1996</td>
<td>IAS</td>
<td>start with 2 NRTIs (+1 PI) if: &lt;br&gt; - CD4+ &lt; 500 \times 10^6/l &lt;br&gt; - VL &gt; 30,000 copies/ml &lt;br&gt; - symptomatic disease</td>
</tr>
<tr>
<td>Dutch AIDS specialists</td>
<td>start with 2 NRTIs +1 PI if: &lt;br&gt; - CD4+ &lt; 500 \times 10^6/l &lt;br&gt; - VL &gt; 10,000 copies/ml &lt;br&gt; - symptomatic disease</td>
<td></td>
</tr>
<tr>
<td>1997</td>
<td>IAS</td>
<td>start with regimen that reduces and maintains VL below level of detection if: VL &gt; 5000 to 10,000 copies/ml</td>
</tr>
<tr>
<td>1998</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* NIAD = National Institute of Allergy and Infectious Diseases (U.S.); IAS = International AIDS Society; NRTI = nucleoside analogue reverse transcriptase inhibitor; PI = protease inhibitor; VL = viral load (plasma HIV RNA copy number)

The first recommendations from a state-of-the-art conference in the U.S. were published in 1993. Based, amongst others, on the results of the trials that have been discussed above in the paragraph on 'Monotherapy', AZT was considered the drug of choice for patients who were treatment-naive. In asymptomatic patients with CD4+ cell counts between 200 and 500 \times 10^6/l, the limited duration of benefit from AZT had to be weighed against its toxicity profile.\textsuperscript{42}

In the summer of 1996, new data on pathogenesis, methods to determine plasma HIV RNA, and availability of new drugs resulted in a radical change in the treatment recommendations.\textsuperscript{43} In addition to CD4+ cell count and clinical status, the plasma HIV
RNA level from now on was used as an independent marker for assessing a patient's eligibility for combination treatment. Although immunological and virological data had shown that the most potent treatment regimen at that time consisted of two NRTIs and one protease inhibitor and data on viral dynamics had stressed the importance of maximally suppressed viral replication, the 1996 international guidelines recommended to reserve the protease inhibitors for patients at higher risk of progression.

This initial reservedness with regard to triple therapy stemmed from limited (clinical) experience with protease inhibitors as initial therapy and in early HIV disease. As patients with plasma HIV RNA levels between 5000 and 10,000 copies/ml were found to be at a higher risk of disease progression, treatment initiation was to be considered for these patients (but was not recommended, as there were no clinical data available to support treatment at this stage of the disease).

As a result of the increasing availability of clinical and basic science study results, the 1996 recommendations were sharpened in 1997. The rationale for early initiation of more aggressive therapy became stronger, and the viral load became the crucial instrument for assessing treatment eligibility.

Recommendations about when to initiate therapy have remained unchanged in 1998. Therapy still is recommended for any patient with an established HIV infection and a plasma HIV RNA level above 5000 to 10,000 copies/ml. Only drug regimens that are able to achieve plasma HIV RNA levels below the limit of detection are being recommended. The importance of an assessment of the patient's ability and willingness to commit to a complex and potentially toxic regimen prior to the start of therapy is being stressed, as less than excellent adherence may result in virus breakthrough and drug-resistant strains.

Dutch treatment recommendations and HIV testing policy

The first Dutch treatment recommendations were published in 1991. They were agreed upon during a national consensus meeting of AIDS treatment specialists. Following the Vancouver AIDS Conference, when protease inhibitors became available for all patients in the Netherlands, the AIDS specialists revised their earlier recommendations conform the prevailing international views. These new guidelines were published in May 1997 (Table 1).

For a long time there has been a restrictive policy with regard to HIV testing in the Netherlands. As no effective treatment was available, the test was considered to be of limited value for persons who had been at risk. Disadvantages of knowing one's HIV status were generally considered to outweigh the advantages, and the decision to be tested was left to the patient. As a result of this policy, only a minority of the HIV-infected persons is currently aware of their serostatus.
Since 1997, in view of the positive results of treatment with triple therapy, this restrictive policy has gradually made place for a more active approach. Initially physicians were only recommended to inform individuals who were considering the test about the new treatment options and individuals belonging to one of the known HIV risk groups who had not been tested yet. In the latter case it was suggested that the physician could actively try to raise the issue of HIV testing.

However, at the beginning of 1999 the Dutch Health Council officially stated that this restrictive policy should be discontinued, since the HIV infection is no longer considered incurable. Physicians are now being recommended to actively offer the HIV test to any person who is at risk. In particular in case of pregnant women an infection with HIV should not remain undiagnosed.

TREATMENT DECISION-MAKING IN HIV INFECTION

The developments in the field of HIV treatment over the past years and the subsequent change in the guidelines discussed in part I of this introduction without doubt had consequences for the decision-making between doctors and patients concerning the question whether and when to start antiretroviral therapy. While the emphasis initially lay on the treatment of patients with advanced HIV disease, the current views and recommendations indicate that therapy should ideally be initiated in every patient with a detectable viral load. Treatment decision-making, however, involves more than living up to treatment recommendations; it is a complicated process in which both patient- and physician-related factors play a role.

The patient’s role in the decision-making process

The paternalistic physician-patient relationship of the past decades, in which the doctor decides what treatment is in the best interest of the patient and the patient carries out the doctor’s instructions, has gradually evolved into a more equal relationship. It has become evident that patients in general want to be well-informed and want to be involved, albeit in varying degrees, in the medical decision-making process.

A younger age, higher education and social class, good communicative skills, a worse prognosis, and a chronic condition, are patient characteristics that were found to be associated with an increase in information exchange and/or participation in the decision-making process. Besides, situational factors such as the length of the interaction and the number of patients seen by the doctor appeared to be related to the amount of information that was transmitted.
Results of research into the effect of shared decision-making on outcome were found to be inconsistent; this was partly due to methodological limitations. Nevertheless, a number of positive effects have been observed. Patients who participated in treatment decision-making felt they had better control of their health.

This is an important finding, as a feeling of control has been shown to play an important role in drug-taking behaviour. Patients might self-regulate their medication in an attempt to assert some personal control of their condition. Even the patients’ perceptions regarding the efforts of their doctor to encourage their participation, and their perceptions regarding the information exchange during the medical visit were found to be related to the patients’ levels of understanding, control, reassurance, expected functional improvement and satisfaction with their physician. It must be remarked, finally, that the provision of more information on the disease and on treatment does not necessarily result in decisions that are in accordance with the treatment recommendations.

A limited number of studies have examined the decision-making on treatment between HIV-infected patients and their physicians. The quality of the relationship with the health care provider appeared to be associated with the patient’s acceptance of treatment and with adherence. A high preference for information and for involvement in the decision-making process was observed, and patients who had felt pressured by their physician to take AZT were more likely to discontinue their medication than patients who had felt encouraged but not pressured. In one study, the patients’ desire to exert control of their own condition and to preserve their health led to the initiation of treatment in some of the patients, but in others it led to the rejection or delay of treatment.

The patient’s attitude towards treatment: reasons for accepting or rejecting therapy

Recent developments in HIV treatment should be taken into account when the patient’s attitude towards treatment is assessed. The widespread publicity on the results of the Concorde trial for example, which showed a lack of benefit of AZT in early HIV infection, resulted in a more negative attitude towards AZT and in a decline of AZT prescriptions. For many years, anti-HIV treatment was only able to slow down disease progression. It was not until 1996, after the introduction of triple combination therapy, that this treatment was also found to prolong survival substantially.

Drugs used for the treatment of HIV are all potentially toxic and can cause possibly severe adverse effects. With the introduction of triple therapy the complexity of the prescribed regimens has increased. Although efforts are being made to simplify therapy, most regimens still have to be taken two or three times a day, with regular intervals.
Some drugs have to be taken on an empty stomach, others with a meal. The number of pills to be taken per day varies for each regimen, but can be over twenty.

The patient’s attitude towards antiretroviral therapy, such as concern about toxicity and faith in efficacy and personal benefit, was found to be associated with acceptance of treatment and/or adherence to recommendations. Apart from attitudinal barriers towards the use of therapy, a decreased therapy adherence was also found to occur in patients who had started therapy and who had actually experienced disadvantages, such as complexity of the regimen or side effects.

Patients generally tend to adhere better to medication that relieves symptoms than to prophylactic treatment. For chronic, ‘asymptomatic’ diseases, such as hypertension and diabetes, patients do not see the importance of therapy, and non-compliance is a major health problem. Patients’ perceptions of their condition as serious were found to be predictive of compliance. It can therefore be expected that asymptomatic HIV-infected patients feel less motivated to start therapy and to comply with treatment recommendations than symptomatic patients and patients who have developed AIDS.

Findings on the relationship between disease stage and acceptance or adherence to antiretroviral therapy are inconsistent though. Asymptomatic HIV-infected patients were found to delay treatment because they were afraid to upset the biological balance that currently kept them ‘healthy’ or because they did not want to accept the ‘sick role’; prior opportunistic infections (AIDS) were found to be a predictor of compliance in patients who had started antiretroviral therapy. In another study, however, no relationship between adherence and disease stage was observed.

Both the extent to which patients perceive their condition as severe and their attitude towards therapy may be related to factors as, for instance, knowledge (of the disease and of treatment), way of coping (acceptance or denial), level of education, and risk group. These factors themselves may be mutually related.

Physician characteristics that may influence the decision-making on treatment

The level of the physician’s interest in, and experience with a disease was found to be associated with his knowledge of, and his views on treatment and patient outcomes. In the case of treatment decision-making on breast cancer, concurrence of opinion on consensus treatment guidelines was more likely to occur in surgeons, in physicians who participated in information networks on cancer, and in physicians with a large number of cancer patients.

Particularly in case of myocardial infarctions, depression and AIDS, there is evidence that the knowledge and quality of care provided by specialists exceeds that of generalists. Studies in hospitals and among primary care physicians showed an association between experience in the management of AIDS and patient survival.
which may be partially explained by the fact that general practitioners (GPs) also were found to adopt new HIV treatments at a slower rate than AIDS specialists. The attitude of the health care provider towards gay lifestyles, finally, has been shown to be an important factor in the relationship with his/her homosexual patients. GPs with a (perceived) supportive attitude towards homosexuality and GPs who were believed to be homosexual themselves, were judged as being more competent by their homosexual patients (HIV-infected and non-HIV-infected). Besides, gay patients with supportive health care providers and patients who believed their health care provider to be homosexual reported fewer communication problems.

HIV/AIDS IN THE NETHERLANDS

Epidemiologic data

Amsterdam, the capital of the country, is the epicentre of the Dutch HIV/AIDS epidemic. Almost 50% of the 4921 cumulative reported AIDS cases in January 1999 were found in this city. Men with homosexual contacts accounted for the majority of all reported AIDS cases (69%). Although their relative contribution has strongly decreased over the years, in 1998 homosexual/bisexual men still accounted for the majority (48%) of the 114 new cases. The second and third groups are formed by heterosexuals and intravenous drug users, who accounted for 35 and 13% of the new cases in that year, respectively.

In view of the availability of effective antiretroviral treatment and, consequently, the increased AIDS-free period, it has been generally recognised that AIDS-case surveillance is no longer the method of choice for monitoring the HIV epidemic. Because a national HIV-surveillance system is still lacking, estimates on HIV prevalence in the Netherlands are based on various survey systems as well as on 'back-projection' of reported AIDS cases. In 1994 the (possibly unbiased) HIV prevalence in Amsterdam was estimated to be around 4000; this was based on extrapolation from surveys on HIV infection and risk behaviour. The other method, back-projection, resulted in a somewhat lower number of cases (n=2391). As from 1997 the total number of HIV-infected patients in the country is estimated to be around 15.000.
Provision of care

The Netherlands has a system of shared care for HIV-infected patients. In general, patients are registered with a GP, who at a certain moment after a positive HIV diagnosis will refer the patient to an AIDS specialist in one of the country’s regional HIV centres. Determination of the best moment to refer a patient differs among GPs; GPs who are inexperienced in HIV care may refer the patient directly after learning about his or her serostatus, whereas more experienced GPs may wait a while. In addition, there are several sexually transmitted disease clinics as well as a clinic for homosexual men in Amsterdam where patients with HIV-related problems can go. Of all Dutch GPs approximately 30% have one or more HIV-infected patients in their practice. As is to be expected, this situation is different in Amsterdam. A study performed in 1996 among 269 GPs in 238 of the 314 (76%) Amsterdam general practices showed that at that time 1149 HIV-infected patients were registered in 192 practices. Eighty-one percent of the responding practices had one or more HIV-infected patients on their list. From this study it also appeared that the relatively small number of thirty GPs (11%) had attracted the majority (57%) of patients (unpublished data). These GPs, of whom some have an HIV caseload of more than one hundred patients, have become very experienced in HIV care. They are likely to care for their patients themselves until there is a perceived need for therapy. At that moment the patient will be referred to a specialist for the first prescription for antiretroviral treatment. This implies that most of the initial decision-making on antiretroviral treatment takes place during the interaction between patient and GP.

In order to gain an insight into the decision-making on the initiation of antiretroviral treatment in the general practice, a sample of principally Amsterdam GPs and their (initially) untreated HIV-infected patients was followed in the HIV Intervention Study from March 1995 to April 1997.

THE HIV INTERVENTION STUDY

Aims

The main objectives of this observational study in a sample of general practices were to assess the decisions made when patients meet the criteria for treatment, to study the role of the patients and their doctors in the decision-making, and to assess when therapy is actually started in comparison to the prevailing treatment recommendations. In addition, we aimed to identify factors associated with the acceptance or rejection of treatment.
Design

Selection of practices
All Amsterdam GPs with five or more untreated HIV-infected patients in their practice were asked to participate in the HIV Intervention Study. In the second instance, GPs outside Amsterdam were also asked to participate in order to increase recruitment. As a result, 19 GPs in Amsterdam (13 practices, accounting for approximately one third of the Amsterdam HIV caseload at that time) and six in other parts of the country (three urban, three suburban) were included in the study.

Pilot study
Prior to the actual start of the HIV Intervention Study, a pilot study was performed in 14 Amsterdam general practices. These were the 13 Amsterdam practices that were going to participate, plus one additional practice that in the end did not participate, as at the start of the study it no longer had any untreated patients on its list. Of all patients registered in these practices the clinical and treatment situation was assessed as a starting point for further research.

Study population HIV Intervention Study
Enrolment of antiretroviral therapy-naive patients for the HIV Intervention Study took place during the first six months of the study. Patients were eligible for participation if they had never received antiretroviral treatment, and if they were able and willing to complete multiple extensive (Dutch) questionnaires throughout the study. Patients were approached for the study during a scheduled visit with their GP; they were not actively contacted.

Of the total number of 94 patients, who were included in the study after informed consent had been obtained, nine were included by the six GPs elsewhere in the country. Within the 13 Amsterdam practices 85 patients were included, which was approximately 30% of the total number of untreated patients in these practices. This low response rate was partially due to the fact that in two practices only a fraction of the total number of 103 untreated patients had been asked to participate. Because of a high workload, the GPs in these practices were only willing to include a very small number of patients. Compared to the total group of untreated patients in the 13 practices, the study participants had less frequently been infected through intravenous drug use (5% versus 13%) but they were comparable with regard to HIV disease stage and median CD4+ cell count.

Two patients changed practices during the study. Their new GPs (both practising in Amsterdam) agreed to participate as well, so finally a total of 27 GPs were included.

Measuring instruments
At baseline and at every six months throughout the study, both the patients and their GPs completed multiple semi-structured surveys on a range of factors likely to be related to treatment decision-making. These questionnaires were for the most part specifically constructed for use in this study and based on a study of the relevant literature and
discussions with various experts in the field. Some components of the patient questionnaire, however, had been validated earlier. Visit registration forms on the patient’s clinical situation and on the actual decision-making on treatment were filled in by the GPs after each patient’s visit. Prior to their use in this study the questionnaires were tested for clarity within specific groups of GPs and patients. More detailed information on the content of the different questionnaires will be provided in chapters III to VI of this thesis.

Initiation of antiretroviral therapy was the main study endpoint.

Substudy in secondary care

As stated earlier, the actual initiation of antiretroviral therapy occurs in consultation with the AIDS specialist. In order to complete the information obtained within the HIV Intervention Study, we also conducted a study within the three main Amsterdam outpatient HIV clinics (Academic Medical Centre, Onze Lieve Vrouwe Gasthuis, and Slotervaart Hospital). The aim of this substudy was to assess the moment at which patients present to the HIV clinic for the first time, and furthermore to determine the subsequent time to treatment initiation. For this purpose data were collected on all therapy-inexperienced patients who had been referred to one of the three hospitals in the period between April and October 1996, and on a sample of patients who had been referred to in the same period one year later.
Outline of the thesis

Chapter II presents data on a pilot study that was performed in 14 Amsterdam practices of which 13 ultimately participated in the HIV Intervention Study. Of 472 HIV-infected patients who were registered in these practices by the end of 1994, the treatment status was compared with the 1991 Dutch treatment recommendations.

In Chapter III, changes in attitude towards antiretroviral therapy are described for 21 GPs who participated in the HIV Intervention Study until the end of the follow-up period.

Chapter IV describes the role of the patient in the decision-making on treatment initiation in a group of patients who became eligible for treatment during the study, based on the prevailing recommendations.

In Chapter V results are presented of a multivariate analysis of factors independently and significantly associated with the initiation of treatment for patients who qualify for treatment.

Chapter VI describes how patients who started antiretroviral therapy during the follow-up of the study look back on their decision to start, and how they view their current treatment, which in most cases consists of triple therapy.

Chapter VII describes referral characteristics, patient characteristics (e.g. risk group, disease stage, CD4+ cell count, viral load) and time to initiation of treatment for all 146 untreated patients who were referred to one of the outpatient HIV clinics between April and October 1996, and for a sample of fifty untreated patients who were referred one year later.

In Chapter VIII the results of the various studies are discussed.
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