REPORT 2003

MONITORING OF HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION IN THE NETHERLANDS

STICHTING HIV MONITORING

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Introduction

The short-term beneficial effect of highly active antiretroviral therapy (HAART) in populations of patients is most clearly shown in a dramatic decline of the HIV-related morbidity and mortality and, for individual patients, in the decrease in HIV-RNA concentration and increase of CD4+ cell number in peripheral blood [1-7]. However, mortality in HAART treated HIV-infected patients is still higher when compared to age and gender matched non-infected individuals [8, 9]. Moreover, adverse events and toxicity, as well as development of resistance are serious complications of treatment with antiretroviral drugs, which possibly change the course and the epidemiology of the infection. In addition, world-wide travelling and migration have an effect on the epidemiology of HIV and the efficacy of HAART in a changing population of infected patients [10-15]. Finally, after 7 years of using HAART for regular treatment, its longer-term effects become apparent.

In this report of the HIV Monitoring Foundation (HMF), data will be presented on the changes in the HIV infected population in the Netherlands following the introduction approximately 8 years ago of HAART. The HMF was appointed in 2001 by the Dutch Minister of Health. Its mission is to register all HIV infected patients seen in 24 hospitals as part of 22 HIV treatment centres in the Netherlands, and to collect and analyse data obtained from those patients in order to study the natural history and the effects of treatment of HIV. Following a comprehensive description of the method of data collection and quality control and after an overview of the characteristics of the study population at baseline, an attempt will be made in this report to answer questions regarding

- The changes over time of the prevalence of newly diagnosed HIV-infections per year and the predicted number of HIV-infected patients in The Netherlands;
- Prevalence of resistant HIV among newly diagnosed patients without prior antiretroviral treatment and the incidence among patients failing on HAART;
- Efficacy of HAART regimens, i.e. the beneficial effect on immunological and virological parameters versus the effect of toxicity;
- The various HAART outcome patterns, including results of HAART regimen switches en interruption;
- The changes in the HIV-related morbidity and mortality.

In the absence of any ongoing randomised trial or study to assess issues like the (long-term) efficacy of HAART regimens, changes in outcome patterns and in morbidity and mortality, studies using (observational) data obtained from prospectively followed patients are needed. However, interpretation of findings from those studies is not straightforward, as serious biases can be present [16]. When carefully interpreted, observational data can nevertheless be informative. Its value largely depends on the number of patients included and in follow-up, as well as the consequent registration of well-defined events. With this in mind, it is of importance to note that the ATHENA-HMF cohort participates in a number of international collaborations, of which the AntiRe-Troviral (ART) cohort collaboration, the collaboration on Data Collection on Adverse Events of Anti-HIV Drugs (DAD) are of importance, especially with respect to analysis of more or less specific clinical data merged from a large numbers of cohorts. Another important but somewhat different collaboration is the one between HMF and the Department of Infectious Disease Epidemiology (DIDE) of Imperial College in London, combining three large datasets together for analysis if needed for certain research questions, but also investing in the methodology and development of mathematical and analytical models to be used with observational data. In this type of studies, prognostic factors for clinical outcome of HAART were firmly established: CD4 cell count and high levels of HIV replication at baseline, older age, a history of AIDS and infection through intravenous drug use were found to be associated with increased rates of clinical progression [1], but also the initial response to HAART [17]. Differences in the residual reproductive capacity of virus (R(0)) in the average patient in a treatment group and therefore between different regimens could be estimated by fitting a mathematical model of the interaction among CD4+ T-cells, HIV-1, and antiretroviral drugs to the viral load decline following initiation of combination therapy [18]. For the first time, it was possible to study the effectiveness of different initial HAART regimens: it became clear that regimens could differ by stage of infection at start of HAART. Moreover, survival and progression to AIDS after starting HAART could be examined in the ATHENA cohort data, pointing at the advantage in this respect of treatment in an early phase of the infection [8]. The DAD study revealed that use of the NNRTI and PI drug classes (alone and especially in combination), particularly among older subjects with normalised CD4 cell counts and suppressed HIV replication, was associated with a lipid profile known to increase the risk of coronary heart disease [19]. Analysis of observational data collected in the ATHENA-HMF cohort - either separate or as part of larger datasets – could be improved by participating in these studies. Subsequent collaboration with other observational cohorts and research groups has anchored the HMF registration and research programme at both national and international level.

In addition to the regular HMF registration and research programme, a number of separate research projects using ATHENA-HMF data have started since 2001. An overview of their results will be presented in this report as well.

The organisational structure of the HMF is largely based on the structure created for the ATHENA project. Data collectors, crucial in recording data and adding data to the national database, are on site and the quality control by the data monitors is ongoing. The HMF analysis unit is essential in the execution of its registration and research programme and its support of groups who have approval to use data from the ATHENA-HMF dataset. HMF working groups and its Advisory Board meet regularly, advising the HMF director and governing board on policy matters as well as the usage of the data collected. However, several important tasks still need to be established. The registration of children born to HIV-infected mothers has just started, yet without a sufficient adaptation of the database. The same holds true for the registration of HIV-infected pregnant women. In part, this is due to the change from one database system to another, which proves to be quite a complex process. Nevertheless, our aim is to improve the data-entry of these two specific HIV infected groups before the end of the 2003.

The total number of HIV-infected patients included in the monitoring as of November 1, 2003 is 8.940. For the analyses discussed in this report, data of in total 8.496 patients were used as of August 1, 2003. Half of these patients started HAART without prior antiretroviral therapy. In comparison to the HMF report 2002 [9], the number of patients included in the study population increased by 3.394 patients. More than half of these patients were treated, most of them with HAART. The remaining patients were not on any antiretroviral therapy. This increase in general, and in the number of patients on HAART in particular, together with the growing number of new antiretroviral drugs since 1996-1999 [7] lead to the question about possible changes in the costs and benefits of HAART. It is fair to assume that the total costs of treatment of HIV will be higher when compared to figures from the early HAART era. Given the new drugs that are currently in use, the costs per patient are likely to have gone up as well. Since recent mortality and morbidity data are available, we recently decided to start a new cost-benefit study. We will publish its results as soon as February 2004.

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Summary

Background

Clinical care for HIV infected patients in the Netherlands is provided by 24 hospitals that are part of 22 HIV Treatment Centres especially appointed by the Dutch Minister of Health. Infected patients followed-up by HIV/AIDS treating physicians in these centres are included in an observational prospective study. Aim of the study is to monitor - mainly from a clinical, but also from a public health perspective - changes in the epidemic of HIV and the effect of treatment of infected patients with antiretroviral combination therapy in The Netherlands.

Methods

Clinical, epidemiological, socio-demographic, virological and immunological data were obtained from the patients at each hospital visit. Co-ordination of the data monitoring and -collection of the is organised within the framework of the national HIV Monitoring Foundation (HMF) in Amsterdam. Central in this framework is the collection of data and its subsequent entry into the HMF monitoring database by dedicated data collectors in each participating hospital. Assessment of the data quality is based on source verification of the data by HMF's data monitors in approximately 10% of the patients newly included into the study.

Study group

Per 1st November 2003, 8.940 patients were participating in the cohort, 2.638 more than in 2002 and between 38.9 and 55.9% of the estimated total HIV-infected population in The Netherlands. For this report, data of 6.637 male and 1.859 female patients obtained until August 1, 2003 were used. Between 1998 and 2000, 3.554 patients >18 years and who started HAART since 1996 were registered as part of the ATHENA project after signing an informed consent form. Thereafter, another 4.942 patients were included, irrespective of age and antiretroviral treatment. A majority of 8.282 patients is infected with HIV-1. Another 28 patients are diagnosed as HIV-2 infected, while for 186 patients the virus type is not yet known. The results presented in this report are from analysis of the HIV-1 infected group only.

Results

The HIV-1 epidemic in The Netherlands is changing as the number of men and women newly diagnosed with HIV-1 is steadily increasing over time. Men having sex with men are still the largest risk group. The prevalence of newly diagnosed HIV-1 cases among homosexual men <30 year stabilises, in contrast to older homosexual men, where an increase of new HIV-1 diagnoses is found.

Heterosexual contact was registered as the route of HIV transmission in 27% of the total study group population - and 72% of the women in the study group. The relative contribution of women to the total population of HIV-1 infected patients doubled in 10 years, increasing from 15% in 1992 to more than 30% in 2002/2003. Median age of women at HIV diagnosis was 29 years, 6 years younger compared to the median age of men. Overall, 40% of the total study group and 68% of the women were of non-Dutch origin. Women from sub-Saharan countries were the largest subgroup, even larger than the group of native Dutch HIV-infected women.

Non-B subtypes were found in half of the non-Dutch patients. Among the sub-Saharan African patients, subtypes other than B were more prevalent. A close relationship between the distribution of non-B subtypes found in this group and the countries of origin was found. Women of non-Dutch origin generally have lower CD4+ counts at diagnosis than Dutch women. Clearly, there was a rise in the number and proportion of relatively young HIV-1 infected women from non-Dutch origins, who acquired the infection in the region of origin and who were diagnosed in a later stage of the infection. Transmission of non-B HIV-1 subtypes within the Netherlands was limited.

Based on the prevalence per year of newly diagnosed HIV-1 infections, we predict an increase of new HIV diagnoses with 9% among homosexual men in 2004 in comparison to 2003, despite the current decline among younger homosexual men. Heterosexual transmission will account for a 13% increase of new HIV-1 diagnoses and is estimated to be higher among women (14.5%) than men (9.6%)

Almost 80% of the study population was treated with highly active antiretroviral therapy (HAART), 2/3 without prior antiretroviral treatment. Nineteen percent of the study population was not treated at all; they had low median HIV-1 RNA plasma levels and relatively high CD4+ cell counts at entry in the cohort. One percent of the population was on an antiretroviral drug regimen other than HAART.

Pre-existing resistance did occur in 4.8% of the newly diagnosed HIV-1 infections and in 6% of the newly infected population. Of the patients on HAART, 3.3% of those who started without prior antiretroviral treatment and 13% of those who started after a period of prior antiretroviral treatment were harbouring resistant virus. This is, however, likely to be an underestimation of the true prevalence as only in a relatively small percentage (9.8%) of the patients failing on HAART, resistance is determined.

Efficacy of HAART appears to be a trade off between virological and immunological success and toxicity. Over time, the most frequently used NRTI backbones in the HAART combination was AZT+3TC (69% of the eligible 4.261 patients) or D4T+3TC (17%). The addition of an NNRTI or PI to the NNRTI backbone varied over time. IND, RTV and SAQ were frequently used in 1996, but are no longer used as an initial regimen. In 1999, NFV - and in 2002/2003 LOP+RTV, EFV, NVP and ABC - were the most frequently used PI's and NNRTI's, respectively.

In 58% of the 2.673 patients that were eligible for short-term effect analysis, viral load levels declined to <500 copies/ml, along with a CD4 rise of 100 cells/mm^3 over a median period of 5.5 months. There were no significant differences between the NRTI backbones AZT+3TC or d4T+3TC, or between the NNRTI's and PI's that were added most frequently in 2002/2003. Toxicity was more often the reason for stopping or interrupting HAART including d4T+3TC as backbone as compared to AZT+3TC. Adding LOP+RTV, EFV, NVP or ABC did not result in a significant difference in this respect.

Differences in long-term efficacy between various HAART regimens were studied in 1.349 adult HIV-1 infected patients without prior antiretroviral treatment, using the initial HAART combination for at least 18 weeks. End-point for long-term efficacy was the slope of CD4 cells from 18 weeks of treatment on. In patients who had a CD4 T cell number <200/mm^3 after the first 18 weeks of HAART, the specific combination of drugs with AZT+3TC or d4T+3TC as backbone did not differ. However, in patients with CD4 T cell counts >200 cells/mm^3 at 18 weeks, differences in CD4 slope after 18 weeks between combinations of HAART were found. IDV or NFV in combination with AZT+3TC or d4T+3TC showed significantly higher CD4 cell slopes than combinations with LOP+RTV, ABC or NFV.

The rate of therapy success, i.e. the number of patients that reached an increase of 100 CD4 cells/mm^3 and a decrease to <500 HIV-RNA copies/ml plasma, was slower among patients of non-Dutch origin. Rapid therapy failure was seen more frequently in this group as well. Predictors for success or failure were CD4 cell number and HIV-1 RNA levels at baseline.

Interruption of HAART was still a common phenomenon. The general pattern was that patients who interrupted HAART had started earlier in time and had

a longer follow-up. CD4 cell number at the end of a HAART treatment period (or at the beginning of an interruption) was the strongest predictor for overall outcome. Patients with a low CD4 cell count at the beginning of an interruption showed a faster decline in CD4 cell counts during the interruption. More time was needed for immunological and virological recovery after re-initiation of therapy.

HAART regimen changes were very frequent as well. Approximately 90% of the patients had their initial regimen changed. Women were at higher risk for HAART regimen change than men were.

The incidence of a first CDC-C event per 100 person-years of follow-up steadily declined from 15.3 in 1996 to 1.8 in 2002. The morbidity rate among patients on HAART having had prior antiretroviral drugs treatment was 18 in 1996, compared to 6.3 in patients without prior antiretroviral drug treatment. After 1996, the morbidity rates between these two populations were the same.

Mortality rates declined further from 4.6 in 1996 to 1.7 in 2003. HIV-related mortality declined from 3.4 in 1996 to 0.61 in 2003, and non-HIV related mortality increased slightly but not significantly over time from 0.46 in 1996 to 0.84 in 2003. The mortality risk was 0.49 times smaller in patients who started HAART in 1998 or thereafter in comparison to patients who started before 1998. Response to HAART, i.e. each unit increase in log transformed CD4 cell count after 24 weeks of HAART, reduced the mortality risk by a factor 0.43.

Recommendations

Based on these findings the following recommendations are made.

- Further research on the changes of the risk of infection in the group of older homosexual men is needed with the aim to improve prevention strategies for this particular group.

- Both from a clinical and from a public health perspective, it is of vital importance to develop a dedicated research programme supporting specific information, awareness and prevention programmes aiming at migrant sub-groups, especially at young women of non-Dutch origin.

- A more accurate knowledge of transmission patterns among migrants by using results of HIV-1 subtyping will help to develop prevention strategies aiming at specific migrant groups. In view of an increasing number of non-Dutch patients receiving HAART along with their higher failure rate on HAART, it is of importance to further investigate adherence to HAART regimens in these specific patient groups. Since women are more likely to switch HAART regimens than men and stop treatment more likely because of toxicity, research on adherence should be combined with therapeutic drug monitoring.

- To monitor whether resistance will increase among the treated population and, subsequently, will be transmitted more frequently; measurement of resistance both at baseline and at therapy failure is needed. In addition, resistance must be measured in all new primary infections. Moreover, more research is needed into changing adherence patterns of HIV-infected patients on treatment. Adherence and resistance data used together in mathematical modelling of resistance would allow for an estimate of the transmission probability of resistant virus.

- Differences in efficacy between second and third HAART regimens should be analysed, considering the efficacy of prior HAART combinations. When analysing the effects of several different regimens together, a large number of variables will be involved which will require substantial computer capacity, which is not currently available. Moreover, a larger dataset will be needed for a thorough statistical analysis. Collaboration with other research groups with the aim to obtain such datasets and to develop analytical models that can handle large datasets and numbers of variables is needed to achieve more insight in the efficacy of various subsequent HAART regimens.

- Registration of mortality and, especially, the particular causes of death must be improved in order to better understand the HIV and antiretroviral drug relatedness. The same holds true for the registration of morbidity where an improvement of the registration of toxicity-related clinical signs and symptoms as well as laboratory results are needed.

Samenvatting

Achtergrond

De klinische zorg voor patiënten met een HIV-infectie is in 24 ziekenhuizen, behorend tot 22 door de Minister van Volksgezondheid, Welzijn en Sport aangewezen HIV Behandelcentra, geconcentreerd. Tenzij patiënten te kennen hebben geven dit niet te willen, worden de data van alle patiënten die in één van de centra door een HIV/AIDS behandelaar worden gevolgd, geïncludeerd in een observationele prospectieve studie. Doel van deze studie is om vanuit een klinisch, maar ook vanuit een public health-perspectief het effect van behandeling van HIV te bestuderen en de ontwikkeling van de HIV-epidemie in Nederland te volgen en te beschrijven.

Methoden

Klinische, epidemiologische, socio-demografische, virologische en immunologische gegevens worden bij elk bezoek aan de HIV/AIDS-behandelaar verzameld. De coördinatie van de monitoring en verzameling van gegevens wordt op verzoek van de Minister van VWS uitgevoerd door de Stichting HIV Monitoring (SHM). Centraal bij het verzamelen van gegevens en monitoren van patiënten staat de aanstelling in elk ziekenhuis van één of meer dataverzamelaars specifiek voor het uit de medische status van een patiënt bijeenbrengen en het in de SHM database invoeren van gegevens over het individuele beloop van de HIV infectie. De kwaliteit van de gegevens wordt bewaakt door datamonitors van de SHM die bij ongeveer 10% van de nieuw in de studie opgenomen patiënten de ingevoerde gegevens met de brongegevens vergelijken.

Onderzoekspopulatie

Per 1 november 2003 namen 8.940 patiënten deel aan het observationele prospectieve SHM cohort. Dat zijn er 2.638 meer dan in 2002; wij schatten dat daarmee tussen de 38.9 en 55.9% van de totale groep met HIV geïnfecteerde patiënten in Nederland wordt gevolgd. Voor het nu voorliggende rapport 2003 zijn gegevens gebruikt van 6.637 HIV-geïnfecteerde mannen en 1.859 vrouwen die op 1 augustus 2003 waren geïncludeerd. Van de totale groep van 8.496 patiënten werden er 3.554 in de studie opgenomen tussen 1998 en 2000, als onderdeel van het ATHENA project. Deze patiënten waren bij inclusie >18 jaar, werden allemaal behandeld met highly active antiretroviral therapy (HAART) en namen deel op basis van informed consent. Een tweede groep van 4.942 patiënten werd geïncludeerd na 2000. Hier golden geen restricties voor leeftijd en behandeling. Het principe van informed consent werd vervangen door een opt-out procedure. Een grote meerderheid van 8.282 patiënten was geïnfecteerd met HIV-1 en 28 met HIV-2, terwijl van 186 patiënten nog niet bekend is of ze met type 1, 2 of met allebei zijn geïnfecteerd. In het nu voorliggende rapport wordt alleen gerapporteerd over de grootste groep, de 8.282 patiënten met een HIV-1 infectie.

Resultaten

De HIV epidemie in Nederland is aan het veranderen. Het aantal mannen en vrouwen, waarbij HIV-1 wordt ontdekt neemt gestaag toe. De prevalentie van HIV-1 onder homoseksuele mannen <30 jaar blijft min of meer gelijk, terwijl deze onder mannen >30 jaar juist weer toeneemt.

Heteroseksuele transmissie van HIV-1 maakt nu 27% uit van de totale HIV-1 geïnfecteerde populatie en 72% van de vrouwen. De relatieve bijdrage van vrouwen aan de totale populatie van HIV-1 patiënten is in 10 jaar gestegen van 15% in 1992 tot meer dan 30% in 2002/2003. De mediane leeftijd van vrouwen op het moment van HIV diagnose is 29 jaar. Vrouwen zijn daarmee op het moment van HIV diagnose 6 jaar jonger dan mannen. Veertig procent van de totale HIV-1 positieve heteroseksuele populatie komt niet uit Nederland, van de vrouwen is een meerderheid (68%) niet in Nederland geboren. Van de groep niet-Nederlandse vrouwen is die afkomstig uit midden en zuidelijk - 'sub-Sahara' - Afrika veruit de grootste, zelfs groter in aantal dan de groep geïnfecteerde autochtone vrouwen.

Resultaten van subtypering van HIV-1 laten zien dat in de helft van de niet-Nederlandse geïnfecteerden sprake is van een non-B infectie, het meest prevalente subtype in Nederland. In de groep patiënten uit midden en zuidelijk Afrika komen meer non-B dan B subtypen voor; er bleek een nauwe relatie te bestaan tussen de prevalentie van non-B subtypes en het land van herkomst. Vrouwen van niet-Nederlandse afkomst hadden bovendien vaker een lager aantal CD4 cellen bij diagnose dan Nederlandse vrouwen. Er is dus sprake van een toename van zowel het aantal als de proportie jonge vrouwen van niet-Nederlandse afkomst, die zijn geïnfecteerd in het land van afkomst en die pas in een latere fase van de HIV infectie worden gediagnosticeerd. Transmissie van non-B subtypes in Nederland is op dit moment nog beperkt.

Als de huidige trend doorzet, dan zal het aantal nieuwe HIV-diagnoses als gevolg van homoseksueel contact in 2004 met 9% toenemen ten opzichte van 2003, ondanks een lichte daling onder jonge mannen met homoseksuele contacten. Het aantal nieuwe diagnoses als gevolg van heteroseksueel contact neemt in 2004 naar onze verwachting met 13% toe en sterker onder vrouwen (14.5%) dan mannen (6%).

Bijna 80% van de onderzoekspopulatie werd behandeld met HAART, twee derde hiervan zonder voorafgaande behandeling met antiretrovirale middelen. Negentien procent van de populatie werd in het geheel niet met antiretrovirale middelen behandeld. Deze groep had op het moment van inclusie in de studie een in vergelijking met de behandelde groepen lage mediane HIV-1 RNA spiegel in plasma en een hoog aantal CD4 cellen. Tenslotte werd 1% van de populatie behandeld met een combinatie van antiretrovirale middelen die niet onder de HAART-definitie valt.

Preëxistente resistentie van HIV-1 tegen antiretrovirale middelen kwam voor bij 4.8% van de nieuwe HIV diagnoses en bij 6% van de nieuwe infecties. Sinds 1996 zijn deze percentages niet veel veranderd. Resistentie werd bij 3.3% van de patiënten gevonden die zonder ooit eerder te zijn behandeld met antiretrovirale middelen met HAART begonnen. Dit percentage was echter bijna vier keer zo hoog (13%) in de groep patiënten die wèl waren voorbehandeld voordat ze met HAART begonnen. Deze percentages zijn mogelijk een onderschatting van de omvang van de groep patiënten die wordt behandeld en waarbij HIV-1 resistent is, omdat slechts bij 9.8% van de patiënten die op HAART virologisch faalden resistentie werd bepaald.

Efficacy van HAART bleek een delicate balans te zijn tussen virologisch en immunologisch succes en toxiciteit. De meest gebruikte nucleoside RT remmers (NRTI's) in HAART waren AZT+3TC (69% van de 4.261 voor dit deel van de in de studie beschikbare patiënten) en d4T+3TC (17%). Protease-remmers (PI's) of non-nucleoside RT remmers (NNRTI's) die aan deze 'backbone' combinaties werden toegevoegd veranderden in de loop van de studieperiode. In 1996,werden IDV, RTV en SAQ nog vaak gebruikt maar deze middelen maken nu geen deel meer uit van initiële HAART combinaties. In 1999 was NVP het meest gebruikte middel, in 2002/2003 waren dit LOP+RTV, EFV, NVP en ABC.

Voor een studie naar het korte-termijneffect van HAART konden de gegevens van 58% van 2.673 niet voorbehandelde patiënten worden gebruikt. In mediaan 5.5 maanden daalde de virale load in plasma tot <500 kopieën/ml in combinatie met een stijging met 100 CD4 cellen/mm^3. Tussen de NRTI combinaties AZT+3TC en d4T+3TC werd geen significant verschil gevonden en evenmin tussen de NNRTI's en PI's die sinds 1999 het meest frequent in HAART werden gebruikt. Toxiciteit bleek vaker een reden tot stoppen van HAART indien d4T+3TC werd gebruikt in plaats van AZT+3TC. Toevoegen van LOP+RTV, EFV, NVP of ABC resulteerde niet in significante verschillen.

Verschillen in langetermijneffect tussen de HAART regiems werden bestudeerd in 1349 volwassen patiënten die, zonder te zijn voorbehandeld, tenminste 18 weken met hetzelfde regiem werden behandeld. Eindpunt voor het langetermijneffect was de stijging of daling in het aantal CD4 cellen vanaf 18 weken. Alleen in de groep patiënten die na de eerste 18 weken behandeling met HAART een CD4 cel aantal >200/mm^3 bereikte, konden verschillen worden waargenomen tussen de gebruikte HAART combinaties. IDV of NFV in combinatie met AZT+3TC of d4T+3TC resulteerden in significant hogere stijgingen van het aantal CD4 cellen na 18 weken dan de combinaties met LOP+RTV, ABC of NVP.

Het aantal patiënten dat onder HAART zowel een stijging van 100 CD4 cellen/mm^3 als een daling van HIV-1 RNA plasmaconcentraties <500 kopieën/ml bereikte, was lager in de groep niet-Nederlandse patiënten. Therapiefalen komt niet alleen vaker, maar ook eerder voor in deze groep. Voorspellers voor succes waren het aantal CD4 cellen en de HIV-1 RNA spiegel bij start van HAART.

HAART interrupties kwamen veel voor en vooral bij die patiënten die kort na 1996 met therapie begonnen en bij patiënten die een langere follow-up hadden. Bij patiënten met een laag aantal CD4 cellen aan het begin van een interruptie werd gedurende de interruptie een snellere daling tot <350 gevonden. Bovendien hadden zij meer tijd nodig voor immunologisch en virologisch herstel nadat zij HAART hadden hervat. Wijzigingen van het HAART regiem kwamen eveneens vaak voor. Ongeveer 90% van de patiënten veranderde tijdens de onderzoeksperiode tenminste een keer van HAART regiem en vrouwen veranderden vaker van HAART regiem dan mannen.

De incidentie voor een eerste CDC-C diagnose per 100 persoonsjaren follow-up daalde van 15.3 in 1996 tot 1.8 in 2003. Deze morbiditeit was oorspronkelijk hoger onder patiënten die voorafgaand aan HAART waren voorbehandeld met antiretrovirale middelen: 18 in 1996 tegen 6.3 in patiënten die niet waren voorbehandeld. Na 1996 verdween het verschil tussen deze twee groepen.

Mortaliteitratios daalden van 4.6 in 1996 tot 1.7 in 2003. HIV-gerelateerde mortaliteit daalde van 3.4 in 1996 tot 0.61 in 2003 en niet aan HIV-gerelateerde mortaliteit steeg licht van 0.46 in 1996 naar 0.84 in 2003. Het risico van overlijden was 0.49 maal kleiner in patiënten die vanaf 1998 met HAART startten in vergelijking met die patiënten die voor 1998 waren begonnen. Elke eenheid toename in het log getransformeerde aantal CD4 cellen na 24 weken HAART reduceerde het risico van overlijden met een factor 0.43.

Aanbevelingen

Op basis van de resultaten die werden gevonden in het observationele cohort van HIV geïnfecteerde patiënten met een mediane follow-up duur van 5.4 jaar, doen wij de volgende aanbevelingen:

- Versterk het onderzoek naar de veranderingen in het HIV-infectierisico in de groep oudere homoseksuele mannen om strategieën voor preventie van HIV-transmissie beter op de informatiebehoeften van deze doelgroep aan te laten sluiten.

- Vanuit klinisch oogpunt en vanuit een public health-perspectief is het van belang om een research-programma te ontwikkelen dat kan helpen bij de opzet en uitvoering van informatieprogramma's voor niet-Nederlanders, vooral voor de groep jonge vrouwen.

- Meer kennis is nodig van de transmissiepatronen in bevolkingsgroepen met een hoog infectierisico. Hierbij is moleculaire epidemiologie van HIV met behulp van subtypering van HIV essentieel. De resultaten zullen van waarde zijn voor het ontwikkelen van doelgroepgerichte preventieprogramma's die zo kunnen worden toegespitst op de specifieke transmissiepatronen binnen deze groepen.

- Het aantal niet-Nederlandse patiënten dat wordt behandeld met HAART stijgt. Tegelijkertijd is HAART efficacy bij niet-Nederlanders lager dan bij autochtone HIV-geïnfecteerde patiënten. Daarom is nader onderzoek naar de therapietrouw van deze groep van belang.

- Vrouwen veranderen vaker van therapie dan mannen. In dit verband is multidisciplinair onderzoek naar de gender-specifieke aspecten van therapietrouw, naar spiegels van antiretrovirale middelen en naar hun toxiciteit van groot belang.

- Om na te kunnen gaan of resistentie in de behandelde populatie zal toenemen en vervolgens zal leiden tot een hogere transmissie rate, is meting van resistentie bij falen en op baseline nodig. Bovendien zou altijd resistentie bepaald moeten worden bij patiënten met een primaire HIV-infectie. Daarnaast is ook in Nederland onderzoek nodig dat voldoende kwantitatieve gegevens oplevert over patronen van therapietrouw die bepalend zijn voor de ontwikkeling van resistentie.

- Verschillen in efficacy tussen tweede- en derdelijns HAART regiems moeten in de toekomst verder worden onderzocht, rekening houdend met het effect van het initiële regiem.Bij analyse van deze verschillen is het grote aantal variabelen een kernprobleem. Samenwerking met andere observationele cohorten is nodig.

- Registratie van mortaliteit en, meer specifiek, van de doodsoorzaken dient te worden verbeterd om meer zicht te krijgen op HIV-gerelateerde mortaliteit en de mortaliteit die gerelateerd kan zijn aan het gebruik van antiretrovirale middelen. Bij de morbiditeitsregistratie is zowel een verbetering nodig van de registratie van klinische symptomen als van de aan toxiciteit van antiretrovirale middelen gerelateerde laboratoriumresultaten.

Data collection

Improvement of the quality of the HIV monitoring data

Introduction

In the ATHENA project, the first priority was to develop a data collection structure that could process high quantities of clinically relevant data. However, because of the substantial increase in the number of included patients, the quality of the data collected and stored in the database was of major concern. Analysis of the observational data in order to answer questions regarding morbidity and mortality of a treated HIV infection, the efficacy of drugs, toxicity and resistance required a well-balanced quality control structure in addition to efficient collection and storage of the data. To achieve high quality data, their validity and reliability had to be maximised [1,4,8]. In this chapter, the different phases in data collection are discussed.

Inclusion

The treating physician in each of the HIV Treatment Centres is responsible for the inclusion of his or her patients. Patients are not asked for their consent by default, but are informed about the possibility to formally object to, and thus prevent, the inclusion of their medical data in the national database. The patient is enrolled by means of an enrolment form, which contains the date of enrolment, demographic data, country of birth and nationality. This form also contains a checklist, which enables the treating physician to indicate whether the patient has been properly informed about the monitoring. Upon receipt, the information on the enrolment form is collected in a separate enrolment database. A unique code is assigned to the patient. Subsequently, the patient data are collected and matched to this unique code identifier. For patients who object the data collection is blocked.

Data

Upon entry into the HIV Monitoring Foundation, the following information is collected:

Demographic data:
Date of birth, gender, first and second nationality, country of birth, height

History of HIV infection
Date of the last negative HIV-1 and HIV-2 test
Date of the first positive HIV-1 and HIV-2 test
Chance of infection with non-B HIV-1 subtype

HIV transmission:
The most likely transmission route: homosexual, heterosexual, IDU, blood and blood products, during pregnancy/partus, via breastfeeding, other and unknown;

In case of sexual transmission, the most likely transmission source: either a steady sexual partner or various sexual contacts;

Country where the patient has become infected.

Data, including clinical data, are collected on a continuous basis every time the patient is seen by his or her treating physician. These data contain the following information:

Clinical examination
Weight, blood pressure

HIV-related events according to CDC classification
Start and stop date, definition of diagnoses (possible, presumptive or definitive) using standard protocol and the status of an event at the current visit (ongoing: yes or no)

Adverse events
Start and stop date and the status of event at current visit (ongoing: yes or no).

Every event that results in a change of antiretroviral treatment is collected. In addition, the following events are always recorded:

Peripheral neuropathy
Myopathy
Lactate acidosis
Hepatic cirrhosis
Osteopenia / Osteoporosis
Hepatic steathosis
Hepatic encephalopathy
Pancreatitis
Nephrolithiasis
Renal failure
Lipodystrophy, fat loss of extremities
Lipodystrophy, central fat accumulation
Rash
Sexual dysfunction (loss of libido, erection failure)
Alcohol or drug abuse
Non-CDC malignancies
Diabetes mellitus
Myocardial infarction
Hypertension
Arrhythmia
Stroke
Coronary artery by-pass grafting
Coronary angioplasty / stenting
Carotic endarterectomy
Pregnancy
Hospital admission

Antiretroviral therapy
Start and stop date, dosage and units, route of admission, reason for stop and the status of medication at current visit (ongoing: yes or no)

The list of standard stop reasons is as follows:

Virological failure
Immunological failure
Patient's decision
Toxicity
New CDC-B and or CDC-C events
Interaction with co-medication
Simplification of the regimen
Drug levels related
Structured treatment interruption
Newly available medication
Other
Unknown

Co-medication
Start and stop date and the medication status at current visit (ongoing: yes or no)

The list of co-medication contains the following classes of medication:

CDC events prophylaxis
CDC events treatment
Anti-epileptic agents
Anti-coagulant agents
Platelet aggregation inhibitors
Anti-hypertensive agents
Anti-arrhythmic agents
Lipid lowering agents
Anti-diabetic agents
Insulin and its derivatives
Anabolic steroids and appetite stimulants
Hepatitis B treatment
Hepatitis C treatment
Medication that interacts with antiretroviral therapy
Miscellaneous: megestrol acetate, dranabinol and methadone

Lab results
HIV virology
Value (copies/ml), laboratory, sample date, VL assay type, sample material, cut-off and undetectable: yes or no

Immunology
Value, units, laboratory and sample date
The following assessments are collected:
CD4 count, CD8 count, CD4 percentage, CD8 percentage, CD4/CD8 ratio

Chemistry
Value, units, sample date and laboratory
The following assessments are collected:

Glucose	If >N
Amylase	If >250 mmol/l
ALAT/SGPT	If >3 x N
ASAT/SGOT	If >3 x N
Alkaline phosphates	If >3 x N
Gamma GT	If >3 x N
Lactate	If >N
Triglycerides	Always
Cholesterol	Always
Cholesterol HDL	Always

N= normal value; this value varies between different laboratories.

Haematology
Value, units, sample date and laboratory
The following assessments are collected:

Haemoglobin	If <5.5 mmol/l
Leukocytes	If <2.0 10e9/l
Thrombocytes	If <75 10e9/l

Other viral infections
Value (positive or negative), laboratory, sample date
The following assessments are collected:

HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV-DNA, HCV-Ab, HCV-RNA, CMV, IgG, IgM

Patient's participation in clinical trials
Trial name, start and stop date

Discontinuation

The patient's participation is ended by means of a discontinuation form, which contains the following information: patient objects to incorporation of his or her HIV infection into the national database; patient has moved to another country; patient is lost to follow-up; patient has not been seen by his or her treating physician for more than one year; Patient is deceased: date of death, physician's diagnosis for cause of death, is the cause of death HIV-related (yes, no and unknown), is the cause of death antiviral therapy-related (yes, no and unknown), suicide (yes, no and unknown), euthanasia (yes, no and unknown), autopsy (yes, no and unknown).

Data collection

Patient data are collected in 24 hospitals that are part of 22 specifically appointed HIV Treatment Centres by the Dutch Minister of Health. Data are obtained directly from the patient's medical file, and a limited number of case report forms. These case report forms are completed by or under the responsibility of the patient's treating physician and are used to support the data collection and entry into the local and the national database. Treating physicians also take responsibility for the collection and quality of the data obtained from their patients. So-called data collectors, who work under the supervision of the treating physician, enter the data into local databases and subsequently add these data to the national database on a regular basis. Data are collected and stored in the national database under a unique code that identifies the patient. On a national level, no identifying information is available in conjunction with the patient's data.

Database

As per March 2000, data are stored in a local database using Microsoft Access. Data are collected in a cumulative manner, and a separate data entry screen is available for each item. At every follow-up visit, new data are entered in a cumulative list for each of the items. Ongoing data are recorded as open items, i.e. without stop date. A patient's visits to the outpatient clinic are prospectively entered in a specific screen starting from the date of enrolment.

Since the inclusion criteria changed from restricted to HAART-treated adults giving informed consent in ATHENA to no restrictions at all with an opt-out possibility in ATHENA-HMF, the number of patients included in the HIV Monitoring Foundation more than doubled. With this increase in the number of patients - and, consequently, an increase in data - the Access database became inadequate for the requirements of the HIV monitoring.

In order to improve the quality of the data collection it was decided to switch to a new database developed in Oracle Clinical, a database specifically designed for the data management of clinical trials. This database complies with all guidelines of the Food and Drug Administration (FDA) and of Good Clinical Practice (GCP). An important advantage is that by using this system the privacy of patients will be better protected. Further, Oracle Clinical has a number of specific advantages that makes it suitable for large-scale collection of observational clinical data:

- Data are collected at different locations and entered directly into the central database (Figure 4.1).
- Oracle Clinical provides highly sophisticated discrepancy checks and an on-line discrepancy database for a quick resolution of queries.
- Oracle Clinical provides tracking options like overdue/forgotten visits and missing pages.
- Oracle Clinical supports the uploading of laboratory data and cross-checking these data with reference ranges.
- Oracle Clinical supports the classification of events and medication, with an automated coding option and manual classification schedules.
- Oracle Clinical offers the possibility to export data to analysis software.

Figure 4.1 gives an overview of the technical architecture of the database system. The Oracle Clinical Application and the database each run on a separate server. These servers are located behind the firewall of the Academic Medical Centre (AMC). Users from inside and outside the AMC have access to the application but not to the database. Only the data managers and the programmer(s) have access to both the application and the database program. Data are solely stored on the central database server.

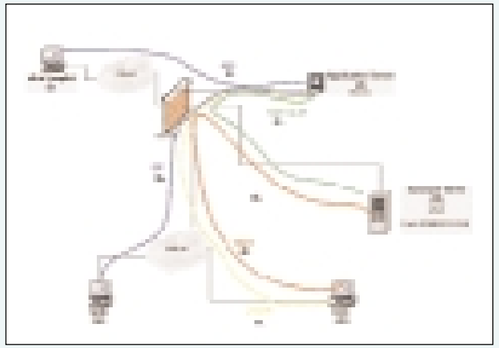

Figure 4.1: Technical architecture of Oracle Clinical. KEB: department of Clinical Epidemiology and Biostatistics of the AMC; the developers of the database. SHM: HIV Monitoring Foundation

The database security is of outstanding quality. It consolidates the management of all remote users and enhances the security of the network. Upon entering the database, users identify themselves by means of database user identification and a unique password. The database user identification further defines the type of user and his or her assigned access rights. Oracle security components include access control for external users with passwords and end-users who are granted system privileges alike.

At the time of writing, Oracle Clinical is still in the process of being implemented. Development of the data entry screens has started in the middle of 2002. Special

attention is given to the factors that improve the quality of data collection in various ways:

Data collection in Oracle Clinical is structured so as to enable a clear distinction between items collected only once directly upon enrolment and repetitive items collected at every subsequent follow-up visit. Such repetitive items are linked to each visit in sub-screens, which allows for checks for repetitive data to be incorporated. All visits to the outpatient clinic are captured in the patient's medical file, both prospectively and retrospectively, with respect to the date of enrolment. Besides start and stop date, one has to indicate for every item at each visit whether or not the item is ongoing.

Special attention is paid to the recording of negative information by a classification that includes "not performed", "unknown whether or not it has been performed" and "has been performed, but the date is unknown"[1].

Free-text variables cannot easily be quantitatively analysed. Their use is therefore very limited in the new database. By contrast, the use of categorical variables is emphasised because it simplifies data recording and increases accuracy [1].

A co-medication list, including both generic and trade names, is available on-line containing every medication required. Since new medications are continuously being introduced, the list is updated on a regular basis. This approach simplifies data recording and avoids interpretation.

Many data entry checks are programmed. Both single-item checks and complex queries are displayed immediately on the screen and can be resolved or forwarded to the right party. With this approach, many data entry errors are resolved well before the data analysis phase.

After the development of the data entry screens, the implementation of Oracle Clinical in the HIV treatment centres was started in May 2003. The present report contains data from ten hospitals where Oracle Clinical has been implemented.

Data quality

Data quality is monitored by data monitors from the HIV Monitoring Foundation, using quality control procedures. They compare the data added to the local database with the source document, i.e. the patient's medical file. Differences between source documents and data in the database are discussed and clarified and, if needed, corrected under supervision of the treating physician.

At present, quality control procedures are restricted to the follow-up data of a random selection of 10% of the patients and to the retrospectively collected data of a random selection of 10% of the newly admitted patients per year. Each treatment centre is visited by a data monitor at least twice a year, depending on the number of patients monitored. Using the new database system, data monitors can identify missing data and data entry errors and review and resolve discrepancies on-line.

Discussion

Collecting data from patient's medical files is complex. To secure a continuously high data quality, strict procedures are needed for data collection, data entry and quality control. Key to accurate data collection is simplification of data abstraction methods and avoidance of data interpretation and assumption [1]. First steps towards improvement have been made by implementing a new database; others, however, are still to be made:

- Manual entry of laboratory results into the database should be replaced by uploading them directly from laboratory data systems, followed by cross-checking of the data with reference ranges. This approach will improve the quality of the data collected from the patients' medical files.
- Although a written data collection manual is already available for training the data collectors, an integrated help section in the database would help data collectors to improve data quality in less time. This help section should be variable-specific.
- Both source data verification performed by the data monitors and consistency checks performed in the analysis phase are essential to guarantee a continuous and high data quality level. Changes in these performance levels might indicate structural problems that need to be addressed. To do so, a customised monitoring program and a customised training program for the data collectors will be developed.
- Last but not least, the data collector's assumption and interpretation are the most important problems in data collection from a patient's medical file [1]. Differential interpretation of data is a reflection of both the complicated nature of a patient's clinical status and the level and the variability of data documentation in the medical file [1,3]. Documentation of symptoms without documentation of the actual diagnosis is one of the most disturbing factors in data collection, which eventually might lead to assumptions and interpretations by the data collector. The use of synonym lists and training of data collectors will be useful but cannot completely resolve this problem. In this respect, guidelines to standardise documentation of diagnosis and data extraction from medical files and regular investigators meetings would be very useful [2,5,6,7].

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Study population

Characteristics of a changing HIV-infected population at baseline

Introduction

For both an untreated and a treated HIV infection, prognosis is strongly associated with CD4 cell count and HIV replication level at baseline [1-9]. Older age, a history of AIDS and transmission through intravenous drug use are also associated with increased rates of clinical progression. The characteristics of HIV-infected patients at their start of antiretroviral therapy can thus be used to predict their probability of disease-free survival and overall survival [10]. Based on the above-mentioned factors, we showed in a collaborative study between thirteen cohorts from Europe and North America that patients who started highly active antiretroviral treatment (HAART) after having had treatment with antiretroviral drugs for the previous three years had a higher probability of progression to AIDS [5].

In the HIV Monitoring Foundation's preceding cohort, ATHENA, data were collected only from HIV-infected patients who were ≥18 years of age and had signed an informed consent. Since the start of the current monitoring project, all HIV-infected patients seen in one of the 22 HIV treatment centres are eligible for inclusion, irrespective of the antiretroviral treatment they receive, if any (see also Chapter 4). In this chapter, we will describe the baseline characteristics of the study population used for the analyses of the changes over time in the epidemiology of the HIV infection in the Netherlands, the effects of first and second-line HAART regimens, and the reasons for and effects of change of HAART regimen and therapy interruption.

Total number, median follow-up time and geographic distribution

As of the first of November 2003 in total 8.940 HIV-infected individuals were registered for monitoring. The total number of patients included in the study population used for the present report was 8.496; these were the patients from whom data were available in the HMF database as of July 31, 2003, the date of the data freeze. This number exceeded that of the November 2002 report [11] with 3.394 patients.

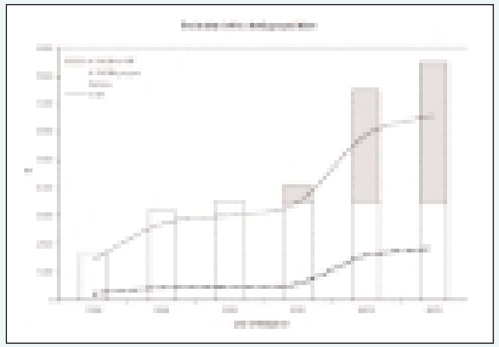

Figure 5.1: Inclusion in ATHENA-HMF over time.

Of the study population, 6.637 (78.1%) patients were men and 1.859 (21.9%) women. The year of registration is summarised in Figure 5.1, showing the inclusion between 1998 and 2000 into the ATHENA project, with restrictive entry criteria, and the year 2001 as the year in between, followed by the inclusion under ATHENA's successor, the HMF, during 2002 and 2003.

Consult interval	Total		Male		Female	
Months	N	%	N	%	N	%
0 – 3	3736	46.2	2950	46.5	786	45.4
3 – 6	2167	26.8	1728	27.2	439	25.4
6 – 12	1800	22.3	1387	21.8	413	23.9
Unknown	379	4.9	285	5.3	94	5.4
Total	8082*	100.0	6350	100.0	1732	100.0

*N missing data: 414

Table 5.1: Distribution of consult intervals of the study population of HIV-infected patients followed-up in one of the 22 HIV treatment centres.

The median follow-up of the study population was 5.4 years (IQR 2.3-9.2), 5.6 (2.6-9.6) for the men and 4.0 (1.7-7.9) for the women. The median interval between follow-up visits was 91.3 days (70 – 118), indicating that 50% of the study population had ≥1 consultation with an AIDS treating physician every three months. There were no differences between men and women. The median number of visits for the study population was 3.2 (2.0-4.5) visits per year. The distribution of the study population per visit interval is shown in Table 5.1.

Region	Total		Male		Female	
	N	%	N	%	N	%
Amsterdam	3757	44.9	3119	37.3	638	7.6
Western provinces	2590	31.0	1927	23.1	663	7.9
Northern provinces	418	5.0	302	3.6	116	1.4
Eastern provinces	681	8.2	513	6.2	168	2.0
Southern provinces	911	10.9	679	8.1	232	2.8
Total	8357*	100.0	6540	78.3	1817	21.7

*N missing data: 139

Table 5.2: Geographic distribution in The Netherlands of the study population of HIV infected patients (Western provinces excluding Amsterdam).

The geographic distribution in the Netherlands is summarised in Table 5.2, pointing at Amsterdam and the Randstad area - the densely populated western provinces of North and South Holland and Utrecht - as the most affected.

Antibodies to	Total		Male		Female	
	N	%	N	%	N	%
HIV-1	8282	97.5	6502	78.5	1780	21.5
HIV-2	28	0.3	14	50.0	14	50.0
HIV-1 and/or HIV-2?	186	2.2	121	65.0	65	35.0
Total	8496	100.0	6637	78.1	1859	21.9

Table 5.3: HIV antibody diagnosis among the study population by gender.

HIV Diagnosis

Infection with HIV is usually diagnosed using an HIV-1/HIV-2 antibody and HIV-1 p24 antigen immunoassay [12] followed by western blot confirmation of either an antibody response specific for an HIV-1 or an HIV-2 infection or both. Based on this procedure, 8.282 (97.5%) individuals were reported and registered in the ATHENA-HMF database as being infected with HIV-1 (Table 5.3). Twenty-eight patients (0.3%) were reported as HIV-2-infected. From the remainder - 186 patients or 2.2% of the total population - results were confusing. Part of this subgroup encompasses HIV-1-infected patients showing a relatively high level of cross-reactive antibody responses to HIV-2; another part might be the other way around and HIV-2-infected and a third part might be HIV-1/HIV-2 double-infected. For the sake of clarity, we will report only on the population of 8.282 HIV-1- and 28 HIV-2-infected patients.

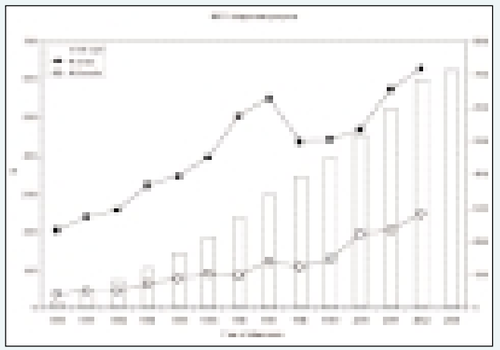

Figure 5.2: Year of HIV-1 diagnosis over time.

HIV-1

Diagnoses and trends over time

Out of 8.282 HIV-1-positive patients, 892 (11.1%) were diagnosed before 1990. The number of HIV-1 diagnoses by year of diagnosis from 1990 on is depicted in Figure

5.2, showing a steady increase over time from 246 to 878 diagnoses per year between 1990 and 2002. The number of women increased continuously from 40 per year in 1990 to 249 in 2002. The number of men increased as well from 206 per year to 629 per year over the same period. The drop in numbers in 1998 is most probably the result of the differences in inclusion procedures between the ATHENA project and the ATHENA-HMF monitoring. The relative contribution of men and women changes over time. In 1990, 83.7% of the HIV diagnoses were found among men and 14.7% among women. In 2002 these percentages were 71.6 and 28.4, and in 2003, although data are still incomplete at the time of writing this report, 69.5 and 30.5 for men and women, respectively (Figure 5.3).

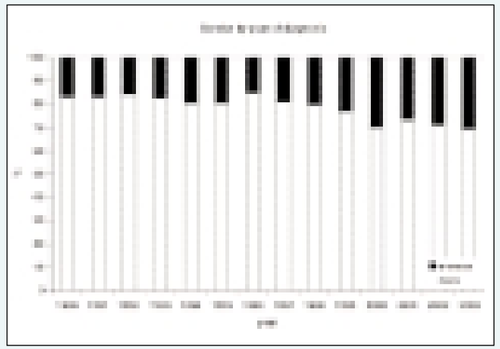

Figure 5.3: Percentage men and women diagnosed with HIV-1 per year of diagnosis.

General characteristics of the HIV-1-infected population

In total 6.502 (76.8%) men and 1.780 (21.0%) women were diagnosed as being HIV-1-infected. General characteristics are given in Table 5.4. The largest transmission risk group is still that of men having sex with men (MSM), covering a little over half of the total and 65.4% of the male infected population. Heterosexual transmission accounts for 26.9% of the infections, 14.6% in men and 71.8% in women. Intravenous drug use (IDU) is the route of transmission in 5.5% of all cases, in 5% of the men and 7.1% of the women. From quite a large group of patients, 1.152 (13.9%), the HIV transmission route is unknown. The majority of the HIV-1 study population and 66.9% of the men is born in the Netherlands. Of the women, only 31.9% is Dutch. Most HIV-1 patients were asymptomatic at diagnosis; here the proportion of women is slightly higher than of men.

Characteristic	Total		Male		Female	
	N	%	N	%	N	%
Total	**8282**	**100.0**	**6502**	**100.0**	**1780**	**100.0**
Transmission group						
Homo/bisexual	4281	51.7	4281	65.4	0	0
Heterosexual	2225	26.9	947	14.6	1278	71.8
IDU	452	5.5	325	5.0	127	7.1
Blood contact	152	1.8	111	1.7	41	2.3
Mother to child	20	0.2	9	0.1	11	0.6
Other/unknown	1152	13.9	829	12.8	323	18.2
Country of birth						
The Netherlands	4917	59.4	4349	66.9	568	31.9
Any other country	3365	40.6	2153	33.1	1212	68.1
Clinical status (% total group)						
Asymptomatic	6968	84.1	5402	83.1	1566	88.0
CDC-B	411	5.0	352	5.4	59	3.3
CDC-C	903	10.9	748	11.5	155	8.7

Table 5.4: General characteristics of the HIV-1 infected study population.

The median age for the entire population was 34 years (IQR 28-41); 35 (30-42) for men and 29 (24-36) for women. Thus women were significantly younger at HIV diagnosis than men ($p<0.0001$; Wilcoxon rank sum). The age distribution at diagnosis is given in Figure 5.4, showing the peak of HIV diagnoses to be 26.4% amongst women 26-30 years of age and 22.6% amongst men 31-35 years of age. In 2003, men were a median 6.5 years older at diagnosis compared to women, indicating that women are indeed infected earlier in life than men.

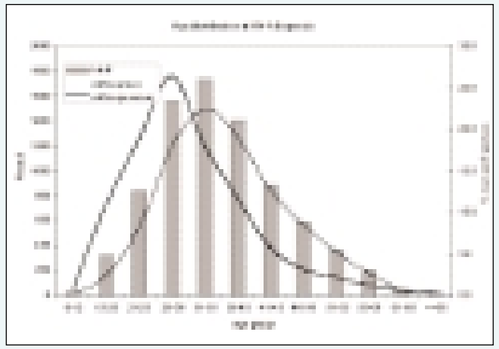

Figure 5.4: Age distribution at HIV-1 diagnosis.

Characteristic	Total		Male		Female	
	N	%	N	%	N	%
CD4 count measured	4196	50.7	3305	78.8	891	21.2
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
CD4 cells/mm^3	280	279-490	279	100-480	290	120-500
	N	**%**	**N**	**%**	**N**	**%**
HIV-RNA measured	3642	44.0	2798	76.8	844	23.2
< detection level	191	5.2	133	4.7	58	6.9
> detection level	3541	94.8	2665	95.3	786	93.1
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
logHIV-RNA copies/ml	4.9	4.3-5.3	5.0	4.4-5.4	4.5	3.8–5.0

Table 5.5: CD4 cell counts and HIV-1 RNA plasma levels at HIV-1 diagnosis.

CD4 cell counts and plasma HIV-1 RNA levels at diagnosis or shortly thereafter are given in Table 5.5. The median CD4 cell number at diagnosis was 280 cells/mm^3 (IQR 279-490) and not significantly different between men and women. HIV-1 RNA levels were median 4.9 log HIV-1 RNA copies/ml (4.3-5.3), being somewhat lower among men compared to women. Around 5% of the population measured had HIV-1 RNA plasma levels <500 copies/ml.

HIV-1-infected children

From 34 children, 19 boys and 15 girls, with a median age of two years (IQR 0-6), date were available in the ATHENA-HMF database (Table 5.6). Most of these infections were registered before the year 2000 and the majority of the children was infected vertically. Of the children included, 61.8% was Dutch. Although registration of HIV-1-positive children through the HMF monitoring system has recently started, inclusion of data from HIV-infected children and children born to an HIV-infected mother is still limited, due to insufficient database facilities. In this report no further analysis will therefore be presented.

Characteristic	N	%
Male	19	55.9
Female	15	44.1
Year of diagnosis		
<1990	10	30.3
1990 – 1999	19	57.6
2000 – 2003	3	9.0
Transmission group		
Blood products	8	24.2
Vertical	19	57.6
Other	6	18.2
Region of origin		
Dutch	21	61.8
Other	13	38.2
	Median	**IQR**
Age at diagnosis	2	0-6
CD4 cells/mm^3 at diagnosis	1385	680-2820
log HIV-1 RNAcopies /ml	4.8	4.4-5.5

Table 5.6: General characteristics at diagnosis of 34 HIV-1 infected children included in the database.

Pregnant women

With regard to pregnancy, only data on whether HIV-1-infected women are pregnant or not are currently collected. The registered pregnancy dates do not by definition represent the first day of the last period as the starting point and birth or abortion - whether spontaneous or induced, early or late - as the end of a pregnancy. Therefore, pregnancy in relation to HIV-1 diagnosis was defined as having a pregnancy registered in the ATHENA-HMF database up to 24 months before the registered HIV-1 diagnosis.

Characteristic		N	%
Total HIV+ women registered as pregnant		377	
N pregnancies	1	312	82.7
	2	55	14.6
	3	9	2.4
	4	1	0.3
Region of origin	The Netherlands	68	18.0
	Sub-Saharan Africa	220	58.4
	Other	89	23.6
Transmission risk group	Heterosexual	324	85.9
	IDU	12	3.2
	Other	41	10.9

Table 5.7: General characteristics HIV-1 infected women who were or became pregnant.

In total 377 women were reported as having had one or more pregnancies while (most probably) being HIV-1-infected (Table 5.7). Sixty-eight (18%) of the pregnant women were of Dutch origin. The majority of the women had become infected through heterosexual contact. The age distribution among the women at the time of their pregnancy is displayed in Figure 5.5, showing that more than half of the women became pregnant between 25 and 35 years of age. More than half of the women was diagnosed with HIV-1 >3 months before and 36.9% during their pregnancy (Table 5.7). HIV-1 was diagnosed before 1996 in 22% of the women and in 80% thereafter.

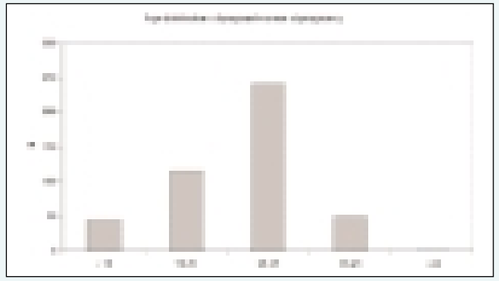

Figure 5.5: Age distribution pregnant women at pregnancy.

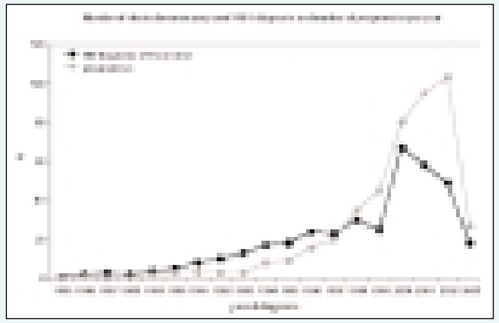

Figure 5.6: Number of HIV-1 infected pregnant women and number of pregnancies per year of HIV diagnosis.

The distribution per year of HIV diagnosis in women who had been, were, or became pregnant, and the number of pregnancies per year of registration is shown in Figure 5.6. From 1998 on, the number of pregnancies exceeded the number of HIV-1-diagnosed women. This probably indicates that since the introduction of HAART, becoming pregnant once again became an option for those women who had been diagnosed before 1998. Pregnancies among women with a known HIV-1 infection increased from 1999 on. The increase in the number of HIV-1-infected women who were or became pregnant in 2000/2001 coincides with the increase in the total number of HIV-1-infected patients.

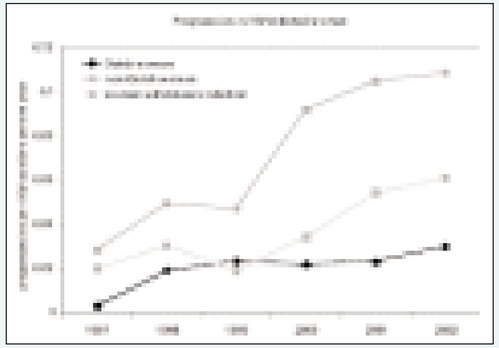

Figure 5.7: Number of pregnancies per HIV-1 positive person year

Characteristic		N	%
Total n of pregnancies			453
HIV diagnosis	24-3 months before start of pregnancy	276	60.9
	3 months before-9 months after start of pregnancy	167	36.9
	>9 months after start of pregnancy	10	2.2
Start antiretroviral therapy	Before pregnancy	190	41.9
	During pregnancy	207	45.7
	After pregnancy	56	12.4
Duration of the preganancy	> 26 weken	284	62.7
	0-26	61	13.5
	Still pregnant	71	15.7
	Missing start or stop date	37	8.2
age mother	≤18	45	9.9
	19-25	116	25.6
	26-35	241	53.2
	36-45	50	11.0
	>45	1	0.2

Table 5.8: General characteristics of the 453 pregnancies amongst the 388 HIV-1 infected women

The number of pregnancies registered was 453 in total, with a peak during 2000-2002, which might also be the result of an increasing number of second and third pregnancies (Table 5.8). The incidence of pregnancies per HIV-1-positive woman / year (Figure 5.7) showed an increase of pregnancies from 0.03 in 1997 to 0.11 per HIV-1-positive woman / year in 2002, especially amongst women of non-Dutch origin. Antiretroviral therapy was started before pregnancy in 42%, during pregnancy in 45.7%, and after pregnancy in 12.4% of the women, respectively.

HIV-2

In total 28 patients were infected with HIV-2, fourteen men and fourteen women. Six HIV-2 infections were diagnosed before and 22 after 1996. Sixteen of the 28 patients were reported to have become infected through intravenous drug use. Sixteen were reported to be connected to a Sub-Saharan country, nine were Dutch. The median age of the group of HIV-2-infected patients was 44 years (36-49), 12 of them were ≥46 years old at diagnosis and there was no difference between men and women. Twenty were asymptomatic at entry into the cohort. Immunological and virological parameters of the HIV-2-infected patients at diagnosis are summarised in Table 5.9. Because the number of patients with a confirmed HIV-2 infection in the dataset is very limited, no further analyses have yet been performed on the data obtained from this group.

In a separate observational study the clinical, immunological and virological response and the emergence of resistance towards antiretroviral therapy (ART) was assessed in a cohort of HIV-2-infected patients. Development of resistance mutations proved to be similar to that observed in HIV-1-infected patients, with the exception of a higher occurrence of the Q151M mutation within the reverse transcriptase gene. In a prospective study it was concluded that sustained viral suppression in HIV-2-infected patients could be achieved using an antiretroviral regimen of two NRTIs and boosted indinavir or lopinavir [13].

Characteristic	Total		Male		Female	
	N	%	N	%	N	%
CD4 count measured	17	69.7	7	41.2	10	58.8
	Median	IQR	Median	IQR	Median	IQR
CD4+ T cells/mm³	100	30-260	180	40-370	70	30-260
HIV-2 RNA measured	8	28.6	3	37.5	5	62.5
< detection level	3	37.5	1	33.3	2	40.0
> detection level	5	62.5	2	66.6	3	60.0
	Median	IQR	Median	IQR	Median	IQR
logHIV-2 RNA copies/ml	4.5	4.1-5.1	4.49-5.11		4.1; 4.1; 5.5	

Table 5.9: Immunological and virological parameters of the study population of 28 patients at HIV-2 diagnosis by gender.

Characteristics of the HIV-1-infected population subdivided into treatment groups

The effects of antiretroviral therapy over time will be the main subject in the present report. In this paragraph, the general characteristics of four subpopulations will be described. The first subpopulation is the group of HIV-1-infected patients that started treatment with a highly active antiretroviral therapy (HAART) combination of drugs, i.e. a combination of at least three different antiretroviral drugs from two different drug classes. Although not strictly HAART, the combination AZT+3TC+ABC was also included in the HAART group.

The second group consists of HIV-1-infected patients who started treatment with mono- or dual antiretroviral therapy and subsequently switched to HAART. The third group is the group of HIV-1-infected patients that started with mono- or dual antiretroviral treatment and stayed on that medication until the end of follow-up. Finally, the last group encompasses those patients who did not receive any medication until the end of the study period. The 28 HIV-2-infected patients discussed in the previous paragraph were not included in the various analyses regarding treatment patterns, effect of treatment, and development of resistance.

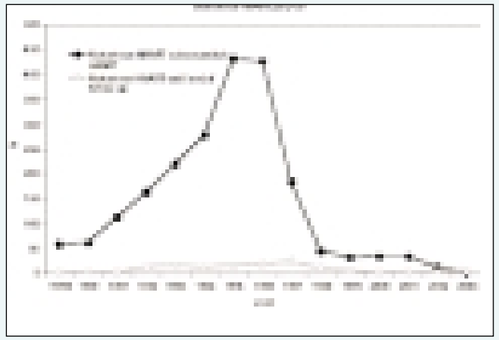

Figure 5.8: Number of patients starting non-HAART antiretroviral treatment over time.

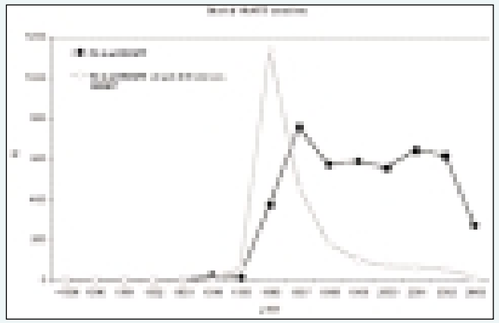

Figure 5.9: Number of patients starting HAART over time.

HAART and non-HAART

In total 6.703 of 8.282 (80.9%) HIV-1-infected patients started therapy with some form of antiretroviral drug regimen. The distribution of patients per year of start of antiretroviral therapy is shown in Figures 5.8 and 5.9. From 1994 on, HAART regimens were registered both in patients with and without prior antiretroviral drug treatment experience. Of the 8.282 patients, 4.403 (53.2%) were antiretroviral-drug-naïve at start of HAART, i.e. 52.7% of the men and 54.7% of the women in the total study population (Table 5.10). One-third of this group had had a CDC-B or C event at or before start of HAART and two-third was in the asymptomatic phase of the infection. The median CD4 cell count at start of HAART was 200 (IQR 80-331) and the median HIV-1 RNA plasma concentration was 5.0 log copies/ml (4.5-5.4; Table 5.11). In terms of the proportion of patients treated and the laboratory values indicating treatment, there were no significant differences between men and women.

Characteristic	Total		Male		Female	
	N	%	N	%	N	%
Total on HAART and % total population	**4403**	**53.2**	**3429**	**52.7**	**974**	**54.7**
Transmission group						
Homo/bisexual	2278		2278		0	
Heterosexual	191		138		53	
IDU	1395		620		775	
Blood contact	80		56		24	
Mother to child	7		4		3	
Other/unknown	452		333		119	
Country of birth % of total on HAART per cat.						
The Netherlands	2563	58.2	2273	66.3	290	29.8
Any other country	1840	41.8	1156	33.7	684	70.2
Clinical status at start HAART % of total on HAART per cat.						
Asymptomatic	2913	66.2	2184	63.7	729	74.9
CDC-B	507	11.5	432	12.6	75	7.7
CDC-C	983	22.3	813	23.7	170	17.5

Table 5.10: General characteristics of the study population of 4403 HIV-1 infected patients at start of HAART by gender.

In total 2.300 (27.8%) HIV-1-infected patients started mono- or dual antiretroviral therapy, 2.141 (93.1%) of whom switched to HAART and 159 (6.9%) of whom remained on non-HAART therapy during follow-up. In contrast to the group of patients starting HAART without prior antiretroviral treatment, the fraction of men in the group previously treated before start of HAART was somewhat higher compared to the fraction of women (27.2% versus 20.8%, respectively). A majority of 77.9% of the patients started non-HAART treatment while asymptomatic; 22.1% had experienced a CDC-B or CDC-C event before or at start of non-HAART treatment.

Characteristic	Total		Male		Female	
Population on HAART	N	%	N	%	N	%
CD4 count measured	3517	79.9	2783	81.2	734	75.4
	Median	IQR	Median	IQR	Median	IQR
CD4 cells/mm³	200	80-331	200	70-330	214	100-350
	N	%	N	%	N	%
HIV-RNA measured	3593	81.6	2812	82.0	781	80.2
< detection level	72	2.0	51	1.8	21	2.7
> detection level	3521	98.0	2761	98.2	760	97.3
	Median	IQR	Median	IQR	Median	IQR
logHIV-RNA copies/ml	5.0	4.5-5.4	5.0	4.6-5.4	4.8	4.1-5.2

Table 5.11: Immunologic and virologic status of the study population of HIV-1 infected patients at start of HAART by gender.

Median CD4 cell count at start of non-HAART was 200 (108-310) and was lower in the men than in the women (Table 5.12). HIV-1 RNA plasma levels were median 4.9 log copies/ml (4.3-5.3) in the group that was assessed and equal in the men and women. At switch to HAART median CD4 cell counts were 180 (75-320), again lower in the men than in the women. The median HIV-1 RNA plasma level at switch was 0.3 to 0.5 log copies/ml lower compared to the levels at start of non-HAART.

Characteristic Non-HAART switching to HAART at start non-HAART	Total		Male		Female	
	N	%	N	%	N	%
CD4 count measured	1170	54.6	973	54.9	197	53.2
	Median	IQR	Median	IQR	Median	IQR
CD4 cells/mm³	200	108-310	100	40-200	200	120-340
	N	%	N	%	N	%
HIV-RNA measured	461	21.5	368	20.8	93	25.1
< detection level	16	3.5	9	2.5	7	7.5
> detection level	445	96.5	359	97.5	86	92.5
	Median	IQR	Median	IQR	Median	IQR
logHIV-RNA copies/ml	4.9	4.3-5.3	4.9	4.4-5.3	4.9	4.2-5.4
Characteristic Non-HAART switching to HAART at switch	**Total**		**Male**		**Female**	
	N	%	N	%	N	%
CD4 count measured	1661	77.6	1383	78.1	278	75.1
	Median	IQR	Median	IQR	Median	IQR
CD4 cells/mm³	180	75-320	180	70-310	207	90-370
	N	%	N	%	N	%
HIV-RNA measured	1371	64.0	1120	63.2	215	58.1
< detection level	156	11.4	119	10.6	37	14.7
> detection level	1215	88.6	1001	89.4	214	85.3
	Median	IQR	Median	IQR	Median	IQR
logHIV-RNA copies/ml	4.6	3.8-5.1	4.6	3.8-5.1	4.4	3.6-5.0

Table 5.12: Immunologic and virologic status of the study population of 2141 HIV-1 infected patients switching from non-HAART to HAART at start of non-HAART and at switch from non-HAART to HAART by gender.

Among the 159 patients that remained on non-HAART treatment during the entire follow-up period were 128 men and 31 women, which is equal to the proportions in the total group of HIV-1-infected men and women. All of these patients were asymptomatic at start of non-HAART treatment; the median CD4 cell count at start of non-HAART was relatively high (260 cells/mm³ IQR: 120-370; Table 5.13). The median plasma HIV-1 RNA level was low as well (4.4 log copies/ml; IQR: 3.1-4.9).

Characteristic Non-HAART staying on non-HAART	Total		Male		Female	
	N	%	N	%	N	%
CD4 count measured	81	50.9	61	47.7	20	64.5
	Median	IQR	Median	IQR	Median	IQR
CD4 cells/mm³	260	120-370	260	120-400	210	115-365
	N	%	N	%	N	%
HIV-RNA measured	42	26.4	33	25.8	9	29.0
< detection level	6	14.3	4	12.1	2	22.2
> detection level	36	85.7	29	87.9	7	77.8
	Median	IQR	Median	IQR	Median	IQR
logHIV-RNA copies/ml	4.4	3.1-4.9	4.6	3.7-5.2	3.0	2.7-3.7

Table 5.13: Immunologic and virologic status of the study population of 159 HIV-1 infected patients staying on non-HAART at start of non-HAART by gender

Characteristic	Total		Male		Female	
	N	%	N	%	N	%
Total non treated (% of total group)	**1579**	**19.1**	**1174**	**18.1**	**405**	**22.8**
Transmission group						
Homo/bisexual	594	37.6	594	50.6	0	0
Heterosexual	379	24.0	148	12.6	231	57.0
IDU	46	2.9	37	3.2	9	2.2
Blood contact	8	0.5	7	0.6	1	0.3
Mother to child						
Other	552	35.0	388	33.1	164	40.5
Unknown						
Country of birth						
The Netherlands	814	51.6	707	60.2	107	26.4
Any other country	765	48.4	467	39.8	298	73.6
Clinical status						
Asymptomatic	1579	100	1174	100	405	100
CDC-B	0	0	0	0	0	0
CDC-C	0	0	0	0	0	0

Table 5.14: General characteristics of the study population of 1579 non treated HIV-1 infected patients at entry in ATHENA/SHM by gender.

Non-treated patients

Finally, 1.579 (19.1%) individuals out of the study group of 8.282 HIV-1-infected patients were registered as non-treated, 18.1% of them men and 22.8% of them women. In comparison to the total group of infected patients, a slightly higher fraction in the non-treated group was of non-Dutch origin (Table 5.14). All non-treated patients were registered as being asymptomatic at entry into the study. Moreover, immunological and virological parameters at entry were undoubtedly better when compared to the groups treated with antiretroviral drugs. The median CD4 cell count was 540 cells/mm³ (390-720) and the HIV-1 RNA plasma level was 4.1 log copies/ml (3.3-4.7), indeed indicating a relatively good clinical condition in the non-treated patient group (Table 5.15).

Conclusions

The total number of HIV-infected patients included in the monitoring of the (HMF) has increased with 3.394 patients since 2002 to a total of 8.496 patients. Compared to last year, 3.180 HIV-1-infected patients were added, bringing the total number to 8.282 HIV-1-infected patients included in the study. In addition, 28 HIV-2-infected patients were identified. Of 186 patients, the precise HIV diagnosis remained unclear. The median follow-up period was 5.4 years with the time between follow-up visits being a median three months and the median number of follow-up visits 3.2 per year. In comparison to the previous reports [11,14] the frequency of outpatient clinic visits tended to decrease slightly. Geographically, there are no real changes. The large majority of HIV-infected people still live in Amsterdam and in the other larger cities in the Western part of the country.

The number of patients registered is still on the increase. Together with the growing number of newly diagnosed HIV infections over time, this could indicate that either a rather large 'reservoir' of HIV-1-infected patients was awaiting diagnosis and registration, or the number of people getting infected is increasing, or both. In its 2002 annual report on sexually transmitted diseases (STDs), the National Institute for Public Health and the Environment (RIVM) reported that the number of positive HIV tests among visitors to STD clinics in the Netherlands is increasing once again (15). Moreover, the shift towards a larger proportion of non-Dutch HIV-1-infected patients and the relatively recent arrival of these patients in the Netherlands may account for the increase in newly diagnosed HIV-1 as well. Both trends, an increase in HIV-1 incidence and the increasing prevalence through newly arrived patients who were infected abroad, have also been reported in other Western European countries.

Another striking trend is the steady increase in the number of HIV-1-infected women. At present, 30% of the newly diagnosed HIV-1 infections is among women and this percentage has doubled since 1996. This trend is related to the increase in newly diagnosed HIV-1 infections as part of immigration: 68% of the HIV-1-infected women originate from a country other than the Netherlands. In addition to this, a clear age difference was found between men and women. Women were a median 29 years of age at HIV-1 diagnosis, six years younger than men.

Based on the characteristics of a subpopulation of pregnant women, it seems that the introduction of HAART has boosted the number of pregnancies amongst infected women, although again immigration might play a role in this increase as well.

A large number of patients started HAART treatment, either with or without prior mono- or dual antiretroviral drug treatment. Both the group of patients who were naïve at start of HAART and those who switched from non-HAART to HAART had median baseline CD4 cell counts and HIV-1 RNA plasma levels that were in

accordance with existing guidelines for start of antiretroviral therapy. In terms of the proportion of patients treated and the laboratory values indicating treatment, there were no differences between men and women.

The population of patients that made a switch from non-HAART to HAART did so in the early phase of the introduction of HAART treatment, i.e.1996-1998. This might indicate that the clinical condition of this group of patients was worse, resulting in a change to HAART as soon as it became available (16). Together with the poorer response to HAART in general in previously treated patients [6,11,14,17,18], this tends to result in a less beneficial result of HAART. Moreover, these previously treated patients will be more prone to resistance. In terms of therapy effect, analyses of the results in this particular group will be done separately and will not be part of the present report.

A substantial number of people were untreated. HIV was diagnosed in this group between 1999 and 2003 and the median number of CD4 cells was above 500/mm^3. In addition, the median HIV-1 RNA plasma level was relatively low. This indicates that the large majority of these 1.579 non-treated patients have recently become infected with HIV-1.

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Trends over time

Increasing proportion of young HIV-1 infected women from sub-Saharan Africa

Introduction

An estimate of the future development of the number of diagnoses was obtained by extrapolating the observed linear trend in the quarterly number of diagnoses beyond 2003. To achieve this, three different linear models were fit to both age groups. The first model was a fit to the number of diagnoses between 1998 and the third quarter of 2002. Data before that time were not taken into account because of a temporary interruption in the trend in 1996 and 1997.

In chapter 5, the general characteristics of the HIV-1-infected population at diagnosis and start of therapy were described. It was shown that a large fraction of the patients was of non-Dutch origin and infected via heterosexual contact. This suggests that the HIV-infected population evolves from a population dominated by the classical risk groups of - Dutch - homosexual men and intravenous drug users to a population of which heterosexuals and patients of non-Dutch origin form a substantial part. The emphasis in this chapter will therefore be on the changes over time in risk groups, the origin of HIV-infected patients, and the differences between these groups at diagnosis.

Study population and methods

The population studied was a subgroup of the HIV-1-infected patients. As discussed in the previous chapter, children were excluded. In addition, the year of the first HIV-1-positive test had to be known. In order to compare changes between the different age groups, the population was divided into 'young' patients who were 30 years of age or younger at diagnosis and 'older' patients who were over 30 years of age at diagnosis.

Changes over time in the proportions of gender-transmission groups were analysed using a logistic model. A subgroup of patients was defined in which a negative HIV-test was performed within two years prior to the first HIV-1 positive test. For these patients, the time of infection was estimated as the midpoint between the two tests. An estimate of the future development of the number of diagnoses was obtained by extrapolating the observed linear trend in the quarterly number of diagnoses beyond 2003. To achieve this, three different linear models were fit to both age groups. The first model was a fit to the number of diagnoses between 1998 and the third quarter of 2002. Data before that time were not taken into account because of a temporary interruption in the trend in 1996 and 1997.

This interruption was probably the result of differences in the inclusion procedure between the ATHENA project and ATHENA-HMF. Another explanation might be that in 1996 and 1997 the beneficial effects of HAART on disease progression became apparent, which lowered the barrier for testing. The second model was a fit to the same data, but the number of diagnoses in 2002 had been increased by 10% to take into account a possible delay in inclusion. The third model used only data from the third quarter of 2000 to the third quarter of 2002, thus taking only recent trends into account.

Changes over time were assessed by studying changes in the patient characteristics at time of diagnosis. Proportions were compared via a $\chi 2$-test or Fisher's exact test if sample sizes were small. Differences in age, CD4 cell count and HIV-1 RNA levels were tested using Wilcoxon Mann-Whitney and $\chi 2$ non-parametric tests. The significance of changes over time in proportions was assessed with the Cochran-Armitage test for trend. Changes over time in continuous variables were studied using analysis of variance. For continuous variables, medians are reported together with the inter-quartile range (IQR).

Results

The HIV-1-infected population consisted of 8.282 patients, of which 34 patients were children. Table 6.1 shows the number of men and women per region of origin for this population, excluding the children. The majority of the

	men		women		total	
region of origin	**N**	**%**	**N**	**%**	**N**	**%**
Netherlands	4337	52.6	559	6.8	4896	59.4
Western Europe	460	5.6	113	1.4	573	7.0
Central Europe	88	1.1	17	0.2	105	1.3
Eastern Europe	23	0.3	6	0.1	29	0.4
North America	122	1.5	4	0.0	126	1.5
Caribbean	185	2.2	94	1.1	279	3.4
Latin America	392	4.8	139	1.7	531	6.4
North Africa & Middle East	60	0.7	21	0.3	81	1.0
Sub-Saharan Africa	572	6.9	720	8.7	1292	15.7
South Asia	157	1.9	84	1.0	241	2.9
Australia & Pacific	30	0.4	1	0.0	31	0.4
unknown	57	0.7	7	0.1	64	0.8
	6483	78.6	1765	21.4	8248	

Table 6.1: Number of men and women per region of origin in the HIV-1-infected population excluding children.

8.248 adult infected patients were men of Dutch origin (52.6%). The largest non-Dutch group was formed by Sub-Saharan Africans, i.e. 1.292 (15.7%) patients. For 625 patients, the year of diagnosis was unknown. As a result, the total population that was analysed consisted of 7.623 patients, 6.052 (79.4%) men and 1.571 (20.6%) women.

In table 6.2, the number of patients is listed per year of diagnosis, gender and transmission group. From 1996 to 2003, the percentage of newly diagnosed men decreased from 85.0% to 70.3%. In the population diagnosed before 1996, 62.7% of the patients were homosexual men. Thereafter, this proportion decreased from 62.6% in 1996 to 43.8% in 2003 ($P<0.001$). Corresponding with this decrease there was an increase in the proportion of diagnosed heterosexual women from 11.6% in 1996 to 25.8% in 2003 ($P<0.001$). In the heterosexual male population there was an initial increase from 11.3% in 1996 to 19.4% in 2000, but the proportion thereafter declined again to 15.3% in 2003.

The male homosexual population consisted of 4.241 patients, 2.366 (55.8%) of whom were infected in or after 1996. The majority, 3.186 (75.1%), was of Dutch origin; other prevalent regions of origin were Western Europe (7.9%), Latin America (5.4%), South Asia (2.8%) and North America (2.5%). These proportions did not change across the years of diagnosis. At the time of

	male										female							
	homosexual		heterosexual		IVD		blood		unknown		heterosexual		IVD		blood		unknown	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
<1996	1875	62.7	208	7.0	214	7.2	50	1.7	153	5.1	325	10.9	98	3.3	18	0.6	51	1.7
1996	366	62.6	66	11.3	26	4.4	3	0.5	36	6.2	68	11.6	10	1.7	3	0.5	7	1.2
1997	367	55.8	92	14.0	30	4.6	5	0.8	46	7.0	96	14.6	4	0.6	3	0.5	15	2.3
1998	294	54.9	91	17.0	10	1.9	6	1.1	29	5.4	87	16.3	2	0.4	4	0.8	13	2.4
1999	281	51.0	88	16.0	12	2.2	5	0.9	42	7.6	103	18.7	3	0.5	4	0.7	13	2.4
2000	277	44.3	121	19.4	6	1.0	3	0.5	33	5.3	160	25.6	3	0.5	2	0.3	20	3.2
2001	339	46.8	130	18.0	9	1.2	6	0.8	51	7.0	170	23.5	3	0.4	2	0.3	14	1.9
2002	336	47.3	98	13.8	5	0.7	12	1.7	61	8.6	173	24.4	0	0	3	0.4	22	3.1
2003	106	43.8	37	15.3	5	2.1	1	0.4	21	8.7	60	25.8	0	0	1	0.4	11	4.6
	4241	55.6	931	12.2	317	4.2	91	1.2	472	6.2	1242	16.3	123	1.6	40	0.5	166	2.2

Table 6.2: Number of HIV-1-infected patients per year of diagnosis, gender and transmission group.

diagnosis, Dutch homosexuals were on average 4.5 years older than patients from other regions: 38.5 years versus 34.0 years (P<0.0001). Moreover, the median age of the Dutch homosexuals at diagnosis increased from 36.9 (IQR: 31.7–45.7) years in 1996 to 40.1 (IQR: 35.0–48.9) years in 2003 (P=0.004). The median CD4 cell counts and HIV-1 RNA plasma levels at diagnosis were 300 (IQR: 120-500) x 10^6 cells/l and 4.9 (IQR: 4.3–5.4) $\log^{10}$ copies/ml, respectively, and did neither differ between patients from different regions nor vary over time.

The population infected via heterosexual contact consisted of 931 men and 1242 women. Compared to the male homosexual population, a larger proportion was infected in or after 1996: 723 (77.7%) men and 917 (73.8%) women. The larger number of heterosexual women compared to heterosexual men was mainly due to patients originating from Sub-Saharan Africa (292 men versus 464 women; P<0.0001) and South Asia (6 men versus 54 women; P<0.0001).

For heterosexual men the most prevalent regions of origin were the Netherlands (377, 40.5%), Sub-Saharan Africa (322, 34.6%), Latin America (84, 9.0%), the Caribbean (44, 4.7%) and Western Europe (43, 4.6%). This sequence was different for women: Sub-Saharan Africa (536, 43.2%), the Netherlands (388, 31.2%), Latin America (99, 8.0%), the Caribbean (77, 6.2%) and South Asia (67, 5.4%). From 1996 to 2003, the proportion of newly diagnosed Dutch heterosexuals declined from 44.8% to 20.6% (P<0.0001). This was compensated by an increase in the proportion of Sub-Saharan patients, 32.8% in 1996 and 58.8% in 2003 (P<0.0001). For patients from other regions, no significant changes over the years were observed.

In table 6.3 the median age, CD4 cell count and $\log^{10}$ HIV-1 RNA at diagnosis are listed for heterosexual men and women from the most prevalent regions of origin. The median age of men was 36.3 years versus 29.7 years for women (P<0.0001), whilst the difference in age between heterosexual and homosexual men was not significant

	men			women		
	age (yr)	CD4 (x 10^6 cells/l)	HIV-1 RNA ($\log^{10}$ copies/ml)	age (yr)	CD4 (x 10^6 cells/l)	HIV-1 RNA ($\log^{10}$ copies/ml)
Netherlands	40.2*	240*	5.0*	30.8*	415*	4.4*
	32.0-48.7	50-475	4.4-5.5	25.5-39.0	170-660	3.5-5.0
Western Europe	40.0	292	5.0	33.6	409	4.2
	33.5-51.9	80-484	4.3-5.5	29.5-44.333.6	242-625	3.0-5.1
Sub-Saharan	33.6*	161*	4.9*	28.0*	270*	4.3*
Africa	27.9-38.0	70-330	4.2-5.3	23.3-33.4	130-423	3.4-4.9
Latin America	38.3*	155	4.8	30.9*	255	4.3
	32.5-47.0	30-325	4.2-5.4	24.5-38.0	100-437	3.8-5.0
Caribbean	34.7	90	4.6	30.7	360	4.3
	30.4-42.9	25-258	4.1-5.4	25.9-38.1	110-580	3.8-5.0
South Asia	38.4*	212	3.8	31.6*	165	4.8
	33.5-48.7	50-405	3.0-4.8	25.7-35.3	28-300	4.2-5.1
total	36.3*	192*	4.9*	29.7*	300*	4.4*
	30.3-44.6	50-390	4.3-5.0	24.6-36.0	130-500	3.6-5.0

Table 6.3: Median age, CD4 cell count and HIV-1 RNA plasma level at diagnosis for heterosexual men and women from the most prevalent regions of origin.

(P=0.03). For every region of origin separately, men were older than women, although the difference in age did not reach significant levels in patients from Western Europe and the Caribbean. Both men and women originating from Sub-Saharan Africa were younger than Dutch men and women (P<0.0001). The median age at diagnosis did not change with year of diagnosis.

At the time of diagnosis, male heterosexuals had a lower CD4 cell count and higher HIV-1 RNA levels than females (P<0.0001). There were no significant differences in CD4 cell counts and HIV-1 RNA levels between Dutch men and men from other regions. In contrast, women from South Asia, Sub-Saharan Africa and Latin America had lower CD4 cell counts than Dutch females but did not differ in HIV-1 RNA level. CD4 cell counts and HIV-1 RNA levels did not vary with year of diagnosis.

A small part of the HIV-infected patients had not become infected via sexual contact. Of the patients diagnosed before 1996, 11.3% had become infected via intravenous drug use. Thereafter this percentage decreased from 36 (6.2%) patients in 1996 to 10 (1.1%) patients in 2002/3. The majority of the drug users had become infected before 1996; 214/317 (67.5%) men and 98/123 (79.7%) women. Most patients originated from the Netherlands, 245 (77.3%) men and 73 (59.4%) women, and Western Europe, 29 (9.2%) men and 46 (37.4%) women. The median age at diagnosis of the male intravenous drug users was 33.9 (IQR: 29.2–39.5) years of age and was higher (P<0.0001) than the median age of the females, 29.7 (IQR: 24.6–34.7) years of age. CD4 cell counts and $\log^{10}$ HIV-1 RNA levels at diagnosis were 284 (IQR: 140-502) x 10^6 cells/l and 4.9 (IQR: 4.2–5.5) $\log^{10}$ (copies/ml), respectively, and did not differ between men and women.

The annual incidence of newly diagnosed patients who had become infected via blood transfusion, contact with blood products or a needle stitch accident varied between six and ten with a sudden peak of 15 patients in 2002. From 1996 on, a total of 63 patients had become infected this way, 32 (50.8%) of whom were of Dutch origin. Figures 6.1a and 6.1b show the proportions of male and female patients per year of diagnosis infected via homosexual (male only) or heterosexual contact or via other or unknown transmission routes. Transmissions via contact with blood products or intravenous drug use were combined with the group of unknown transmission routes, yielding five different gender-transmission groups.

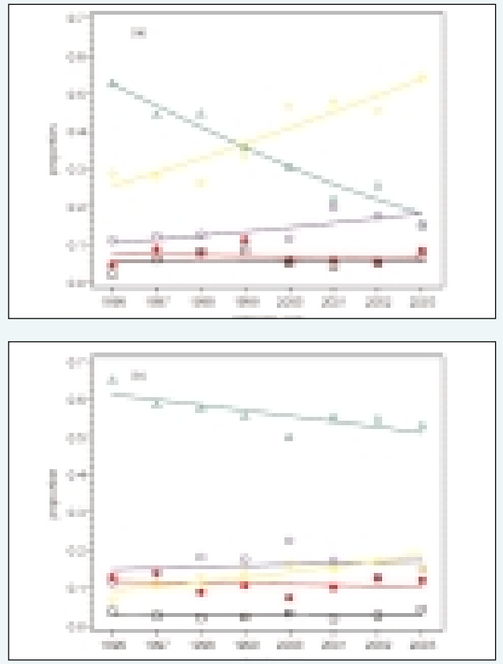

Figure 6.1: Annual proportions of diagnoses per gender-transmission group for patients 30 years of age or younger (a) or older (b) than 30 years. Symbols indicate the observed proportions, whilst the lines show the results of the logistic fit. Green: homosexual men; blue: heterosexual men; red: men infected via other or unknown transmission routes; yellow: heterosexual women; black: women infected via other or unknown transmission routes.

The proportion of homosexuals younger than 30 years of age decreased from 52.8% in 1996 to only 15.3% in 2003 (P<0.0001). In absolute numbers this is a reduction from 66 diagnoses in 1996 to 47 in 2002. This decrease was compensated for by an increase in the proportion of heterosexual women (P<0.0001) and, to a lesser extent, heterosexual men (P=0.02). This effect was much less pronounced in patients older than 30 years of age where the decline in the proportion of homosexual men from 65.1% to 53.0% (P=0.002) was counterbalanced by an increase in heterosexual women from 7.0% to 15.3% (P<0.0001). In absolute terms, however, the number of diagnoses among homosexuals above 30 years of age was 299 in 1996, decreased to 219 in 2000, and increased again to 289 in 2002. Infections via unknown or other transmission routes remained stable over time.

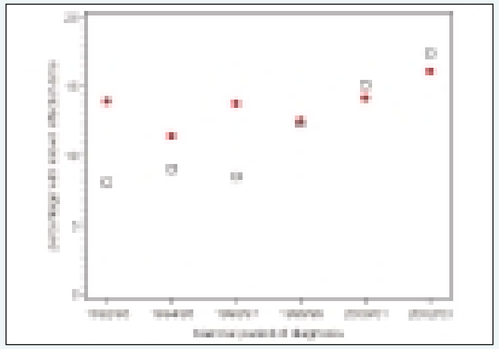

Figure 6.2

Recent infections and predictions

For 688 patients out of the total group of 7.623 HIV-1-infected patients, the time of infection could be estimated. The majority of these patients, 500 (72.7%), were homosexual men, whilst for only 44 (6.4%) heterosexual men and 66 (9.6%) heterosexual women the estimated time of infection was available.

Figure 6.2 shows the percentage of diagnoses with an estimated infection time among homosexual men younger and older than 30 years of age per two-year period of diagnosis. For patients younger than 30 years of age the percentage of recent infections amongst the new diagnoses increased from 13.9% in 1992/93 to 16.1% in 2002/03, but this increase was not significant (P=0.6).

On the other hand, the percentage of recent infections amongst homosexuals above 30 years of age increased from 8.1% to 17.4% during the same period (P<0.0001). In the heterosexually infected group 4.8% of the patients had a known recent infection. This percentage did not differ between men and women (P=0.7) or across the years of diagnosis (P=0.2).

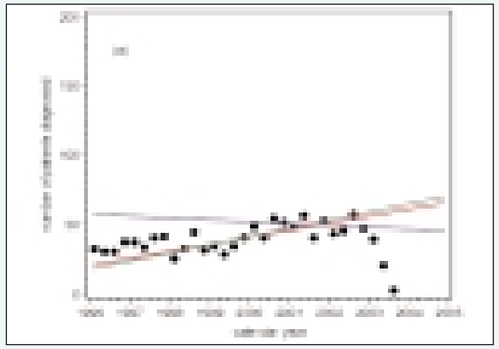

Figure 6.3.a

Figure 6.3 shows the number of patients diagnosed quarterly from 1996 onwards, differentiated for patients who were 30 years old or younger at time of diagnosis and older than 30 years. The annual number of diagnoses in the group of patients younger than 30 years of age increased from 128 in 1996 to 193 in 2002. For patients older than 30 years of age at diagnosis the number of diagnoses increased from 464 in 1996 to 542 in 2002, although this rise was not monotonically. The results of the three model fits are also shown in figure 6.3. For patients over 30 years of age, all three models predicted an increase in the quarterly number of diagnoses from around 140 in 2002 to 180 at the end of 2004. This was not the case for patients younger than 30 years of age; for them the models predicted a quarterly number of diagnoses between 50 and 70 in 2003 and 2004. It should be emphasised, however, that these predictions were only based on observed past trends.

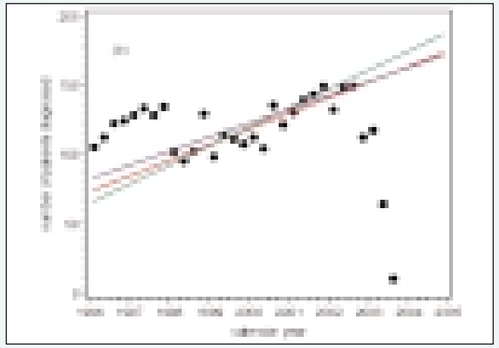

Figure 6.3.b

The expectations of the number of future diagnoses in figure 6.3 were combined with an extrapolation of the proportions of transmission groups in figure 6.1 towards 2004. The results of this are depicted in figure 6.4, which shows the expected number of diagnoses in 2003 and 2004 of homosexual men and heterosexual men and women younger and older than 30 years of age. The small error bars represent the minimum and the maximum prediction of the three models.

The model predicted that the number of diagnosed homosexual men younger than 30 years of age slightly declined over time, from 42 in 2003 to 38 in 2004. On the other hand, the number of diagnoses among homosexuals older than 30 years of age increased from 322 in 2003 to 363 in 2004. For heterosexuals younger than 30 years of age the predicted number of diagnoses amongst men was 42 in 2003 and 49 in 2004 compared to 125 in 2003 and 146 in 2004 amongst women. For heterosexuals older than 30 years of age an increase in the number of diagnoses was also predicted: 107 in 2003 and 116 in 2004 amongst men and 117 in 2003 and 137 in 2004 amongst women.

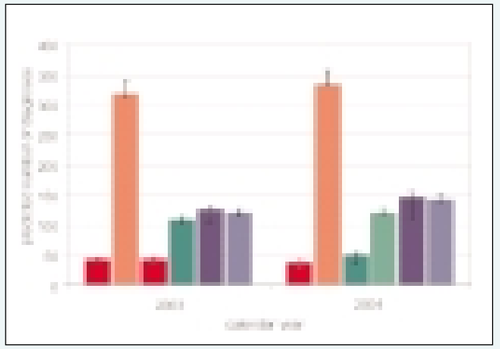

Figure 6.4

Discussion

The composition of the HIV-infected population in the Netherlands is changing over time. Although the majority of the known infected patients still consists of Dutch homosexual men, the relative contribution of this group to the newly diagnosed patients is decreasing. This decrease was most pronounced among young homosexual men. In the group of patients older than 30 years of age, the relative contribution of homosexual men decreased slightly, but combined with an increasing annual number of diagnoses the absolute number of new diagnoses increased [1]. Overall, the median age of homosexuals at diagnosis increased over time.

Amongst patients for whom the moment of infection could be estimated with a two years uncertainty level, the number of new infections increased in homosexual men over 30 years of age but did not change in the group of young homosexuals. This is compatible with the observed increase in new diagnoses. A similar increase was also observed in a study amongst homosexuals in Amsterdam [2].

It is difficult to determine the underlying cause of the increase in infections in the older homosexual population. In part, the increase in the number of patients with an estimated infection moment will be the consequence of an increase in the number of patients tested and thus in the number of patients with a negative HIV-test [3]. Hence, when a patient is tested HIV-positive, there is an increasing likelihood that this patient had been tested HIV-negative in the past. A second explanation might be that the HIV-infected population becomes older. Assuming that most homosexuals have sexual contact with men in approximately the same age group, the probability that transmission of HIV will occur between two young homosexuals should decrease, whilst it should increase for older homosexuals.

There are, however, strong indications that sexual behaviour is changing as well. Compared to 2001 the number of diagnoses of chlamydia, gonorrhoea and syphilis among homosexuals increased by 28%, 8% and 162% in 2002, respectively. At the same time, the number of STI consultations increased as well (41%) [3]. Hence, the number of unprotected sex acts is growing. Despite the aging HIV-infected population, an increasing number of unprotected sexual contacts will eventually lead to a larger probability of unprotected contacts with HIV-infected homosexual men. Therefore, it remains of the utmost importance to continue prevention strategies and to increase public awareness of the dangers of unprotected sexual contacts.

The composition of the heterosexual population is subject to change as well. Whereas the proportion of newly diagnosed Dutch heterosexuals steadily decreases, the proportion of Sub-Saharan Africans increases. A similar trend has been observed in other European countries [4,5,6]. The disparity in the number of HIV infections between men and women from Sub-Saharan African origin is also observed in Sub-Saharan Africa itself amongst heterosexuals of 25 years of age or younger [8,9,10]. In part, this is due to the tendency for women to have older partners.

On the other hand, women have a greater susceptibility to HIV infection than men [10]. As a result of this, women are on average younger at the moment of diagnosis than men, which is also observed in the total HIV-infected population and in the population presenting at the STI clinic [3]. This age effect is also influenced, however, by the fact that heterosexual men are in a later stage of their HIV infection at diagnosis than heterosexual women (and homosexual men), whilst patients from migrant populations in their turn are diagnosed in a later stage of the infection than Dutch patients.

These findings have important implications, both for the treatment of HIV and for public health issues. Patients initiating HAART at a lower CD4 cell count or after an AIDS diagnosis are at higher risk of dying or developing AIDS compared to patients with higher CD4 cell counts [11,12]. With regard to public health, late presenters form a major potential reservoir for the spread of HIV. Moreover, the treatment of AIDS-defining illnesses, in particular possible hospitalisations, is expensive. These expenses are likely to be larger than the costs of treating patients with antiretroviral drugs that could have been prescribed if these patients had presented earlier [4,13,14,15,16].

Most HIV-infected patients in the Netherlands are from Dutch or Sub-Saharan African origin. On 1 January 2003 the total population of first-generation Sub-Saharan Africans living in the Netherlands was 110.210, 63.831 (57.9%) men and 46.379 (42.1%) women [17]. Given the known HIV-infected population from Sub-Saharan African origin in the Netherlands (Table 6.1), this implies a prevalence of 0.9% and 1.6% for men and women, respectively. These percentages probably underestimate the actual prevalences, as not all people originating from Sub-Saharan Africa living in the Netherlands will be aware of their serostatus. Country-specific prevalences are even higher, e.g. 5.5% of the people originating from Côte d'Ivoire is HIV-infected, 4.8% of the people from Burundi, and 8.0% of the people from Rwanda. These data should, however, be interpreted with care, as the migration patterns of those groups are largely unknown.

The group of Sub-Saharan Africans does not contribute to the same extent to the spread of other sexually transmitted infections in the Netherlands [3]. Of the heterosexuals infected with chlamydia, gonorrhoea or syphilis, 8% to 38% of the men and 9% to 19% of the women originated from Suriname, Aruba or the Dutch Antilles. In addition, 12% of the heterosexual men with gonorrhoea was of Turkish or Moroccan origin, whilst 12% of the women with syphilis originated from Eastern Europe. Although HIV is not as prevalent in these groups as amongst Sub-Saharan Africans, it might quickly spread once it is introduced in these populations. Prevention strategies should therefore focus especially on these migrant groups.

Model predictions showed that among older homosexuals the number of diagnoses will increase by 13% in 2004 compared to 2003, whilst in the group of homosexuals younger than 30 years of age no changes are expected. New diagnoses in the heterosexual group will increase by 17%. It should be noted, however, that these predictions were obtained by mere extrapolation of observed trends. Moreover, the predictions reflect diagnoses among people that will largely have become infected this year or earlier. Nevertheless, these predictions show that the prevalence of HIV in the Netherlands still rises.

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Molecular epidemiology

HIV-1 non-B subtypes are mainly imported and not yet transmitted in The Netherlands

Introduction

Both HIV-1 and HIV-2 viruses can be subdivided into genetically distinct groups, so-called subtypes [1]. Analysing the distribution of subtypes across an infected population in combination with geographical and demographic data is useful to achieve a better insight into the epidemiology of the HIV infection [2,3]. In the patients included in the HMF programme, no subtypes were determined in the HIV-2-infected patients. Therefore, this chapter will solely concentrate on HIV-1 virus subtypes.

Study population and methods

The population studied in this chapter consisted of 8.282 HIV-1-infected patients and 186 HIV-1/2-infected patients. As discussed in chapter 5, part of this latter group probably encompassed HIV-1-infected patients showing a high cross-reactive antibody response to HIV-2. For 1.071 (12.6%) of these 8.468 patients, the HIV-1 subtype could be determined, using the nucleotide sequences of protease and RT. Sequences were obtained in four different virology laboratories: AMC-UvA in Amsterdam (Suzanne Jurriaans, Nicole Back, Lia van der Hoek and Ben Berkhout), EMC-Dijkzigt in Rotterdam (Martin Schutten and Ab Osterhaus), UMCU in Utrecht (Charles Boucher and Rob Schuurman) and LUMC in Leiden (Louis Kroes and Eric Claas).

The subtype was determined separately for every sequence available for each patient. Sequences were compared pair-wise using the Kimura 2-parameter model for distances [4]. A representative set of reference sequences was obtained from the Los Alamos sequence database - http://www.hiv-web.lanl.gov - and included in the distance calculations. Sequences were clustered using the neighbour-joining method [5] and were assigned a specific subtype when the bootstrap value of the cluster containing the sequences and a reference sequence exceeded 85%.

HIV-1 is divided into three major groups. The M(ain)-group includes nine subtypes labelled as A-D, F-H, J and K [1,6]. The two other groups, which are very rare, are O (for 'outlier') and N ('non-M-non-O') [7,8,9]. As yet, these two groups have not yet been detected in the HIV-1-infected population in the Netherlands. Individual patients can be infected with strains of HIV in which segments of the genome are derived from different subtypes. Such mosaic viruses are called recombinants [10]. Some of these recombinants contribute to the HIV epidemic and are called 'circulating recombinant forms' (CRFs) [11]. In ATHENA the most prevalent CRFs are CRF01_AE and CRF02_AG, which will be referred to as AE and AG in brief.

	subtype not available		subtype B		non-B subtype	
geographical region	N	%	N	%	N	%
Amsterdam	3061	80.5	644	16.9	96	2.5
northern provinces	474	94.1	30	6.0	0	0
eastern provinces	654	96.3	24	3.5	1	0.2
southern provinces	869	95.7	32	3.5	7	0.8
western provinces	2339	90.8	174	6.8	63	2.5
	7397	87.4	904	10.7	167	2.0

Table 7.1: Number and percentage of HIV-1 subtypes available per geographical region.

Results

The number of patients with a known subtype varied widely across the country (Table 7.1). For the Amsterdam population the subtype was known in 740 out of 3.801 (19.5%) patients, in the western provinces the subtype could be determined in 237 (9.2%) patients, while in the rest of the country the subtype was known in around 5% of the HIV-infected population.

The prevalence of non-B subtypes was very low in the northern and eastern provinces in the Netherlands, whereas in Amsterdam, the southern provinces, and the western provinces non-B subtypes were seen in 13.0%, 17.9% and 26.6% of the HIV-1-infected population, respectively. However, when the homosexually infected population and intravenous drug users – two groups that are mainly infected with subtype B - were excluded, the percentage of non-B subtypes increased to 48.1% (90/187) in Amsterdam, 58.3% (7/12) in the southern provinces and 50.4% (61/121) in the western provinces.

	male								female							
	homosexual		heterosexual		IVD		blood		unknown		heterosexual		IVD		blood		unknown	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
A	2	0.3	6	7.5					3	4.7	9	6.6					3	11.5
AE	5	0.7	3	3.8					2	3.1	1	0.7						
AG			8	10.0			1	5.9	5	7.8	13	9.5			1	12.5	6	23.1
B	695	98.9	40	50.0	25	100	16	94.1	40	62.5	67	48.9	11	100	4	50.0	6	23.1
C	1	0.1	13	16.3					7	10.9	17	12.4			2	25.0	6	23.1
D			2	2.5					2	3.1	9	6.1			1	12.5	1	3.9
DF											1	0.7						
F1			1	1.3							1	0.7					1	3.9
G			4	5.0					2	3.1	9	6.6					3	11.5
non-B			3	3.8					3	4.7	10	7.3						
	703		80		25		17		64		137		11		8		26	

Table 7.2: HIV-1 subtypes by gender and mode of transmission.

Table 7.2 shows the distribution of subtypes by gender and mode of transmission. Patients infected via intravenous drug use were all infected with subtype B. Among homosexuals the most prevalent subtype was subtype B (98.9%), followed by subtype AE, which is prevalent in South-East Asia [12,13,14]. Three patients were infected with other subtypes and are the first indication that other subtypes than B and AE are entering the male homosexual group. One patient with subtype A was of Thai origin and had been infected in Thailand, while the other two were Dutch and had most probably been infected in the Netherlands.

Amongst patients infected via blood transfusion or contact with blood products, twenty (80%) were infected with subtype B. One patient was infected with subtype C due to a needle accident in the Netherlands. The other four patients were of African and Brazilian origin and had been infected in their country of birth.

In the heterosexually infected population, the most prevalent subtypes were subtype B (49.3%), subtype C (13.8%) and subtype AG (9.7%). There was no significant difference in prevalence of these subtypes between men and women (P=0.8).

Prevalence of subtype B per region of origin was higher than 85% in each region, except in the population originating from Sub-Saharan Africa in which the prevalence of subtype B was only 6%. When homosexual men and intravenous drug users were excluded from the population, the prevalence of non-B subtypes was above 20% in patients originating from the Netherlands and the rest of Western Europe and Sub-Saharan Africa. All different subtypes found in our cohort, except DF, were also found amongst patients originating from the Netherlands and the rest of Western Europe. This introduction of non-B subtypes in predominantly subtype-B areas has been reported previously [15,16,17,18].

Concentrating further on the group of 332 patients infected via heterosexual contact, contact with blood products or unknown transmission, the subtypes were very unevenly distributed throughout the regions of origin. Subtype B dominated in patients originating from Australia, the Caribbean, Europe, the Americas, the Middle East and North Africa with a prevalence of 79%. Subtype AE was only found in patients from Western Europe and South Asia.

Amongst patients from Sub-Saharan Africa the most prevalent subtypes were A (12.5%), C (28.3%), D (10.8%), G (10.0%) and AG (21.7%). Subtypes G and AG were mainly found in patients originating from the countries along the Atlantic stretching from Guinea to Congo [19,20]. Subtypes A and D were mostly prevalent in patients from central Africa, between the west and east coast. Subtype C was found in patients from the eastern and southern part of Sub-Saharan Africa. This distribution over the continent corresponds with the endemic prevalence of these subtypes [21].

For 299 of the 332 patients the year of diagnosis was known. The prevalence of non-B subtypes in patients diagnosed before 1996 was 48/128 (37.5%). In the period between 1996 and 2000, the prevalence increased to 60/110 (54.5%) and did not change significantly in the period after 2000: 35/61 (57.4%).

Discussion

Subtype B is still the most prevalent subtype in all risk groups. The only transmission route through which non-B subtypes spread through the population is sexual contact. However, the prevalence of non-B subtypes in the male homosexual population remains very limited. So far, only two men of Dutch origin could be identified with another subtype than B or AE.

In the population infected via heterosexual contact, the proportion of non-B subtypes increased from 42.5%, as reported in the HMF report of 2002 [22], to 50.7% at present. This higher prevalence is, however, not due to an increase in the annual number of newly diagnosed patients infected with non-B subtypes. Most probably, the increase in the prevalence of non-B subtypes can be attributed to the elimination of the backlog in inclusion in the HMF registration of patients of non-Dutch origin. This backlog was caused by the informed consent inclusion procedure in the ATHENA project, as informed consent was less likely to be given by non-Dutch patients due to language problems.

Currently, the prevalence of non-B subtypes is likely to be underestimated. Until r ecently, genotypic sequences were largely generated in patients who showed virological failure on therapy. Virological failure mostly occurs in pre-treated patients (see chapter 8) while the majority of the migrants (78%) compared to 63% (data not shown) of the Western population were therapy-naïve. Hence, sequences were less likely to be obtained in migrant populations than in Western patients.

Until recently, screening programs in which sequences are obtained to determine subtypes, used to concentrate on homosexual men and intravenous drug users [23,24]. These groups, however, are mostly infected with subtype B. From 2002 on sequences are being obtained at diagnosis for newly diagnosed patients at entry in the HMF, though this is not standard-of-care yet in all hospitals. Apart from detecting possible transmissions of drug-resistant HIV variants, this screening provides early knowledge of the HIV subtype. This information might help physicians in deciding which therapy regimen is most suitable as the starting regimen. For example, it has been shown that subtype G strains are less susceptible to protease inhibitors [25]. In vitro studies showed that subtypes A, B, C and AE do not differ in susceptibility to non-nucleoside RT inhibitors, while subtype D showed a tendency toward a slightly lower susceptibility [26].

The distribution of subtypes across patients from Sub-Saharan Africa corresponded with the endemic distribution observed in this region. This shows that either this population is fed by an import of HIV infections from Sub-Saharan Africa rather than the infections taking place in the Netherlands, or that Sub-Saharan Africans living in the Netherlands form a closed group with HIV transmissions mostly occurring among themselves. As in studies on the spread of subtype B viruses in the Netherlands and Western Europe [23,24,27,28,29], studies among patients infected with non-B subtypes should give more insight into the transmission pattern in specific groups. A more accurate knowledge of transmission patterns among migrants might help prevention strategies to focus more on population-specific transmission characteristics.

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Resistance

Increasing prevalence at therapy failure, but not in newly diagnosed HIV-1 infections

Introduction

Although HAART can suppress plasma virus to undetectable levels, replication is still going on, albeit at a lower rate than in untreated patients. In the end, this might result in a selection of HIV-1 viruses that escape suppression by antiretroviral drugs due to resistance. Recent studies showed that the prevalence of resistant virus strains in patients failing on therapy is as high as 80% [1,2,3]. Prolonged treatment with antiretroviral drugs and, consequently, selection of resistant virus could result in transmission of these resistant viruses to uninfected persons.

In recent years, the prevalence of transmitted drug-resistant viruses in newly infected patients varied between 5% and 25% in Europe and the United States [4,5,6,7,8,9]. This year the CATCH study reported a prevalence of 9.6% in Europe [10]. In the Netherlands, resistance to AZT was found in approximately 9% of the homosexual men and intravenous drug users participating in the Amsterdam Cohort Studies before 1996 [11]. Similar results were found in 56 patients from the same cohorts, seroconverting between 1994 and 2002, where mutations associated with resistance to AZT were found in six (11%) patients [12].

In the present study, the prevalence of resistance amongst treated patients in the ATHENA cohort was evaluated. In addition, transmission of resistant virus strains in recently diagnosed patients was assessed.

Methods

Resistance measurements were based on isolation of HIV-1 RNA from plasma of patients and amplification of the protease and (part of) the RT gene of the virus. Successful amplification was only achieved in patients with a viral load above 1.000 copies/ml. HIV-1 RT and protease were genotyped by using the amplified genes in a sequencing procedure. Sequences were obtained in four different virology laboratories: AMC-UvA in Amsterdam (Suzanne Jurriaans, Nicole Back, Lia van der Hoek and Ben Berkhout), EMC-Dijkzigt in Rotterdam (Martin Schutten and Ab Osterhaus), UMCU in Utrecht (Charles Boucher and Rob Schuurman) and LUMC in Leiden (Louis Kroes and Eric Claas).

Sequences were compared to subtype B wild-type virus and scanned for specific mutations at codons known to be associated with drug resistance. Mutations that can occur as natural polymorphisms were excluded, even if they also contributed to resistance when they were present with other resistance-associated mutations. Nucleoside RT inhibitor resistance mutations included M41L, E44D, A62V, K65R, D67N, T69D, K70R, L74V, V75T, V118I, M184V/I, L210W, T215Y/F/D/N/S/C/E, K219Q, Q151M and an insertion after position 69. Non-nucleoside RT inhibitor resistance mutations included K103N, V106A, V108I, Y181C/I, Y188C/L/H and G190S/A. PI resistance mutations that were scanned for included D30N, M46I, G48V, I50V, V82A/F/T/S, I84V and L90M. These mutations constitute a canonical set, though some reports included somewhat more or fewer mutations [8,13,14].

To study transmission of resistant virus strains only RT and protease sequences were used that were obtained from therapy-naïve patients. Recently infected patients were identified by two methods. The first method estimated the time of infection as the midpoint between the last negative and the first positive HIV-1 test, if the interval between the two tests was less than two years. The second method defined recently infected patients as those patients having a CD4 cell count at diagnosis exceeding 500 x 10^6 cells/l.

To make sure that these patients had really been recently infected, a control group of patients was selected from the total HIV-1 infected adult population in the HMF database for whom the time interval in which seroconversion took place was narrower than one year. The date of seroconversion was again estimated as the midpoint of this interval. For these patients the date at which CD4 cell counts exceeded 500 x 10^6 cells/l for the last time after seroconversion but before initiation of therapy was determined. In addition, the time from the last CD4 cell count above 500 x 10^6 cells/l to the first CD4 cell count below this limit was determined. Patients were only considered if at least one of these two dates was known. A Weibull model taking into account interval-censored survival times was used to determine the time in which CD4 cell counts permanently dropped below 500 x 10^6 cells/l.

The prevalence of drug resistance in the total population was assessed by analysing all sequences with one or more resistance-associated mutations. It was assumed that once a patient had acquired a resistance-associated mutation at a specific codon, this mutation would be present in the patient from that moment on, even if the mutation was no longer detectable in later sequences obtained from this patient. In addition, a patient with one or more mutations associated with resistance to a specific drug class was considered to be resistant to all drugs in that class. The cumulative number of drug-resistant patients was determined per year by summing all patients alive in that year in whom resistance had been measured in or before that year.

In a further analysis, the prevalence of resistance was assessed in the group of therapy-naïve patients who failed therapy at least once. Therapy failure was defined as reaching a plasma viral load exceeding 500 copies/ml after having achieved virological success (see chapter 10). Sequences were not necessarily obtained at the date of first failure. Instead, all sequences obtained at or after this date were assessed.

The significance of changes over time in proportions was assessed with the Cochran-Armitage test for trend. Differences in median values of continuous variables were tested using Wilcoxon Mann-Whitney and $\chi 2$ non-parametric tests. For continuous variables, medians are reported together with the interquartile range (IQR).

Results

Transmission of drug-resistant virus

In 310 patients a sequence was obtained befo re initiation of antiretroviral therapy. For 300 (96.8%) patients both RT and protease sequences could be obtained successfully, while in ten patients only a protease sequence was available.

In 15 patients (5.0%) mutations were found conferring resistance to nucleoside RT inhibitors. Seven patients had only a V118I mutation, which causes resistance to lamivudine (3TC) but only in combination with E44D [15]. One patient had a V118I mutation in combination with K219Q. The remaining patients harboured M41L (4), T69D (2) and K219Q (1). In four patients a mutation was found at codon 215: T215C (1), T215D (1) and T215S (2). It has been shown that these mutations reflect evolution from a transmitted AZT-resistant virus [16]. The T215C mutation is also associated with resistance to zalcitabine (ddC) [17].

Five patients (1.7%) harboured mutations associated with resistance to non-nucleoside RT inhibitors. In four patients the V108I mutation was found, while one patient harboured a K103N mutation. Both mutations confer resistance to nevirapine and efavirenz [18,19].

Only in two of the 310 (0.6%) patients, a protease mutation was found. Both patients harboured a mixture of wild-type virus and the M46I mutation at codon 46. However, one patient was diagnosed in 1991, making it improbable that this was a transmission of a protease inhibitor-resistant virus.

Hence, when leaving out the patients with V118I as single mutation there were 15 (4.8%) out of 310 patients

who were possibly infected with a resistant virus strain. There were no patients with resistance to multiple drug classes. Of the 41 patients (13%) infected with a non-B subtype, no one harboured a resistant virus strain.
The prevalence of resistance slightly decreased with time of diagnosis. In patients diagnosed before 1996 (pre-HAART), between 1996 and 1999 (early HAART) and between 2000 and 2003 (late HAART), pre-treatment drug resistance was found in 4/54 (7.4%), 7/159 (4.4%) and 4/97 (4.1%) patients, respectively, but this decrease was far from significant (P=0.3).

The median duration of the time interval between diagnosis and the date of sequencing was short, 0.2 (IQR: 0.06–1.4) years. No significant difference in the duration of this interval was observed between patients harbouring resistant and non-resistant HIV variants (P=0.6).

Of the 310 patients with a pre-treatment sequence, 79 (25.8%) had recently been infected. For 48 (60.8%) patients the time of infection could be estimated by using the last negative and first positive HIV-1 test. A further 31 (39.2%) recently infected patients were identified by the second method. The control group of recently infected patients contained 283 patients for whom the time interval in which CD4 cell counts dropped permanently to below 500 x 10^6 cells/l could be estimated. The Weibull model showed that the median time from seroconversion to passing the threshold of 500 x 10^6 CD4 cells/l was 0.8 (IQR: 0.2–2.6) years.

Amongst the 79 recently infected patients, transmission of resistant virus strains was found in 1/12 (8%) of those who had been infected before 1996, in 2/34 (6%) infected between 1996 and 1999, and in 2/28 (7%) infected between 2000 and 2003 (P=0.6), an overall prevalence of 6%. The median time to sequencing was 0.7 (IQR: 0.2–1.6) years and 0.5 (IQR: 0.2-1.3) years for patients without and with mutations, respectively, (P=0.9).

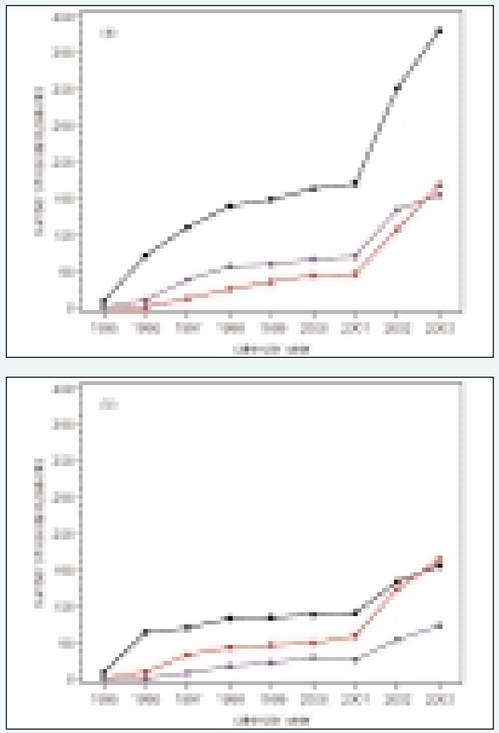

Figure 8.1: (a) cumulative number of patients with resistance to nucleoside RT inhibitors (black line), non-nucleoside RT inhibitors (red line) and protease inhibitors (blue line); (b) cumulative number of patients resistant to one drug class (black line), two drug classes (red line) or three drug classes (blue line).

Resistance over time

In 416 patients, one or more sequences were obtained in which resistance-associated mutations were found. The cumulative number of patients harbouring resistance to one or more drug classes is shown in figures 8.1a and 8.1b. Among the 392 patients still alive on 31 July 2003, the majority, 235 (62.3%), had been pre-treated with antiretroviral drugs before initiation of HAART, 142 (36.2%) patients were therapy-naïve, 6 (1.5%) patients had never been treated with HAART, and of 9 (2.3%) patients therapy data were missing. Resistance to nucleoside RT inhibitors had been found in 380 (96.9%) patients, resistance to non-nucleoside inhibitors in 168 (42.9%) patients, and resistance to protease inhibitors in 154 (39.3%) patients.

Resistance to one drug class was observed in 155 (39.5%) patients of whom 80 (51.6%) had been pre-treated. In 164 (41.8%) patients, of whom 98 (59.8%) had been pre-treated, resistance to two drug classes was found, while 73 (18.6%) patients, of whom 57 (78.1%) had been pre-treated, were resistant to drugs from all three drug classes.

The most frequently observed mutations in protease were L90M (91, 23.2%), V82A/F/T/S (75, 19.1%) and M46I (45, 11.5%), which confer resistance to indinavir, ritonavir and saquinavir [20,21,22]. The D30N mutation conferring resistance to nelfinavir was found in 19 (4.8%) patients [23]. Frequent mutations conferring resistance to non-nucleoside RT inhibitors were K103N (84, 21.4%), Y181C/I (63, 16.1%) and G190S/A (52, 13.3%). The most frequently found nucleoside RT inhibitor mutation was M184V/I, which was present in 266 (67.9%) patients and confers resistance to lamivudine [24]. Other frequent NRTI mutations were T215Y/F, observed in 197 (50.3%) patients, M41L, observed in 174 (44.4%) patients, K70R, observed in 122 (31.1%) patients, and L210W, observed in 115 (29.3%) patients. All these mutations are related to resistance to AZT [25,26,27].

Amongst the 1.044 patients who failed therapy at least once, a sequence was obtained in 102 (9.8%) patients. Resistance was found in 65 (63.7%) of these patients.

Discussion

Transmission of drug-resistant HIV-1 virus strains was observed in 4.8% of the newly diagnosed patients and in 6% of the new infections in the Netherlands. No evidence was found that these percentages are changing over time. They are lower than those found in another recent study among seroconverters conducted in the Netherlands [12]. However, both analyses were hampered by a limited number of patients in whom a sequence was obtained shortly after infection.

In other European countries, transmission of drug-resistant virus is more frequent [10]. There are, however, differences between countries. In the United Kingdom transmission of resistant strains was reported in 27% of patients seroconverting in 2000, while in Switzerland only 5.0% of the new infections in 1999 were transmissions of resistant virus strains [7,9]. In North America resistance to one or more drugs in seroconverters increased from 3.4% during the period 1995 to 1998 to 12.4% during the period 1999 to 2000 [8]. Differences in methods of testing for drug resistance, geographical variation in the accessibility and usage of antiretroviral drugs, and variation in risk factors for exposure may explain these differences [8].

A limitation of assessing transmission using pre-treatment sequences is that the sequences were not necessarily obtained at a time close to the moment of seroconversion. Although the median time from diagnosis to the time of sequencing was short and not significantly different for patients harbouring resistant and non-resistant HIV variants, the time between infection and diagnosis was unknown for most patients. Hence, rates of transmitted resistance might be underestimated as resistant virus strains may be overgrown by wild-type variants shortly after infection. The CATCH-study showed that transmission of resistant virus tended to be more frequently detected shortly after seroconversion than later in the infection, although this was not observed in other studies [8,10]. The present study also showed that resistance was more prevalent among recently

infected patients than among newly diagnosed patients, though the numbers involved were very small.

Presently, 13.0% of the 1.810 pre-treated and 3.3% of the 4.252 naïve patients currently participating in the HMF registration and research programme have been identified as harbouring resistant virus strains. The true prevalence of resistance in the HIV-infected population, however, is likely to be higher, as only 9.8% of the naïve patients failing on therapy were sequenced. Moreover, not all sequences obtained from patients participating in the HMF were as yet available for analysis due to a backlog in submission to the HMF sequence database.

The percentage of patients failing on therapy in whom a sequence was obtained was very low. Apparently the necessity to obtain a resistance profile in these patients was not pressing. Possibly, these patients failed because of a therapy interruption. An indication for this is the considerable number of sequences without resistance-associated mutations. Another reason might be that 'viral blips' - an occasional detectable but low viral load measured in patients who are doing well on therapy - are counted as therapy failure in our definition. These blips form no reason for obtaining a resistance profile, let alone that it is hard or even impossible to obtain a sequence in patients with a low detectable viral load with the currently available techniques.

On the other hand, the number of patients failing on different drugs and multiple drug classes rapidly increased after 2001. This suggests that determining resistance profiles in failing patients is increasingly becoming standard-of-care. If failing patients were sequenced once or twice per year this would generate interesting data for a study on the development of resistance in the treated population. Combined with genotypic determinations at diagnosis this would allow an estimate of the transmission probability of resistant virus strains.

As the prevalence of drug resistance in the HIV-infected population is small, it is of no surprise that the transmission of resistant virus strains is limited as well. Only patients who fail on their therapy are potential transmitters of resistant virus. However, patients with incomplete suppression of viral load during therapy still have lower load levels than untreated patients, which leads to a lower transmission risk. Moreover, the transmission of resistant virus might be less efficient than the transmission of wild-type virus [28]. Mathematical modelling showed that despite a high prevalence of resistance in a treated population the transmission of resistant virus variants is low [29].

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Efficacy of HAART

Trade-off between virological and immunological effect and toxicity

Introduction

Presently HAART consists of a combination of at least three different drugs, in most cases a combination of a backbone of two nucleoside reverse transcriptase inhibitors (nRTI) plus either one or two protease inhibitors (PI) or one non-nucleoside reverse transcriptase inhibitors (NNRTI), or a triple nRTI combination [1]. Short-term efficacy of highly active antiretroviral therapy (HAART) has been assessed in randomised clinical trials [2,3,4,5,6,7,8,9,10,11,12].

However, clinical trials are limited in size and duration of follow-up in contrast to observational cohorts that can be used for long-term efficacy studies of HAART [13,14]. While observational cohorts can provide the data to assess clinical effectiveness of a wide range of HAART combinations, care needs to be taken in interpreting the results because of possible biases as a result of the lack of randomisation and the possibility of unrecorded factors influencing the choice of the initial HAART combination [15,16].

On a population level, HIV-related morbidity and mortality has declined substantially [17] since the introduction of HAART treatment in the Netherlands. HIV-1 RNA plasma concentration and CD4 cell counts are major prognostic markers for these endpoints [17,18,19,20,21]. HAART treatment in infected patients who did not receive any prior antiretroviral therapy results in a rapid decline of viral replication [22], followed by a slower increase in CD4 cells.

Rapid suppression of HIV-1 replication is of vital importance to prevent or deter resistance to antiretroviral drugs [23,24]. Sustained suppression of replication allows for immune reconstitution [25] and subsequent improvement of the patient's quality of life, although this improvement largely depends on the stage of the infection [17,26,27].

Quality of life and adherence to HAART are negatively influenced by the toxicity of the antiretroviral drugs used [28]. Although the number of drugs and the number of possible HAART combinations have increased since 1996, toxicity is still a major reason for change or interruption of HAART [17,18,29]. Risk factors for HAART-associated toxicity obviously include the specific antiretroviral drugs used in the combination [31], but also various underlying conditions and patient characteristics [29].

In this chapter, the most frequently used first- and second-line HAART combinations within the ATHENA-HMF observational cohort will be discussed and for the first-line HAART combinations the short-term efficacy and toxicity will be analysed. Finally, the long-term effect of HAART will be assessed.

Material and methods

Study population, first- and second-line regimens

HAART-treated HIV-1-infected patients ≥12 years of age, without prior antiretroviral treatment at start of HAART and with at least ≥10 weeks of follow-up after start HAART were selected from the ATHENA-HMF observational cohort. Patients were classified according to the nRTI backbone and the addition to the backbone in the first-line HAART regimen. Only patients using Zidovudine+Lamivudine or Stavudine+Lamivudine plus an addition to the backbone that was used by at least 100 patients were included in the analysis. In addition, patients on first-line regimens were only eligible for the analysis of the long-term efficacy if they had stayed on their initial HAART regimen at least ≥18 weeks, had a CD4 measurement between 10-18 weeks after start HAART (referred to as CD4 at 18 weeks) and had at least one CD4 measurement after 18 weeks. The pattern of changes from first-line to second-line HAART is described for patients who stopped first-line HAART.

Endpoints

Endpoints in the short efficacy analysis were time from start of HAART to a first of two consecutive HIV-1 RNA viral load <500 copies/ml measurements, an increase in CD4 cell count of 100 cells/mm^3 and, finally, a combination of both. Endpoint in the toxicity analysis was time from start to change or interruption of a HAART regimen because of toxicity. Patients having either a plasma HIV-1 RNA level <500 copies/ml or no viral load measurement at start of HAART were excluded from the time to reach a viral load <500 copies/ml analysis. Patients without a CD4 measurement at start of HAART were excluded from the analysis of time to an increase in CD4 cell count of 100 cells/mm^3.

Statistical analysis

Kaplan-Meier curves of time to endpoint were constructed for each HAART regimen. HAART regimens were compared using a Cox proportional hazards model adjusted for confounding factors such as gender, transmission risk group, regimen, age, CD4 cell count and HIV-1 RNA levels and occurrence of a CDC-C event at start HAART. Time was censored in case a patient did not reach the endpoint before change or interruption of the first HAART regimen. Estimates of confounding variables are discussed in chapter 10.

Long-term immunological change was estimated from the slope of the regression line of the change in log CD4 cell count between 18 and 96 weeks after start of HAART using a linear mixed effects model. A random slope was included for every patient. To handle dependence of irregular measurements over time, a weighted variance-covariance matrix with a spatial power covariance structure was used. Reported p-values are Tukey p-values adjusted for multiple comparisons.

Results

Distribution of first-line HAART regimens

A total of 4.261 patients was eligible. Zidovudine+Lamivudine was used as nRTI backbone for the initial HAART regimen in 2.937 patients (69%) and Stavudine+Lamivudine in 725 patients (17%). The remaining 599 patients (14%) started with another nRTI combination. The distribution of the different additions to the nRTI backbone is shown in Table 9.1. For the present analysis of the effect of initial HAART, we used data from the 3.525 patients on a regimen including Zidovudine+Lamivudine or Stavudine+Lamivudine plus one of the ten most frequently used drugs or combinations of drugs. The NNRTI Nevirapine was the most frequently used addition to the Zidovudine+Lamivudine backbone, followed by the PIs Indinavir and Nelfinavir. Zidovudine+Lamivudine was therefore used as reference group in the analyses when comparing nRTI backbones; Nevirapine was used when comparing the various additions to the backbone.

	AZT + 3TC	d4T + 3TC	Other	Total
	N	N	N	N
Total	2937	725	599	4261
IDV	431	144	41	616
IDV+RTV	188	60	28	276
SAQ	197	24	40	261
SAQ+RTV	125	106	118	349
NFV	456	110	35	601
LOP+RTV	239	41	76	356
RTV	273	79	16	368
ABC	160	2	0	162
EFV	246	14	82	342
NVP	556	74	103	733
Other	66	71	60	197

Table 9.1: First HAART regimens in 4261 naïve patients. The analysis was limited to regimens consisting out of a AZT+3TC and d4T+3TC nRTI backbone combined with ABC or 1-2 PI or 1 NNRTI.

The distribution of first-line HAART combinations by year of initiation is depicted in Figure 9.1 for combinations with Zidovudine+Lamivudine and in Figure 9.2 for combinations with Stavudine+Lamivudine. The regimens Zidovudine+Lamivudine+Indinavir (31% of all 366 patients who started in 1996), Zidovudine+Lamivudine+

	NRTI backbone				Addition to the 2 NRTI backbone																Total	
	3TC + AZT		3	TC + d4T	IDV		IDV+RTV		SAQ		SAQ+RTV		NFV		LOP+RTV		RTV		ABC		EFV		NVP			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	2871	100.0	654	100.0	575	100.0	248	100.0	221	100.0	231	100.0	566	100.0	280	100.0	352	100.0	162	100.0	260	100.0	630	100.0	3525	100.0
Gender																										
Male	2217	77.2	506	77.4	473	82.3	215	86.7	186	84.2	192	83.1	352	62.2	214	76.4	315	89.5	119	73.5	199	76.5	458	72.7	2723	77.2
Female	654	22.8	148	22.6	102	17.7	33	13.3	35	15.8	39	16.9	214	37.8	66	23.6	37	10.5	43	26.5	61	23.5	172	27.3	802	22.8
Age at start HAART																										
<35	1188	41.4	269	41.1	235	40.9	83	33.5	80	36.2	96	41.6	303	53.5	98	35.0	129	36.6	69	42.6	102	39.2	262	41.6	1457	41.3
35-45	1034	36.0	231	35.3	206	35.8	100	40.3	86	38.9	67	29.0	169	29.9	109	38.9	129	36.6	56	34.6	102	39.2	241	38.3	1265	35.9
≥45	649	22.6	154	23.5	134	23.3	65	26.2	55	24.9	68	29.4	94	16.6	73	26.1	94	26.7	37	22.8	56	21.5	127	20.2	803	22.8
Transmission risk group																										
Homosexual	1446	50.4	353	54.0	323	56.2	148	59.7	143	64.7	131	56.7	216	38.2	124	44.3	228	64.8	67	41.4	123	47.3	296	47.0	1799	51.0
IDU	120	4.2	25	3.8	31	5.4	10	4.0	17	7.7	1	0.4	22	3.9	9	3.2	18	5.1	10	6.2	3	1.2	24	3.8	145	4.1
Heterosexual	952	33.2	208	31.8	145	25.2	61	24.6	40	18.1	77	33.3	271	47.9	101	36.1	84	23.9	52	32.1	99	38.1	230	36.5	1160	32.9
Other	353	12.3	68	10.4	76	13.2	29	11.7	21	9.5	22	9.5	57	10.1	46	16.4	22	6.3	33	20.4	35	13.5	80	12.7	421	11.9
Year first HAART therapy started																										
1996	305	10.6	25	3.8	128	22.3	1	0.4	107	48.4	3	1.3	1	0.2			89	25.3					1	0.2	330	9.4
1997	452	15.7	137	20.9	267	46.4	3	1.2	107	48.4	21	9.1	4	0.7			184	52.3	1	0.6			2	0.3	589	16.7
1998	315	11.0	171	26.1	102	17.7	12	4.8	7	3.2	122	52.8	115	20.3			62	17.6			1	0.4	65	10.3	486	13.8
1999	405	14.1	149	22.8	62	10.8	86	34.7			31	13.4	221	39.0			8	2.3			3	1.2	143	22.7	554	15.7
2000	404	14.1	84	12.8	13	2.3	110	44.4			28	12.1	110	19.4	4	1.4	7	2.0	13	8.0	47	18.1	156	24.8	488	13.8
2001	476	16.6	45	6.9			36	14.5			23	10.0	65	11.5	88	31.4	2	0.6	65	40.1	94	36.2	148	23.5	521	14.8
2002	402	14.0	37	5.7	3	0.5					3	1.3	41	7.2	147	52.5			63	38.9	89	34.2	93	14.8	439	12.5
2003	112	3.9	6	0.9									9	1.6	41	14.6			20	12.3	26	10.0	22	3.5	118	3.3
CD4+ T cells/mm^3 at start HAART																										
<50	443	15.4	132	20.2	115	20.0	58	23.4	23	10.4	45	19.5	102	18.0	90	32.1	45	12.8	10	6.2	35	13.5	52	8.3	575	16.3
50 - 200	765	26.6	178	27.2	140	24.3	82	33.1	57	25.8	63	27.3	134	23.7	103	36.8	90	25.6	49	30.2	60	23.1	165	26.2	943	26.8
200 – 350	649	22.6	101	15.4	106	18.4	42	16.9	49	22.2	39	16.9	100	17.7	40	14.3	91	25.9	50	30.9	47	18.1	186	29.5	750	21.3
350 – 500	362	12.6	72	11.0	72	12.5	18	7.3	44	19.9	36	15.6	76	13.4	20	7.1	58	16.5	24	14.8	13	5.0	73	11.6	434	12.3
>500	209	7.3	46	7.0	56	9.7	8	3.2	19	8.6	14	6.1	49	8.7	6	2.1	30	8.5	15	9.3	10	3.8	48	7.6	255	7.2
Missing	443	15.4	125	19.1	86	15.0	40	16.1	29	13.1	34	14.7	105	18.6	21	7.5	38	10.8	14	8.6	95	36.5	106	16.8	568	16.1
HIV-1 RNA copies/ml at start HAART																										
0 - 500	54	1.9	10	1.5	11	1.9	2	0.8	5	2.3	4	1.7	17	3.0	2	0.7	3	0.9	5	3.1	3	1.2	12	1.9	64	1.8
500 - 10000	241	8.4	59	9.0	42	7.3	8	3.2	20	9.0	19	8.2	55	9.7	13	4.6	30	8.5	31	19.1	11	4.2	71	11.3	300	8.5
10000 - 100000	1051	36.6	225	34.4	173	30.1	75	30.2	65	29.4	82	35.5	195	34.5	80	28.6	114	32.4	91	56.2	97	37.3	304	48.3	1276	36.2
>100000	1105	38.5	289	44.2	216	37.6	143	57.7	80	36.2	105	45.5	222	39.2	159	56.8	152	43.2	24	14.8	119	45.8	174	27.6	1394	39.5
Missing	420	14.6	71	10.9	133	23.1	20	8.1	51	23.1	21	9.1	77	13.6	26	9.3	53	15.1	11	6.8	30	11.5	69	11.0	491	13.9
CDC-C event at start HAART																										
Unknown	166	5.8	19	2.9	8	1.4	4	1.6	3	1.4	2	0.9	22	3.9	53	18.9	3	0.9	22	13.6	35	13.5	33	5.2	185	5.2
No	2398	83.5	557	85.2	500	87.0	218	87.9	188	85.1	208	90.0	481	85.0	202	72.1	301	85.5	130	80.2	197	75.8	530	84.1	2955	83.8
Yes	307	10.7	78	11.9	67	11.7	26	10.5	30	13.6	21	9.1	63	11.1	25	8.9	48	13.6	10	6.2	28	10.8	67	10.6	385	10.9

Table 9.2: Baseline characteristics for the most frequently used HAART combinations.

Saquinavir (26%) and Zidovudine+Lamivudine+Ritonavir (23%), most frequently used in 1996 as starting regimen, are no longer in use as starting regimens. In 1999, Zidovudine+Lamivudine+Nelfinavir was the most popular starting regimen (28% of 581). Although Nelfinavir was still in use in 6% of the patients starting HAART in 2002/2003, other regimens have since become more widely used. In 2002/2003, the most frequently started initial HAART was Zidovudine+Lamivudine+Lopinavir+Ritonavir (21%), followed by Zidovudine+Lamivudine+Efavirenz (14%), Zidovudine+Lamivudine+Nevirapine (14%), and Zidovudine+Lamivudine+Abacavir (11%). The most frequently used combination was Stavudine+Lamivudine +Indinavir (144/4.261 patients, 3%). In 1998 Stavudine+Lamivudine was used in 33% of the starting regimens. Since then its use has been gradually declining.

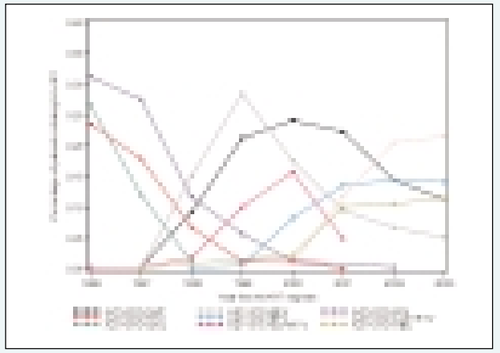

Figure 9.1: Initial highly active antiretroviral regimens based on a AZT+3TC backbone by year of initiation as a percentage of the total number of patients initiating HAART yearly.

Baseline characteristics for patients on Zidovudine+Lamivudine or Stavudine+Lamivudine HAART combinations were similar for these two patient groups and are shown in Table 9.2. Initial HAART regimens containing RTV were used by a relatively small percentage of women (37/352, 10%), in contrast to regimens containing Nelfinavir, which were used in 38% of women.

Furthermore, HAART regimens including Nelfinavir were mostly used by younger patients and patients who had acquired HIV through heterosexual contact. Patients starting with Lopinavir+RTV added to the backbone had a more advanced disease stage at start HAART, as was shown by the proportion of patients that had <50 CD4 cells/mm^3 (32%) and the proportion that had a plasma HIV-1 RNA level of more than 5 log^{10} copies/ml (57%). For the entire patient group, these percentages were 15% and 39%, respectively.

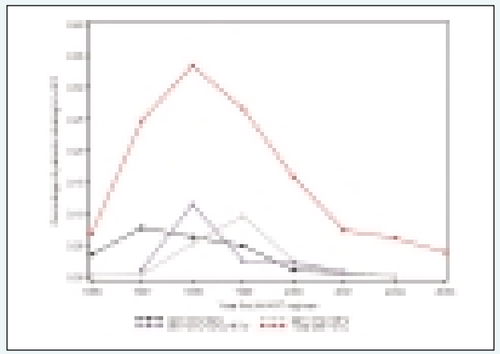

Figure 9.2: Initial highly active antiretroviral regimens based on a d4T+3TC backbone by year of initiation as a percentage of the total number of patients starting HAART yearly.

Time to reach <500 HIV-1 RNA copies/ml

Out of 2.970 patients eligible for analysis (as discussed in the Material and methods section), 2.080 (70%) reached viral load levels <500 copies/ml while still on their first HAART regimen. Overall, the median time to reach <500 copies/ml was 2.5 months but this varied between patients with different additions to the backbone. Figure 9.3 shows Kaplan-Meier estimates of time to <500 HIV-1 RNA copies/ml for selected additions to the nRTI backbone. The median time to reach <500 HIV-1 RNA copies/ml was shortest in patients starting on HAART regimens containing Nevirapine+Efavirenz (1.6 months), and was 2.1 months for Abacavir, 2.5 months for Lopinavir+RTV, and 2.8 for Nelfinavir.

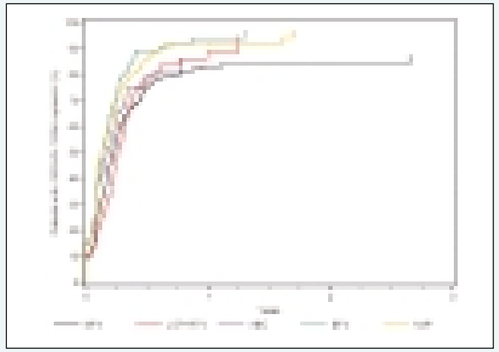

Figure 9.3 Time to <500 HIV-1 RNA copies/ml for currently frequently used additions to a NRTI backbone.

After adjustment for confounding factors, no significant difference for the time to <500 HIV-1 RNA copies/ml between Zidovudine+Lamivudine and Stavudine+Lamivudine was found (p=0.49, see Table 9.3). Time to <500 HIV-1 RNA copies/ml was significantly shorter in patients starting with an NNRTI-containing HAART regimen compared to a PI-containing HAART (HR 1.42; 95% CI: 1.29, 1.58; p<0.0001). Time to <500 HIV-1 RNA copies/ml was shortest in Efavirenz-treated patients.

Time to an increase of ≥100 CD4 cells/mm^3

In total 2.024 (68%) of the 2.957 patients that were analysed had an increase of ≥100 CD4 cells/mm^3 from baseline before the initial HAART regimen was changed or interrupted. Figure 9.4 shows Kaplan-Meier estimates of time to a ≥100 CD4 cell increase for selected additions to the backbone. The median time to reach an increase of ≥100 CD4 cells/mm^3 was 3.5 months for all patients; it was shortest for patients starting HAART containing Lopinavir+RTV (3.0 months). For patients starting on Nevirapine-containing HAART, median time to reach this increase was 4.1 months (Log-rank between Nevirapine and Lopinavir+RTV, p=0.01).

	Total (N=2970)	Number with less than 500 HIV-1 RNA copies/ml during initial HAART regimen (n=2080)	Hazard Ratio	95% CI	p-value
nRTI backbone					
d4T+3TC	573	425	1.04	0.93, 1.16	0.4931
AZT+3TC (reference)	2397	1655	1.00		
Addition to the backbone					
EFV	227	169	1.15	0.95, 1.38	0.1486
NVP (reference)	549	397	1.00		
IDV+RTV	226	164	0.99	0.82, 1.19	0.9041
SAQ+RTV	206	154	0.92	0.76, 1.12	0.4283
IDV	431	343	0.79	0.68, 0.92	0.0019
ABC	146	91	0.78	0.62, 0.98	0.0327
RTV	296	198	0.71	0.60, 0.85	0.0001
NFV	472	311	0.67	0.57, 0.78	0.0000
LOP+RTV	252	147	0.66	0.54, 0.79	0.0000
SAQ	165	106	0.45	0.37, 0.56	0.0000

Table 9.3: Comparison of virological success (time to <500 HIV-1 RNA copies/ml) between initial HAART combinations. Estimates are adjusted for gender, transmission risk group, age, HIV-RNA, CD4 and CDC-C event at start HAART.

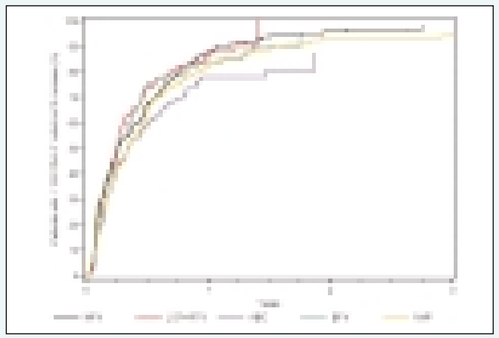

Figure 9.4 Time to ≥100 CD4 cells/mm^3 increase for currently frequently used additions to NRTI backbone.

	Total (N=2811)	Number with an 100 CD4+ T cell increase from baseline (n=2372)	Hazard Ratio	95% CI	p-value
nRTI backbone					
d4T+3TC	509	353	1.07	0.95, 1.20	0.2857
AZT+3TC (reference)	2302	1555	1.00		
Addition to the backbone					
LOP+RTV	280	184	1.34	1.11, 1.62	0.0021
RTV	352	230	1.25	1.05, 1.49	0.0131
SAQ	221	167	1.24	1.02, 1.51	0.0296
EFV	260	168	1.21	0.98, 1.51	0.0782
NFV	566	411	1.20	1.03, 1.40	0.0177
IDV+RTV	248	149	1.15	0.94, 1.42	0.1705
SAQ+RTV	231	138	1.14	0.92, 1.41	0.2433
NVP (reference)	630	434	1.00		
IDV	575	398	0.97	0.83, 1.13	0.6761
ABC	162	93	0.95	0.75, 1.21	0.6730

Table 9.4: Comparison of immunological success (time to 100 CD4+ T cells/mm^3 increase from baseline) between initial HAART regimen. Estimates are adjusted for gender, transmission risk group, age, HIV-RNA, CD4 and CDC-C event at start HAART.

In multivariate analyses, neither significant differences between patients starting on HAART including Zidovudine+Lamivudine or Stavudine+Lamivudine, nor between patients starting HAART with a PI or an NNRTI added to the nRTI backbone were found (p=0.06). Patients on HAART regimens containing RTV showed a shorter time to an increase of ≥100 CD4 cells/mm^3 compared to those on HAART regimens including another PI (HR 1.12; 95% CI: 1.01; 1.24 p=0.04). Time to an increase of ≥100 cells was shortest in patients on a HAART regimen containing Lopinavir+RTV (HR compared with Nevirapine

1.34; 95% CI: 1.11, 1.62; p=0.002). Time to an increase of ≥100 cells did not differ significantly between patients on a HAART regimen that included Efavirenz or Nevirapine, but was significantly shorter in RTV, Nelfinavir and Saquinavir when compared to Nevirapine (Table 9.4).

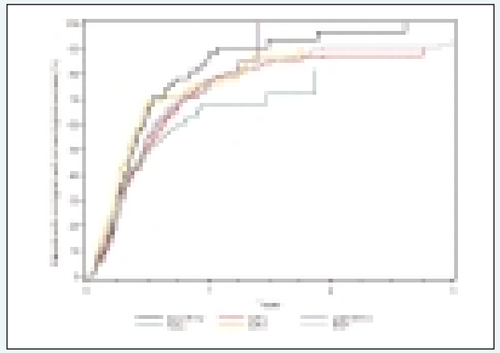

Figure 9.5 Time to ≥100 CD4 cells/mm³ increase and <500 HIV-1 RNA copies/ml for currently frequently used additions to a NRTI backbone.

Immunological and virological success

In 1.557 of the 2.673 patients analysed (58%), a combination of immunological and virological success (a CD4 cell increase of 100 cells/mm³ along with a decline in HIV-1 RNA plasma level of <500 copies/ml) was observed before change or interruption of the initial HAART regimen. In all patients median time to success was 5.5 months. Figure 9.5 shows Kaplan-Meier estimates of time to a ≥100 CD4 cell increase and a decrease to a HIV-1 RNA <500 copies/ml for selected additions to the backbone. The percentage of patients reaching this combined endpoint within one year was 78% for Efavirenz-starting patients and 72% for Abacavir-starting patients (Log-rank, p=0.03 between Efavirenz and Abacavir). In univariate or multivariate analyses, there were no significant differences between HAART regimens including Zidovudine+Lamivudine or Stavudine+Lamivudine (see Table 9.5). In multivariate analyses, time to immunological and virological success was longest in patients with single Saquinavir added to the backbone. Time to immunological and virological success was borderline significantly shorter in patients starting HAART containing Indinavir+RTV or Saquinavir+RTV compared with Nevirapine. Time to immunological and virological success was significantly shorter in patients using HAART including Efavirenz than patients using HAART including Saquinavir (HR 0.61; 95% CI: 0.46, 0.82; p=0.001) or Abacavir (HR 0.68; 95% CI: 0.49, 0.95; p=0.02).

	Total (N=2673)	Number with an 100 CD4+ T cell increase from baseline (n=1557)	Hazard Ratio	95% CI	p-value
nRTI backbone					
AZT+3TC (reference)	2178	1248	1.00		
d4T+3TC	495	309	1.11	0.97, 1.27	0.1274
Addition to the backbone					
IDV+RTV	196	114	1.25	1.00, 1.56	0.0479
SAQ+RTV	190	110	1.25	1.00, 1.58	0.0534
EFV	154	88	1.22	0.96, 1.55	0.1076
RTV	281	156	1.08	0.89, 1.32	0.4235
NVP (reference)	488	298	1.00		
LOP+RTV	243	112	0.98	0.79, 1.23	0.8869
NFV	416	248	0.98	0.82, 1.17	0.8239
IDV	412	280	0.96	0.81, 1.13	0.6329
ABC	140	61	0.83	0.63, 1.10	0.1999
SAQ	153	90	0.75	0.59, 0.95	0.0160

Table 9.5: Comparison of both immunological and virological success (time to 100 CD4+ T cells/mm³ increase from baseline and HIV-1 RNA <500 copies/ml) between initial HAART regimen. Estimates are adjusted for gender, transmission risk group, age, HIV-RNA, CD4 and CDC-C event at start HAART.

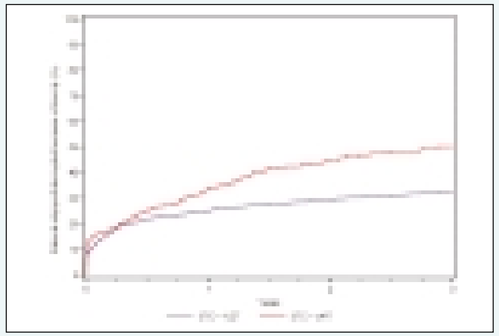

Figure 9.6 Time to change or interruption of first HAART regimen because of toxicity in 3525 patients by NRTI backbone.

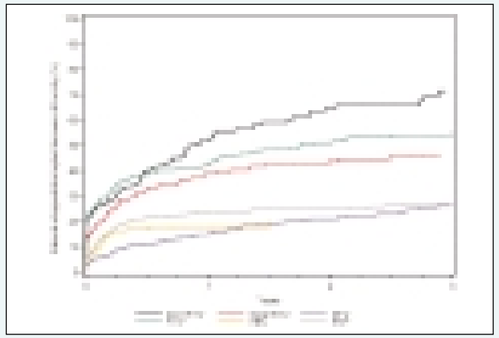

Figure 9.7 Time to change or interruption of first HAART regimen because of toxicity in 3525 patients by different additions to the NRTI backbone.

Toxicity of first-line HAART regimens

In total 1.029 (30%) of the 3.525 patients stopped or interrupted HAART treatment due to emerging toxicity; 26% did so within a year after the start of the initial regimen. Time to stop or interruption due to toxicity for patients starting HAART with an Zidovudine+Lamivudine backbone was longer than for patients starting with Stavudine+Lamivudine (univariate analyses: Log-rank, p<0.0001, see Figure 9.6). Within one year after starting HAART, 25% of Zidovudine+Lamivudine and 33% of Stavudine+Lamivudine patients had stopped or interrupted the regimen. Time to stop or interruption due to toxicity varied largely between patients with different additions to the backbone: only 15% of patients starting HAART including Nelfinavir stopped or interrupted because of toxicity within one year. In contrast, 53% of Indinavir+RTV patients stopped or interrupted within one year (Log-rank, p<0.0001 between Nelfinavir and Indinavir+RTV). Figure 9.7 shows the Kaplan-Meier estimates for selected additions to the backbone.

	Total (N=3525)	Number stopped/ interrupted because of toxicity (m=1028)	Hazard Ratio	95% CI	p-value
Age at start HAART	**(per 10 year increase)**		1.11	1.04, 1.18	0.0020
Gender					
Male	2723	801			
Female	802	227	1.73	1.42, 2.10	0.0000
Risk group					
Homosexual	1799	572	1.00		
IDU	145	44	0.97	0.71, 1.33	0.8493
Heterosexual	1160	305	0.78	0.65, 0.93	0.0055
Other	421	107	0.88	0.71, 1.10	0.2551
NRTI backbone					
AZT+3TC (reference)	2871	772	1.00		
d4T+3TC	654	256	1.33	1.15, 1.54	0.0002
Addition to the backbone					
NFV	566	101	0.72	0.56, 0.93	0.0107
SAQ	221	40	0.76	0.54, 1.08	0.1307
ABC	162	28	0.84	0.56, 1.26	0.4064
LOP+RTV	280	52	0.97	0.70, 1.34	0.8523
NVP (reference)	630	152	1.00		
EFV	260	57	1.11	0.81, 1.51	0.5196
IDV	575	201)	1.39	1.12, 1.73	0.0028
SAQ+RTV	231	91	1.79	1.37, 2.34	0.0000
RTV	352	171	2.43	1.94, 3.05	0.0000
IDV+RTV	248	135	3.22	2.53, 4.09	0.0000

Table 9.6: Comparison of time to stop or interruption of first HAART regimen because of toxicity between first line HAART combinations.

Demographic factors, such as older age at start HAART and female gender, along with homosexual - as opposed to heterosexual – HIV transmission significantly increased the risk of stopping or interrupting due to toxicity (Table 9.6). Moreover, in multivariate analyses, time to stop or interruption was significantly shorter in patients with a Stavudine+Lamivudine nRTI backbone than an Zidovudine+Lamivudine backbone. Time to stop or interruption was longest in patients starting HAART containing Nelfinavir. Patients starting HAART containing Saquinavir+RTV or Indinavir+RTV had a shorter time to change or interruption of therapy because of toxicity than patients starting with single Saquinavir or Indinavir (both: $p<0.0001$). Time to stop or interruption in patients starting HAART including Lopinavir+RTV, Saquinavir, Efavirenz or Abacavir was not significantly different from patients treated with HAART including Nevirapine.

The year of initiating the first HAART combination was a significant predictor for time to stop or interruption due to toxicity in the univariate analyses, but not in the multivariate analyses. CDC-C events, CD4 cell count and HIV-1 RNA viral load at start of HAART were also no significant predictors for time to stop or interruption.

Long-term efficacy of initial HAART

Data of 1.349 patients treated with their initial HAART regimen without interruption for at least 18 weeks were available for the long-term efficacy analysis of various HAART regimens. Because the CD4 cell number at week 18 was the strongest predictor for the further CD4 cell development after 18 weeks and because there were significant differences between different therapies, patients were stratified according to their CD4 cell count at 18 weeks (<200 cells/mm^3 (372 patients) and ≥200 cells/mm^3 (977 patients); see Table 9.7). After stratification, no significant changes in CD4 cell count at week 18 were found between the various HAART combinations.

		3TC + AZT N	3TC + d4T N	Total N
Total		1077	273	1349
CD4 at 18 weeks				
<200 cells/L	Total	278	95	372
	IDV	58	28	86
	IDV+RTV	26	4	30
	SAQ	14	1	15
	SAQ+RTV	13	11	24
	NFV	53	19	72
	LOP+RTV	40	13	53
	RTV	17	6	23
	ABC	8		8
	EFV	20	1	21
	NVP	29	11	40
≥200 cells/L	Total	799	178	977
	IDV	127	51	178
	IDV+RTV	43	16	59
	SAQ	82	2	84
	SAQ+RTV	30	21	51
	NFV	122	34	156
	LOP+RTV	60	5	65
	RTV	77	29	106
	ABC	46		46
	EFV	61	2	63
	NVP	151	18	169

Table 9.7: Distribution of patients on various HAART regimens according to CD4 cell counts at 18 weeks after start HAART.

Table 9.8 summarises the results of the linear mixed effects model. The estimates were adjusted for age, sex, transmission risk group, HIV-1 RNA at start of HAART and at 18 weeks, and CD4 cell count at start of HAART and at 18 weeks. The estimated slope in the first column is based on the observed margins of baseline characteristics in the two patient strata. Thus, the slope for Zidovudine+Lamivudine in the <200 CD4 cells/mm^3 at 18 weeks after start HAART can be interpreted as the mean increase in log (CD4) cells from baseline per log (week) if all analysed patients with <200 CD4 cells/mm^3 in the cohort had been treated with Zidovudine+Lamivudine. Apart from Abacavir and Lopinavir+RTV in patients with ≥200 CD4 cells/mm^3 at 18 weeks, the estimated slopes were all significantly higher than zero, the mean CD4 cell count for the two strata increased significantly over time.

In patients starting on an Zidovudine+Lamivudine or on a Stavudine+Lamivudine backbone with ≥200 CD4 cells/mm^3 at 18 weeks, no significant differences between slopes were found. When analysing the various additions to these nRTI backbones, we found that patients starting with HAART including Indinavir had a higher slope than those with HAART including Lopinavir+RTV, Abacavir or Nevirapine ($p=0.0023$, $p=0.0003$, and $p=0.0003$, respectively). Moreover, patients starting HAART including Nelfinavir had a significantly higher slope than patients starting HAART

	N	Slope estimate	Standard error of the slope estimate	P (estimate of slope = 0)	Difference in slope with the strongest increase	P(difference in slope = 0)
<200 CD4 cells/mm³ at 18 weeks						
NRTI combinations						
d4T+3TC (reference)	95	0.1966	0.0138	<0.0001	0	
AZT+3TC	278	0.1678	0.0084	<0.0001	-0.0289	0.07
Combinations added to the 2 NRTI backbone						
IDV+RTV (reference)	30	0.2032	0.0258	<0.0001	0	
IDV	86	0.1905	0.0132	<0.0001	-0.0127	0.99
NFV	72	0.1831	0.0149	<0.0001	-0.0200	0.99
RTV	23	0.1456	0.0244	<0.0001	-0.0451	0.91
LOP+RTV	53	0.1555	0.0204	<0.0001	-0.0478	0.83
NVP	40	0.1503	0.0211	<0.0001	-0.0529	0.76
EFV	21	0.1456	0.0229	<0.0001	-0.0576	0.99
SAQ+RTV	24	0.1397	0.0250	<0.0001	-0.0635	0.64
≥200 CD4 cells/mm³ at 18 weeks						
NRTI combinations						
d4T+3TC	178	0.0605	0.0065	<0.0001	0	
AZT+3TC	799	0.0493	0.0030	<0.0001	-0.0117	0.12
Combinations added to the 2 NRTI backbone						
IDV (reference)	127	0.0686	0.0057	<0.0001	0	
NFV	122	0.0655	0.0068	<0.0001	-0.0031	0.99
IDV+RTV	43	0.0612	0.0122	<0.0001	-0.0074	0.99
SAQ+RTV	82	0.0610	0.0115	<0.0001	-0.0076	0.99
RTV	77	0.0499	0.0074	<0.0001	-0.0187	0.61
SAQ	30	0.0379	0.0088	<0.0001	-0.0308	0.10
EFV	61	0.0372	0.0111	0.0009	-0.0313	0.28
NVP	151	0.0301	0.0061	<0.0001	-0.0385	0.0003
LOP+RTV	60	0.0123	0.0125	0.32	-0.0562	0.0023
ABC	46	0.0020	0.0134	0.88	-0.0666	0.0003

Table 9.8: Estimates of linear mixed effects analysis of slope of log(CD4) development between 18 and 96 weeks after start HAART. Slopes in 2nd colum are calculated for a reference 'average'patient based on the patient characteristics in the study population. Differences in slopes are relative to the slope of the drug with the highest slope.

including Lopinavir+RTV, Abacavir or Nevirapine (p=0.007, p=0.001, and p=0.004, respectively). Finally, patients starting HAART with Saquinavir+RTV showed a higher increase in CD4 cells than patients starting HAART with Abacavir (p=0.03). No significant differences were found in the patient group with <200 CD4 cells/mm^3, neither between the nRTI backbone, nor between additions to the backbone.

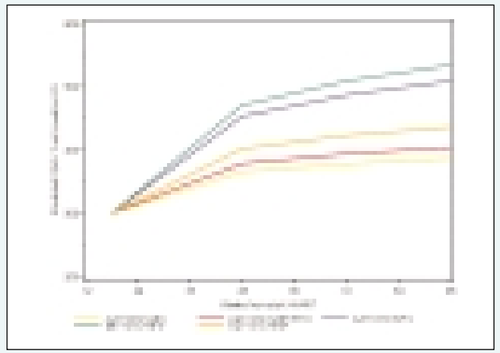

Figure 9.8 Predicted CD4+ T cell count/mm^3 after 48, 72 and 96 weeks for a male, 37 year old, homosexual patient, and CD4+ T cell count between 200 and 350 at start HAART and 300 after 18 weeks for different currently frequently used HAART combinations.

Figure 9.8 shows the predicted CD4 cell count development between 18 and 96 weeks for a patient infected through homosexual contact, aged 37 years at start HAART, with a plasma viral load >5 log^{10} copies/ml at start HAART and undetectable at 18 weeks, a CD4 cell count 200-350 cells/mm^3 at start HAART and 300 cells/mm^3 at 18 weeks, who started HAART with the specific combination shown in the graph. The initial increase is higher than the later increase. The differences between the top two lines and the bottom three (Zidovudine+Lamivudine+Saquinavir, Zidovudine+Lamivudine+Lopinavir+RTV and Zidovudine+Lamivudine+Abacavir) were significant.

Distribution of second-line HAART regimens

Of the 4.261 patients who started HAART, 1.122 (26%) were still on their initial regimen at closure of the database. As will be discussed in Chapter 10, after one year of initial HAART therapy, 47% of the patients had changed or interrupted their regimen, although this depended on demographic and clinical characteristics. Three hundred and thirty-five out of the 3.139 patients who had stopped did not go on to use a second HAART regimen: 54 had died, the remaining 281 either went on to use mono- or dual therapy or did not take any further medication during follow-up. The remaining 2.804 patients continued treatment using a second-line HAART regimen (see Table 9.9).

	AZT + 3TC	d4T + 3TC	Other	Total
	N	N	N	N
Total	1542	681	581	2804
IDV	82	78	33	193
IDV+RTV	147	74	39	260
SAQ	31	27	12	70
SAQ+RTV	125	69	61	255
NFV	172	98	35	305
LOP+RTV	93	30	69	192
RTV	27	37	13	77
ABC	198			198
EFV	106	46	79	231
NVP	464	193	149	806

Table 9.9: Most frequently used second line HAART combinations.

Overall, in 34% of the 1.822 patients who started HAART using an Zidovudine +Lamivudine backbone the backbone was changed. This change was higher in patients with an Abacavir (62%), Efavirenz (49%) or Nevirapine (66%) addition to the backbone. Two hundred and seventy-three of the 591 Stavudine+Lamivudine-starting patients changed to Zidovudine+Lamivudine or to another backbone (Table 9.10). Twenty-six percent of patients using first-line HAART with Indinavir alone and 37% of patients using first-line HAART with Saquinavir alone had their regimen boosted with RTV in their second regimen. Changing the backbone addition to Nevirapine was the most frequently performed change: 666 patients out of 2.554 patients not on Nevirapine during the first regimen switched to Nevirapine in their second regimen (26%). However, this percentage was lower in patients starting HAART including Efavirenz or Abacavir. Other changes were very diverse and constituted relatively small numbers of patients.

	2nd regimen						Total
	3TC + AZT		3TC + d4T		Other		
	N	%	N	%	N	%	N
Total	1542	55.0	681	24.3	581	20.7	2804
1st regimen							
AZT + 3TC	1205	66.1	305	16.7	312	17.1	1822
d4T + 3TC	178	30.1	318	53.8	95	16.1	591
Other	159	40.7	58	14.8	174	44.5	391

Table 9.10: Change of NRTI backbone between first and second regimen.

Discussion

In line with previous studies [32], we found that PI-containing starting regimens have a better immunological outcome than NNRTI-starting regimens, whilst starting regimens containing an NNRTI perform better than regimens containing a PI in terms of virological outcome. When we combined immunological and virological outcome measures there were no significant differences between the two nRTI backbones Zidovudine+Lamivudine and Stavudine+Lamivudine. Of all additions to the backbone, Indinavir+RTV, Saquinavir+RTV, and Efavirenz performed best, although not all differences with other backbone additions were significant. However, short-term efficacy does not necessarily equal therapy success; patients need to be able to sustain therapy with the best long-term immunological and virological benefit possible.

First HAART regimens were more frequently stopped or interrupted because of toxicity in patients starting a regimen containing RTV compared with other PI- or NNRTI-containing regimens and in patients starting with a Stavudine+Lamivudine backbone as compared with patients starting with a Zidovudine+Lamivudine backbone. Compared to Abacavir, Lopinavir+RTV or Nevirapine, patients using Indinavir- and Nelfinavir-containing initial HAART regimens showed a steeper increase in long-term CD4 development between 18 and 96 weeks than patients starting with Abacavir, Lopinavir+RTV or Nevirapine.

Other studies have reported a better longer-term immunological outcome in patients starting with a PI compared with an NNRTI [33,34]. The suitability of Trizivir (Zidovudine+Lamivudine+Abacavir) as first-line HAART of choice has recently come under question because of its poorer virological outcome in the ACTG 5095 trial [35,36,37]. This is in line with our findings of poorer short- and long-term efficacy of first-line HAART including Abacavir, although the toxicity profile of this HAART combination is favourable compared to other medications.

Good short- and long-term immunological efficacy for Lopinavir+RTV has been reported in other studies [38,39]. We also found good short-term immunological results in patients starting Lopinavir+RTV (time to a 100 CD4 cells/mm^3 increase from baseline was shortest in Lopinavir+RTV-starting patients), but surprisingly, the slope of long-term CD4 cell development was low in these patients. Although we have adjusted for baseline differences, this might be due to the more advanced disease stage of patients starting HAART including Lopinavir+RTV in this cohort.

In conclusion, no single HAART combination performed better than any other on both tolerability and virological or immunological outcomes. Zidovudine+Lamivudine is the preferred nRTI backbone because of a better toxicity profile, yet its virological and immunological outcomes were not significantly different from Stavudine+Lamivudine. Judging from the presented results, Nelfinavir could be a good candidate to add to the Zidovudine+Lamivudine backbone. Time to change or interruption because of toxicity was favourable as compared to the other additions and Nelfinavir has a good long-term immunological profile. However, additional factors such as convenience of the regimen, drug-drug interactions, and potential salvageability should also be taken into account when deciding on initial HAART regimens [40].

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HAART outcome patterns

Improved treatment effect when started after 1999

Introduction

In clinical populations of HIV-1-infected individuals, a substantial decrease in virus production and an increase in CD4 cell numbers can be attributed to the introduction of HAART [1-9]. In individual patients, a very rapid decline in viral replication is observed after initiation of HAART [10], with the plasma viral load declining to undetectable levels in approximately four months.

Low viral replication and relatively high CD4 cell counts are directly related to clinical outcome [11-13]. The achievement and maintenance of prolonged suppression of viral replication may be directly related to the long-term efficacy of HAART [4]. However, in a substantial proportion of patients, viral replication, as reflected in plasma HIV-1 RNA levels, may rise again [1,5,14,15], as was shown in previous reports on the monitoring of HIV [8,9]. This rise in viral load may be attributable to serious adverse events and toxicity, changing long-term adherence, and development of resistance. Rates of virological failure, i.e. plasma HIV-1 RNA levels becoming detectable again after a period in which no HIV-1 RNA could be detected, have been reported to lie between 20 and 40% [16,17]. Predictive of virological success or failure is HIV-1 RNA plasma load at start of therapy. In addition, CD4 cell count at start of HAART, as well as the count reached after the initial phase of HAART, is predictive of clinical outcome [18,19].

Changes in HAART regimens and interruptions of HAART also have effect on clinical outcome [9,15,21]. It has been shown that patients who switched therapy had a higher chance of virological failure and a less favourable clinical outcome [9,15]. Additionally, in the 2002 HMF report, it was shown that patients who had stopped their initial HAART regimen had a high chance of subsequently switching from their second and third regimens [9]. Moreover, although short-term interruptions might not have an adverse effect [20], especially when CD4 cell counts are high and pVL are low or undetectable at start of the interruption, the long-term effect of discontinuous HAART is smaller compared to continuous HAART [19,21].

Despite its less favourable outcome, interruption of HAART treatment is common, as is shown by the constant proportion of 10% of the population in the ATHENA-HMF observational cohort that is off therapy at any given time [9]. Main reasons for interruptions are virological failure, adverse events, and toxicity, as well as interruption at the patient's request [9,20]. Similarly, changes in the composition of HAART regimens may also follow from the same factors, in particular failure, adverse events and toxicity.

Through the monitoring of HIV-1-infected individuals, we were able to study the determinants for virological and immunological success of the HAART treatment. Duration of therapy success and subsequent therapy failure were analysed, as were predictors of success and failure. In this chapter, we focus on patients who started HAART without previous antiretroviral treatment.

Occurrence of therapy interruptions and the subsequent effects on the outcome of therapy were studied in the same group of patients. In particular, we wanted to study the effect of the immunological and virological condition of the patient at initiation and at interruption of therapy on the virological and immunological success after reinitiation of HAART. Finally, the frequency of changes in HAART regimens and predictors of change were assessed.

Methods

Study population

Data of 4.261 patients from the ATHENA-HMF observational clinical cohort were analysed. All were over twelve years of age at diagnosis, initiated HAART prior to 31 July 2003, were naïve at start of HAART and had a follow-up of 70 days or longer after start of HAART. Characteristics of the cohort have been described in chapter 5.

Immunological and virological parameters

HIV-1 RNA

Determination of the HIV-1 RNA concentration in plasma was measured in each of the centres by using one of the commercially available quantitative tests. The quantification limit of these assays changed since their introduction in the mid-nineties. For the present report, a set point of 500 HIV-1 RNA copies/ml was used.

CD4 cell count

Absolute numbers of CD4 cells were determined by using immune-fluorescence techniques and flow cytometry. Unless otherwise stated, viral load measurements (pVL) are reported in $\log^{10}$ copies/ml and CD4 cell counts in cells/mm^3.

Definitions

Therapy success and failure

An important surrogate endpoint in monitoring antiretroviral therapy is the level of suppression of the virus production as measured by the effect on the concentration of HIV-1 RNA in plasma. In addition, the immunological status of the patient and thereby the effect of therapy on immunological parameters such as the CD4 cell count is important for the course of the (clinical) infection.

In the present analysis, therapy success was defined by the following parameters:

- Reaching a pVL below 500 copies/ml, which was determined by taking the first moment at which the pVL had been <500 copies/ml for a minimum of 91 days;
- An increase of 100 cells/mm^3 from the CD4 cell count at start of HAART;
- Reaching a CD4 cell count above 350 cells/mm^3.

Therapy failure was defined as:

- Reaching a pVL ≥500 copies/ml after having achieved virological success
- Reaching a CD4 cell count below 350 cells/mm^3 after having achieved immunological success.

Therapy interruptions

An interruption was defined as a period of for more than seven days during which the patient, for whatever reason, did not take any antiretroviral drugs. Although a patient might have interrupted therapy more than once, only the first interruption was taken into consideration.

Change of HAART

Therapy switches were studied by analysing the time to the first, second and third change of regimen. These changes were scored regardless of the actual reason for switching, e.g. virological failure, toxicity or patient's request. Dose changes and therapy interruptions were not counted as separate regimens. When a patient reinitiated HAART after a therapy interruption of less than seven days, it was considered a switch only if the new regimen was different from the patient's regimen before therapy interruption.

Statistical analysis

Characteristics of the total population at start of therapy are presented. For continuous variables, the median and interquartile range (IQR) or mean and standard deviation were calculated. For categorical variables, the percentage of the total was calculated.

Kaplan-Meier survival curves

Kaplan-Meier survival curves were plotted for time to first, second and third therapy change, stratified by gender. In addition, Kaplan-Meier curves for the various aspects of therapy success and therapy failure were plotted, stratified by gender and CD4 cell count at start of HAART. Finally, for all patients who interrupted therapy

for more than seven days, Kaplan-Meier survival curves were plotted for time to CD4 cell count <350 cells/mm^3, time to reinitiation of HAART, time to CD4 cell count >500 cells/mm^3 after reinitiation of HAART, and pVL <500 copies/ml plasma after reinitiation. Results were stratified according to gender, CD4 cell count above or below 500 cells/mm^3 at the start of the interruption and CD4 cell count at reinitiation of HAART.

Cox proportional hazards models

Predictors for the various endpoints were assessed using Cox proportional hazards models. Breslow's method for the handling of tied values was used. Patients were censored at the date of last contact or follow-up, date of death, 31 July 2003, or reinitiation of HAART (for the analysis of time to CD4 cell count <350 cells/mm^3), whichever came first.

Variables considered as predictors in all analyses were: gender, risk group, region of origin, age at start of HAART, year of start of HAART, CD4 cell count at start of HAART, pVL at start of HAART, or CDC-C or B (Center of Disease Control classification) event in the year before start of HAART. In addition, in all the analyses concerning the effects of interruptions, the CD4 cell count at start of the interruption, pVL at start of the interruption, and duration of treatment prior to the interruption were evaluated.

Besides these factors, the duration of the interruption, CD4 cell count at reinitiation of HAART, and pVL at reinitiation were taken into account when the endpoints after reinitiation of HAART were studied. Moreover, in the analysis of time to regimen change, the duration of the previous regimen was considered. Finally, in the analysis of therapy failure, the time to achieving therapy success was taken into account. All analyses were performed using the SAS software for Windows, version 8.02 (SAS Institute Inc, USA).

Results

General characteristics

Characteristics of the 4.261 patients included in the study population are presented in Table 10.1. The majority of the patients was male (78.2%), of Dutch origin (58.8), and had become infected via sexual contact (83.8%). The median CD4 cell count at start of HAART was 200 cells/mm^3 and the median pVL 5.0 log copies/ml. Of all patients, 1.724 (40.5%) initiated HAART before 1999, 1.764 in the period 1999-2001, and 773 after 2001. Patients were followed for a median of 63.2 months (40.7-75.2) after start of HAART, during which time the majority (67.7%) switched to another regimen at least once.

Therapy success and therapy failure

Figures 10.1 to 10.3 depict the time to achieving therapy success, characterised by achieving a pVL below 500 copies/ml, an increase of ≥100 cells/mm^3, or a CD4 cell count above 350 cells/mm^3.

First virological success

Almost the entire population reached plasma HIV-1 RNA levels below 500 copies/ml after starting therapy (Figure 10.1). After three months 47.6% of patients had a pVL <500 copies/ml; after six months this figure was 67.5%. There was a difference in time to virological success by gender (Log-rank, p=0.0002). The median time to success was 3.2 months (IQR: 1.6-8.6) among men and 3.6 months (IQR: 1.5-15.2) among women.

		Total (n=4261)		Never interrupted therapy (n=3105)		Ever interrupted therapy (n=1156)	
		N	%	N	%	N	%
Number of therapy	0	3105	72.9	-			
interruptions >7 days during	1	797	18.7				
follow-up	≥2	359	8.4				
Gender	Male	3331	78.2	2516	81.0	815	70.5
	Female	930	21.8	589	19.0	341	29.5
Region origin	Netherlands	2493	58.5	1852	59.7	641	55.5
	Other	1768	41.5	1253	40.4	515	44.6
Risk group	MSM	2226	52.2	1693	54.5	533	46.1
	IDU	184	4.3	101	3.3	83	7.2
	Heterosexual	1345	31.6	958	30.9	387	33.5
	Unknown/Other	506	11.9	353	11.4	153	13.2
Year of diagnosis	<90	252	5.9	165	5.3	87	7.5
	90-99	2543	59.7	1756	56.6	787	68.1
	00-03	1466	34.4	1184	38.1	282	24.4
Year of start HAART	≤1996	403	9.5	247	8.0	156	13.5
	1997	756	17.7	485	15.6	271	23.4
	1998	565	13.3	389	12.5	176	15.2
	1999	581	13.6	424	13.7	157	13.6
	2000	548	12.9	392	12.6	156	13.49
	2001	635	14.9	488	15.7	147	12.7
	2002	596	14.0	513	16.5	83	7.2
	2003	177	4.2	167	5.4	10	0.9
		N measured	Median (IQR)	N measured	Median (IQR)	N measured	Median (IQR)
Age at start HAART (years)		4260	33 (31-44)	37 (31-44)	35 (30-43)		
CD4 at start HAART (cells/mm^3)		3397	200 (80-333)	2478	190 (70-310)	919	238 (90-400)
pVL at start HAART (log copies/ml)							
- Undetectable		67	49	18			
- Detectable		3415	5.0 (4.5-5.4)	2520	5.0 (4.5-5.4)	895	4.8 (4.3-5.3)
Follow-up after start HAART(months)		4261	63.2 (40.7-75.2)		37.5 (17.8-60.6)	49.1 (28.7-67.8)	
Total number of regimens	1	1376	32.3	1193	38.4	183	15.8
during follow-up	2	1100	25.8	846	27.3	254	22.0
	3	728	17.1	499	16.1	229	19.8
	4	459	10.8	279	9.0	180	15.6
	>4	598	14.0	288	9.3	310	26.8

IQR=interquartile range, pVL=plasma viral load, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.1.: Characteristics of patients who initiated HAART without prior ARV treatment between 1993-2003 and had a follow-up of 70 days or more after initiation.

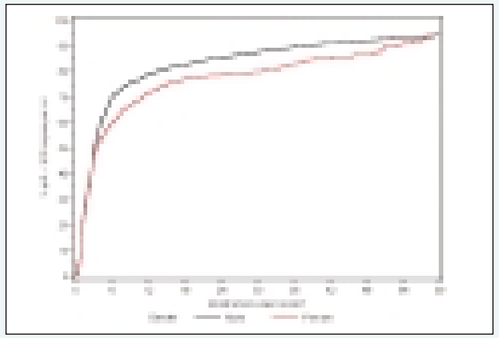


Figure 10.1: Kaplan-Meier plot of time to first virological success (pVL <500 copies/ml), stratified by gender.

Determinant		HR	95% CI
Risk group	Heterosexual	1.0	-
	MSM	1.1	1.0-1.2
	IDU	0.92	0.77-2.1
	Other	0.87	0.76-0.98
Region of origin	Netherlands	1.2	1.1-1.3
Age at start HAART	≤25	0.82	0.70-0.95
	26-40	0.88	-
	>40	1.0	-
Year of start HAART	≤1996	0.84	0.74-0.96
	1997-1998	1.2	1.1-1.4
	1999-2000	1.2	1.1-1.4
	>2000	1.0	-
pVL at start HAART (log copies/ml)	Missing	0.62	0.56-0.69
	≤4	1.2	1.1-1.4
	4-5	1.3	1.2-1.5
	>5	1.0	-
CDC-B/C event within one year prior to start HAART		1.2	1.1-1.3

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.2: Predictors of time to first virological success (pVL <500 copies/ml).

In the multivariate analysis, the difference found between men and women could be explained by several other factors. Table 10.2 shows that patients who were of non-Dutch origin had a lower hazard than persons of Dutch origin to achieve a pVL <500 copies/ml (HR=1.2, 1.1-1.3). Patients who were older than 40 at start of HAART and patients who had a low pVL at start of HAART experienced virological success more quickly than those who were younger and had a higher pVL.

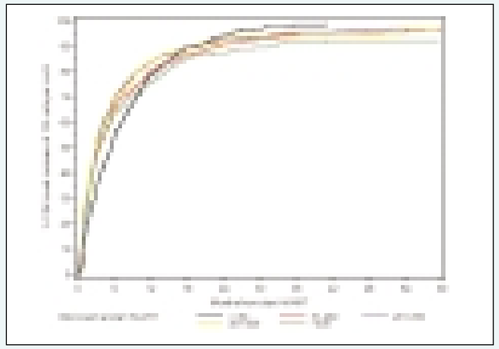


Figure 10.2: Kaplan-Meier plot of time to first immunological success (increase in CD4 cell count of 100 cells/mm^3), stratified by CD4 cell count at start of HAART.

First immunological success

Increase of 100 cells/mm^3

Almost the entire population experienced an increase of 100 cells/mm^3 after initiating HAART (Figure 10.2). After 12 months, 78.3% of patients with counts below <50 cells/mm^3, 80.0% of patients with counts between 50-200 cells/mm^3, and 83.7% of patients with counts above 200 cells/mm^3 had achieved an increase of more than 100 cells/mm^3. The median time to success for the entire population was 4.0 months (IQR: 1.4-10.8).The main predictors of a longer time to an increase of 100 cells/mm^3 were: male gender (HR=0.87, 0.79-0.96), non-Dutch origin, transmission via intravenous drug use, over 40 years of age at start HAART, early year of start HAART (≤1996 vs >2000: HR=0.81, 0.71-0.91) and a low pVL at start HAART (≤4 log vs. >5 log copies/ml: HR=0.73, 0.65-0.82; Table 10.3).

Determinant		HR	95% CI
Gender	male	0.87	0.79-0.96
Risk group	Heterosexual	1.0	-
	MSM	1.2	1.1-1.3
	IDU	0.85	0.72-1.0
	Other	0.99	0.89-1.1
Region of origin	Netherlands	1.2	1.1-1.3
Age at start HAART	≤25	1.2	1.1-1.4
	26-40	1.1	0.96-1.3
	>40	1.0	-
Year of start HAART	≤1996	0.81	0.71-0.91
	1997-1998	0.96	0.88-1.0
	1999-2000	0.92	0.84-1.0
	>2000	1.0	-
CD4 cell count at start	Missing	0.84	0.75-0.93
HAART (cells/mm^3)	≤50	0.90	0.80-1.0
	51-200	1.0	0.93-1.1
	201-350	1.1	1.0-1.2
	>350	1.0	-
pVL at start HAART	Missing	0.81	0.73-0.90
(log copies/ml)	≤4	0.73	0.65-0.82
	4-5	0.91	0.85-0.98
	>5	1.0	-

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.3: Predictors of time to first immunological success (increase in CD4 cell count of 100 cells/mm^3)

Increase to a CD4 cell count >350 cells/mm^3

In total, 3.245 patients achieved a CD4 cell count >350 cells/mm^3 during follow-up. The median time to immunological success after start of HAART was 8.6 months (1.7-28.5) for the entire population. A strong effect on the CD4 cell count was observed at start of HAART. Of patients with counts <50 cells/mm^3 at start of HAART 12.1% reached a CD4 cell count >350 cells/mm^3 within 12 months of initiating HAART compared to 38.9% of patients with counts between 50-200 cells/mm^3 and 83.9% of patients with counts between 200-350 cells/mm^3 (Figure 10.3).

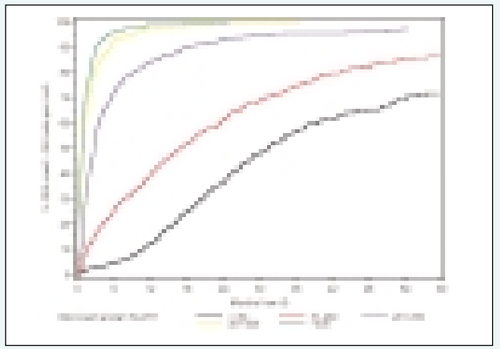


Figure 10.3: Kaplan-Meier plot of time to first immunological success (CD4 cell count >350 cells/mm^3), stratified by CD4 cell count at start of HAART

Determinant		HR	95% CI
Region of origin	Netherlands	1.2	1.1-1.3
Age at start HAART	≤25	1.6	1.3-1.8
	26-40	1.3	1.1-1.5
	>40	1.0	-
CD4 cell count at start HAART	Missing	1.2	0.11-0.14
(cells/mm^3)	≤50	0.06	0.05-0.07
	51-200	0.12	0.11-0.13
	201-350	0.37	0.34-0.41
	>350	1.0	-
pVL at start HAART	Missing	0.77	0.69-0.86
(log copies/ml)	≤4	0.91	0.81-1.0
	4-5	0.98	0.90-1.1
	>5	1.0	-
	0.69-0.86		

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load

Table 10.4: Predictors of time to first therapy success (CD4 cell count >350 cells/mm^3)

In concordance with other parameters of therapy success, patients who were of Dutch origin achieved immunological success as defined by a CD4 cell count >350 cells/mm^3 more quickly than those of non-Dutch origin (HR=1.2, 1.1-1.3; Table 10.4). Patients who were younger at start of HAART reached a CD4 cell count >350 cells/mm^3 within a shorter period than older patients. In addition, pVL at start of HAART and CD4 cell count at start of HAART (<50 cells/mm^3 vs >350 cells/mm^3 at start of HAART: HR=0.06, 0.05-0.07) were predictive of time to success.

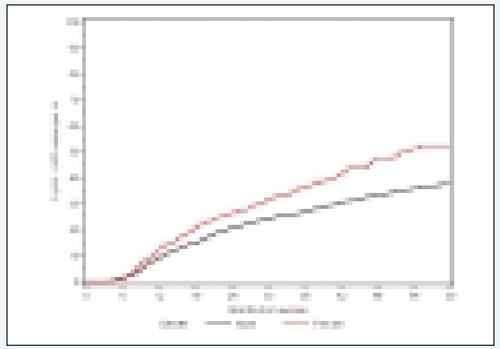


Figure 10.4: Kaplan-Meier plot of time to first virological failure (pVL >500 copies/ml), stratified by gender

First virological failure

Within six months of achieving a pVL <500 copies/ml, 9.6% of those who had achieved therapy success had a pVL above 500 copies/ml. After 66 months, the percentage increased to 41.4%. Women failed therapy more quickly than men did (Figure 10.4): 26.1% of women versus 20.3% of men failed within 24 months of achieving virological success. Of all patients who virologically failed therapy, 35.8% failed on their first regimen and 9.6% were taking no drugs at the time of failure.

Table 10.5 shows the predictors of time to first virological failure. Besides gender (male vs. female: HR=0.72, 0.62-0.84) and region of origin, year of start HAART was predictive of the time during which a patient maintained a low pVL (<copies/ml). The hazard of failure among patients who initiated HAART ≤1996 and those who initiated in 1997-1998 was 2.0 and 1.8 times higher, respectively, than the hazard of failure among patients who initiated after 2000. Moreover, the hazard of failure was higher among patients who initiated HAART at low CD4 cell counts and patients who had achieved a pVL <500 very quickly after initiating HAART.

Determinant		HR	95% CI
Gender	male	0.72	0.62-0.84
Region of origin	Netherlands	0.72	0.62-0.89
Year of start HAART	≤1996	2.0	1.5-2.6
	1997-1998	1.8	1.4-2.2
	1999-2000	1.3	1.0-1.6
	>2000	1.0	-
	1.5-2.6		
CD4 cell count at start	Missing	0.82	0.67-0.99
HAART (cells/mm^3)	≤50	0.70	0.56-0.86
	51-200	0.85	0.71-1.0
	201-350	0.86	0.72-1.0
	>350	1.0	-
Time to pVL <500 copies/ml	0-6 months	1.3	1.1-1.5
after start HAART	7-18 months	1.6	1.3-2.0
	>18 months	1.0	-

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load

Table 10.5: Predictors of time to first virological failure (pVL >500 copies/ml)

Immunological failure

After achieving immunological success, as defined by a CD4 cell count above 350 cells/mm^3, CD4 cell counts fell below 350 again among 50% of patients within 35.3 months of follow-up. After 66 months, this figure had increased to 58.0%. Figure 10.5 clearly shows the

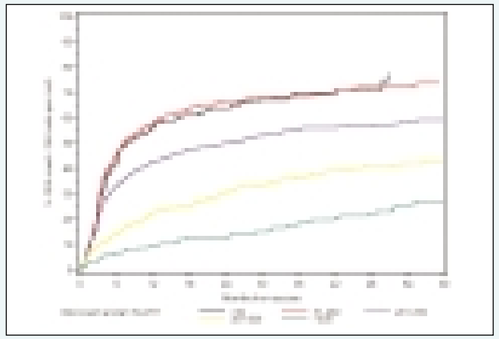


Figure 10.5: Kaplan-Meier plot of time to first immunological failure (CD4 cell count <350 cells/mm^3, stratified by CD4 cell count at start of HAART.

Determinant		HR	95% CI
Risk group	Heterosexual	1.0	-
	MSM	1.2	1.0-1.3
	IDU	1.5	1.2-2.0
	Other	1.0	0.86-1.3
Year of start HAART	≤1996	1.3	1.1-1.6
	1997-1998	1.2	1.0-1.4
	1999-2000	1.1	0.89-1.2
	>2000	1.0	-
CD4 cell count at start	Missing	1.5	1.2-1.8
HAART (cells/mm^3)	≤50	3.6	2.9-4.4
	51-200	3.6	3.0-4.2
	201-350	2.3	2.0-2.7
	>350	1.0	-
pVL at start HAART	Missing	1.3	1.1-1.5
(log copies/ml)	≤4	1.2	1.0-1.5
	4-5	1.1	0.97-1.2
	>5	1.0	-

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.6: Predictors of time to first immunological failure (CD4 cell count <350 cells/mm^3).

difference in rate of immunological failure according to the immunological condition of the patient at start of HAART. Patients with lower CD4 cell counts at start of HAART failed more quickly than those with higher CD4 cell counts: after 12 month the percentages were 56.4%, 57.4%, 42.5%, 22.3%, 9.1% for patients with CD4 cell counts <50, 51-200, 201-350, 351-500 and >500 cells/mm^3 at start of HAART, respectively.

In the multivariate analysis, other predictors of time to failure, besides CD4 cell count at start of HAART, were an early year of start HAART (≤1996 vs >2000: HR=1.3, 1.1-1.6) and transmission via intravenous drug use (IDU vs heterosexual: HR=1.5, 1.2-2.0; Table 10.6). Furthermore, patients with a pVL below 4 log copies/ml at start of HAART had a higher hazard of immunological failure than patients with a higher pVL.

Determinant		HR	95% CI
Risk group	Heterosexual	1.0	-
	MSM	0.96	0.80-1.1
	IDU	0.67	0.46-0.97
	Other	0.86	0.64-1.1
Age at start HAART	≤25	0.65	0.46-0.93
	26-40	0.85	0.59-1.2
	>40	1.0	-
Year of start HAART	≤1996	1.9	1.2-2.9
	1997-1998	1.7	1.1-2.5
	1999-2000	1.5	0.98-2.3
	>2000	1.0	-
pVL at start HAART	Missing	0.77	0.61-0.96
(log copies/ml)	≤4	0.55	0.42-0.73
	4-5	0.86	0.72-1.0
	>5	1.0	-

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.7: Predictors of time to second virological success (pVL <500 copies/ml)

Second virological success

Of the 1.044 patients who experienced virological failure during follow-up, 50.4% achieved a viral load below 500 copies/ml again within six months. The median time to virological success after first failure was 5.9 months (IQR: 2.8-28.9). Predictors of second virological success were similar to predictors of first virological success (Table 10.7). Patients who were classified as intravenous drug users took longer to achieve a pVL <500 copies/ml a second time than other patients. In addition, patients who were younger than 25 years of age at start of HAART had a longer time to second success than older patients (≤25 years vs >40 years: HR=0.65, 0.46-0.93). Contrary to the time to first therapy success, patients who started HAART early and patients who had a pVL above 5 log copies/ml achieved virological success more quickly than other patients did.

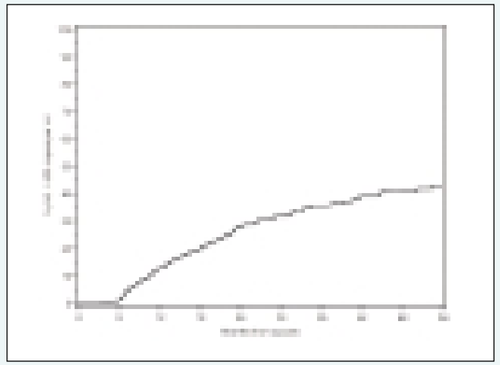


Figure 10.6: Kaplan-Meier plot of time to second virological failure (pVL >500 copies/ml)

Second virological failure

Within 22.4 months one quarter of the patients failed a second time; this number increased to 50% after 64.3 months of follow-up (Figure 10.6). The hazard ratio (95% CI) of patients with a CD4 cell count ≤50, 51-200, 201-350 or a missing count as compared to persons with a CD4 cell count above 350 cells/mm^3 at start of HAART, was 0.62 (0.36-1.1), 0.82 (0.55-1.2), 0.63 (0.42-0.95) and 1.0 (0.65-1.6), respectively. Of all patients who failed therapy, 175 (26.3%) had continued the same regimen after their first therapy failure, and 66 of them (6.6%) failed a second time on this first regimen. Of the remaining patients, 284 (37.3%) failed on the regimen they had initiated after the first failure, and 36.4% had changed regimens more than once after the first failure. At the time of the second failure, 9.2% of patients had interrupted HAART.

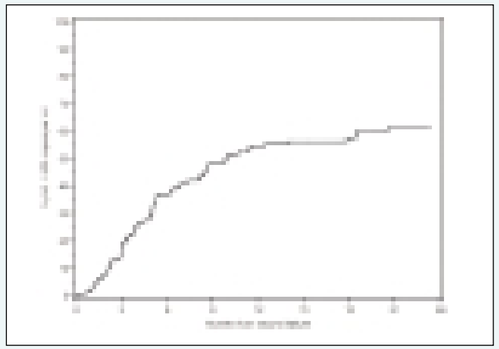


Figure 10.7: Kaplan-Meier plot of time to third virological success (pVL <500 copies/ml)

Third virological success

Only a small number of patients (n=187) remain in follow-up and achieve therapy success a third time after having failed therapy twice (Figure 10.7). The median time to third therapy success is 10.0 months (IQR: 3.9-42.0). No predictors of success after the second virological failure were identified.

Therapy interruptions

Of the 4.261 naïve patients who initiated HAART, 1.156 interrupted therapy at least once during follow-up. As compared to those who never interrupted therapy, patients who interrupted therapy started HAART earlier, were more often female, were younger, had a lower pVL and had a higher CD4 cell count at start of HAART (Table 10.1). Of those who ever interrupted therapy, 70.5% were male and 79.4% had been sexually infected. The median number of regimens among patients who interrupted during the median of 49.1 months of follow-up was three (IQR: 1-5). Of all patients who interrupted therapy, 58.3% did so while on their first regimen, 20.4% on their second and 21.3% had already changed regimens more than twice. The median number of regimens prior to interruption was one (IQR: 1-2). Patients interrupted therapy after a median time of 9.1 months on HAART (IQR: 2.1-25.1). Of the 1.156 patients who interrupted therapy, 311 (26.9%) had a CD4 cell count >500 cells/mm^3 at interruption. The median CD4 cell count was 410 cells/mm^3 (IQR: 220-620). In addition, 522 (45.2%) patients had a pVL <500 copies/ml.

		HR	95% CI
Risk group	Heterosexual	1.0	-
	MSM	1.3	1.1-1.7
	IDU	1.2	0.81-1.6
	Other	1.2	0.89-1.6
Age at start HAART (years)	≤25	0.59	0.38-0.90
	26-40	0.62	0.39-0.97
	>40	1.0	-
CD4 cell count at start HAART (cells/mm^3)	Missing	1.3	0.92-1.8
	≤50	3.5	2.4-5.1
	51-200	3.5	2.6-4.9
	201-350	2.7	1.9-3.6
	>350	1.0	-
CD4 cell count at interruption >500 cells/mm^3		0.47	0.37-0.60

HR=hazard ratio, CI=confidence interval, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.8: Determinants of time to a CD4 cell count <350 cells/mm^3 during interruption of HAART.

After the interruption

Within six months after interrupting, 38.9% had reached a CD4 cell count <350 cells/mm^3. The median time to a CD4 cell count <350 cells/mm^3 was 13.3 months (IQR: 2.5-50.3). Patients with a low CD4 cell count and a high pVL at interruption had a higher hazard of a decrease in their CD4 cell counts to <350 cells/mm^3 than patients who were in a better virological and immunological condition at interruption (Table 10.8). Other factors that were predictive of a decrease in CD4 cell counts were risk group, age, a low CD4 cell count at start of HAART and a low CD4 cell count at start of the interruption.

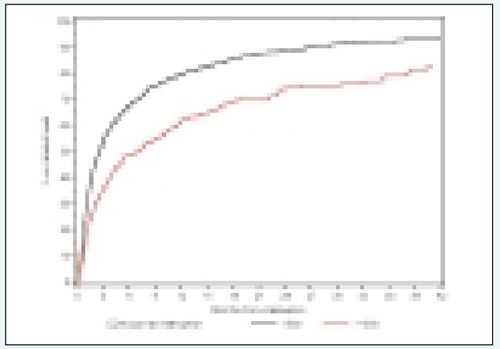


Figure 10.8: Kaplan-Meier plot of time to reinitiation, stratified by CD4 cell count at interruption.

Reinitiation of HAART

Of all patients, 912 (78.9%) reinitiated HAART during follow-up. The median time to reinitiation was 3.5 months (IQR: 1.1-13.0); 7.0 months (IQR: 1.6-25.9) among those who interrupted at CD4 cell counts above 500 cells/mm^3 and 2.6 months (IQR: 0.92-8.9) among those with CD4 cell counts below 500 cells/mm^3 (Log-rank p<0.0001; Figure 10.8). Patients who were younger than 40 years of age (HR=0.64, 0.48-0.87 for ≤25 years vs. >40 years), and patients who were in better immunological and

virological condition at the start of HAART had longer interruptions than those who were older and in worse condition (Table 10.9).

		HR	95% CI
Age at start HAART (years)	≤25	0.64	0.48-0.87
	26-40	0.68	0.50-0.93
	>40	1.0	-
Year of start HAART	≤1996	1.4	1.1-1.8
	1997-1998	1.2	0.98-1.5
	1999-2000	1.1	0.86-1.3
	>2000	1.0	-
CDC-B/C event within one year prior to start HAART		1.2	1.1-1.4
CD4 cell count at start HAART (cells/mm^3)	Missing	1.3	1.0-1.6
	≤50	2.9	2.3-3.8
	51-200	2.3	1.9-2.9
	201-350	1.6	1.3-1.9
	>350	1.0	-
pVL at start HAART (log copies/ml)	Missing	0.87	0.72-1.1
	≤4	0.56	0.44-0.72
	4-5	0.96	0.81-1.1
	>5	1.0	-
Time on HAART (days)	≤182	1.0	-
	182-365	0.86	0.70-1.0
	>365	0.75	0.64-0.88

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load

Table 10.9: Determinants of time to reinitiation of HAART

Other predictors of time to reinitiation were year of start HAART and the duration of HAART use prior to interruption (>365 days vs. 182 days or less, HR=0.75, 064-0.88). The median CD4 cell count among 651 persons with a measurement at reinitiation of HAART was 260 cells/mm^3 (IQR: 130-400). Moreover, 75 of the 674 (11.1%) with a pVL measurement had a pVL <500 copies/ml; the median pVL among those who were detectable was 4.8 log copies/ml (IQR: 4.4-5.3).

During the interruption, 38 (3.3%) patients had experienced a CDC-B event and 42 (3.6%) a CDC-C event. CDC-B or C events occurred more frequently among patients with a pVL >500 copies/ml at interruption than among patients with a lower pVL (8.7% vs. 4.8%, p=0.002) and among patients with a CD4 cell count below 500 cells/mm^3 as compared to patients with a higher CD4 cell count (7.8% vs. 5.2%, p=0.02). Furthermore, 27 (2.3%) patients died while being off therapy. Death was related to the CD4 cell counts at interruption; three (0.81%) of the patients with a CD4 cell count above 500 cells/mm^3 died during the interruption vs. 24 (3.1%) of the patients with lower counts (p=0.006).

		HR	95% CI
Gender	Male	0.80	0.65-0.98
Risk group	Heterosexual	1.0	-
	MSM	1.3	1.1-1.6
	IDU	1.0	0.74-1.4
	Other	0.83	0.65-1.1
Time on HAART (days)	≤182	1.0	-
	182-365	0.89	0.71-1.1
	>365	0.77	0.62-0.97
Duration of the interruption (days)	≤91	0.78	0.63-0.98
	92-182	0.96	0.80-1.1
	>182	1.0	-
pVL at start HAART (log copies/ml)	Missing	0.76	0.62-0.93
	≤4	1.7	1.3-2.2
	4-5	1.1	0.95-1.3
	>5	1.0	-
CD4 cell count >500 cells/mm^3 at interruption		1.2	1.0-1.4
pVL <500 copies/ml at interruption		1.5	1.3-1.8
pVL at reinitiation (log copies/ml)	Missing	1.0	0.84-1.3
	≤4	1.6	1.3-2.0
	4-5	1.3	1.0-1.6
	>5	1.0	-

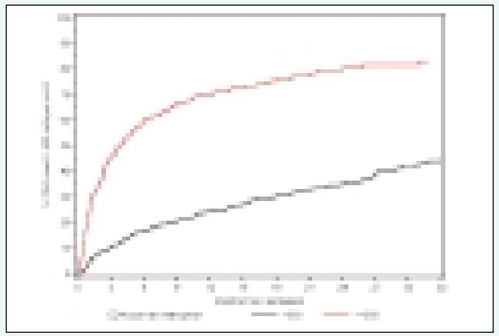
HR=hazard ratio, CI=confidence interval, pVL=plasma viral load

Table 10.10: Determinants of time to pVL <500 copies/ml after reinitiation of HAART.

After reinitiation of HAART

Of the patients reinitiating HAART, 77.1% reached a pVL <500 copies/ml plasma after 12 months of follow-up, increasing to 90.3% after 36 months. The median time to virological success after reinitiation was 3.0 months (IQR: 1.3-10.5). Duration of the interruption was predictive of time to virological success after reinitiation; the shorter the interruption, the longer the time to success after reinitiation of therapy (≤91 days vs. >182 days: HR=0.78, 0.63-0.98; Table 10.10).

Patients who had been on HAART for longer than 365 days prior to the interruption also took longer to achieve virological success than patients who had been on HAART for 365 days or less (>365 days vs. ≤182 days: HR=0.77, 062-0.97). Furthermore, patients who started HAART with a pVL ≤4 log copies/ml, patients whose pVL was still <500 copies/ml when interrupting therapy (HR=1.5, 1.3-1.8), and patients who reinitiated therapy while still having a pVL ≤4 log copies/ml, experienced virological success more quickly than patients whose pVL was higher. In addition, female patients, patients classified as MSM, and patients with a CD4 cell count >500 cells/mm3 at interruption had a shorter time to reaching a pVL <500 copies/ml.



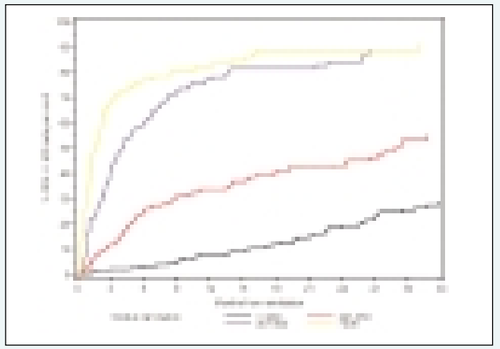


Figure 10.9: Kaplan-Meier of time to CD4 cell count ≥500 cells/mm^3, stratified by CD4 cell count at interruption (A) and CD4 cell count at re-initiation (B).

Moreover, within 12 months 38.0% of all patients who reinitiated therapy had achieved a CD4 cell count >500 cells/mm^3. Figure 10.9 shows that the median time to CD4 >500 cells/mm^3 was shorter among those who interrupted at higher CD4 cell counts (A) and those who still had higher CD4 cell counts at reinitiation (B). Among those who interrupted at CD4 cell counts below 500 cells/mm^3 55.7% versus 81.3% of patients who interrupted at higher counts ever had immunological success again, as defined by a CD4 cell count >500 cells/mm^3.

Predictors of immunological success are presented in Table 10.11. Time to a CD4 cell count ≥500 cells/mm^3 after reinitiation of HAART is longer among patients who had lower CD4 cell counts at start of HAART and patients who had been treated with HAART for longer than 365 days prior to interruption (>365 days vs. ≤182 days: HR=0.75, 0.58-0.97). Patients who reinitiated therapy within 91 days of the interruption achieved immunological success quicker than those who stayed off therapy longer (≤91 days vs. >182 days: HR=2.0, 1.5-2.0). Moreover, patients who had a pVL <500 copies/ml at interruption (HR=1.4, 1.1-1.7) and patients who had a

CD4 cell count >500 cells/mm^3 (HR=2.0, 1.6-2.6) at start of the interruption (and at reinitiation of HAART) achieved immunological success more quickly after reinitiating HAART than other patients.

		HR	95% CI
Time on HAART (days)	≤182	1.0	-
	182-365	0.90	0.65-1.2
	>365	0.75	0.58-0.97
Duration of the interruption (days)	≤91	2.0	1.5-2.5
	92-182	1.2	0.84-1.6
	>182	1.0	-
pVL at start HAART (log copies/ml)	Missing	0.76	0.57-1.0
	≤4	0.65	0.46-0.92
	4-5	0.86	0.69-1.1
	>5	1.0	–
pVL <500 copies/ml at interruption		1.4	1.1-1.7
CD4 cell count at start HAART	Missing	0.43	0.31-0.60
(cells/mm^3)	≤50	0.19	0.12-0.30
	51-200	0.37	0.27-0.51
	201-350	0.58	0.44-0.76
	>350	1.0	-
CD4 cell count >500 cells/mm^3 at interruption		2.0	1.6-2.6
CD4 cell count at reinitiation	Missing	0.47	0.34-0.64
(cells/mm^3)	≤200	0.24	0.16-0.36
	201-350	0.43	0.30-0.61
	351-500	0.95	0.69-1.3
	>500	1.0	-

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load

Table 10.11: Determinants of time to a CD4 cell count ≥500 cells/mm^3 after reinitiation of HAART.

Therapy changes

First regimen change

A large proportion of the patients who initiated HAART changed regimens during follow-up. Female patients changed at a higher rate than male patients (Log-rank, p<0.0001). After 12 months, 677 (53.9%) of the 930 women and 2.462 (45.1%) of the 3.331 men had stopped their initial regimen. This percentage increased to 95.5% and 91.1% after 66 months of follow-up (Figure 10.10). The median time until the first change of therapy was 14.4 months among men (IQR: 4.1-36.5) and 9.9 months among women (IQR: 2.6-28.4).

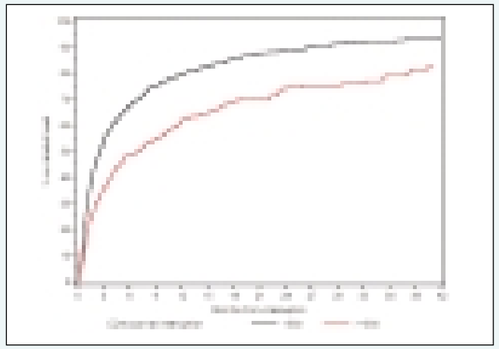


Figure 10.10: Kaplan-Meier plot of time to first change of therapy (duration of first regimen), stratified by gender.

Determinant		HR	95% CI
Gender	male	0.72	0.64-0.80
Risk group	Heterosexual	1.0	-
	MSM	1.1	1.0-1.3
	IDU	1.2	1.0-1.5
	Other	1.1	0.95-1.2
CD4 cell count at start HAART	Missing	0.84	0.75-0.94
(cells/mm^3)	≤50	1.0	0.92-1.2
	51-200	0.91	0.82-1.0
	201-350	0.84	0.75-0.93
	>350	1.0	-

HR=hazard ratio, CI=confidence interval, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.12: Predictors of time to first regimen change

Besides gender, the duration of the first regimen depended on the transmission risk group (IDU vs. heterosexual: HR=1.2, 1.0-1.5) and CD4 cell count at start of HAART (Table 10.12).

Second regimen change

In total, 2.885 patients initiated a second regimen. At start of this second regimen, 2.474 patients had a CD4 measurement and 1.820 had a pVL measurement, of which 799 (43.9%) were below 500 copies/ml. Among those who had a measurement above the detection limit, the pVL was 4.2 log copies/ml (IQR: 3.4-5.4). The median CD4 cell count was 363 cells/mm^3 (IQR: 220-590).

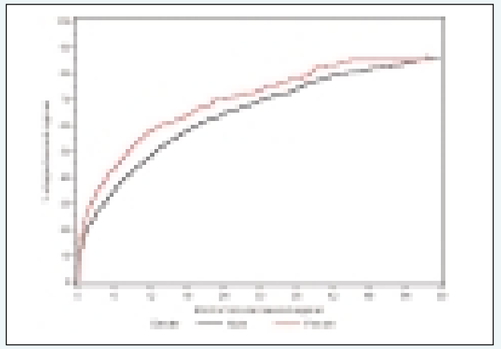


Figure 10.11: Kaplan-Meier plot of time to second change of therapy (duration of second regimen), stratified by gender.

Of all patients, 1.929 changed therapy again. The median duration of the second regimen was 12.2 months (IQR: 2.5-36.6 months). Again, a significant difference was observed between male and female patients (Figure 10.11; Log-rank, p=0.0008). The median duration of the second regimen was 13.0 months (IQR: 3.0-37.0) among men, and 8.6 months (IQR: 1.4-32.9) among women.

In the multivariate analysis, several other predictors of regimen change emerged (Table 10.13). Early year of start of the regimen was predictive of change (≤1996 vs. ≥1999: HR=1.7, 1.4-2.2) as well as a short duration of the previous regimen (<3 months vs. ≥12 months: HR=1.5, 1.3-1.7). In addition, a higher CD4 cell count at start of HAART, a higher pVL, and a lower CD4 cell count at start of the second regimen implied a higher hazard of change.

		HR	95% CI
Gender	male	0.87	0.78-0.97
Year of start second regimen	≤1996	1.7	1.4-2.2
	1997-1998	1.2	1.1-1.4
	≥1999	1.0	-
Duration of previous regimen (months)	<3	1.5	1.3-1.7
	3-12	1.2	1.0-1.3
	≥12	1.0	-
CD4 cell count at start HAART	Missing	0.90	0.77-1.0
(cells/mm^3)	≤50	0.75	0.63-0.90
	51-200	0.92	0.79-1.1
	201-350	0.87	0.76-1.0
	>350	1.0	-
CD4 cell count at start second regimen	Missing	1.2	1.0-1.5
(cells/mm^3)	≤200	1.2	1.0-1.5
	201-500	1.1	0.97-1.2
	>500	1.0-1.5	-
pVL at start second regimen	Missing	0.95	0.77-1.2
(log copies/ml)	≤4	0.77	0.69-0.87
	4-5	0.88	0.78-0.99
	>5	1.0	-

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load

Table 10.13: Predictors of time to second regimen change.

Third regimen change

At start of the third regimen, the median CD4 cell count among the 1.646 persons with a measurement was 380 cells/mm^3 (IQR: 220-590). Of 1.185 patients with a measurement, 581 had a pVL above 500 copies/ml; the median pVL was 4.3 log copies/ml (IQR: 3.5-5.0).
In total, 1.157 patients changed from their third regimen. Twelve months after starting their third regimen 50.8%

of patients had stopped this regimen again (Figure 10.12); median duration of this third regimen was 11.7 months (IQR: 2.4-34.1). There was no difference between men and women in duration of the third regimen (Log-rank, p=0.29).

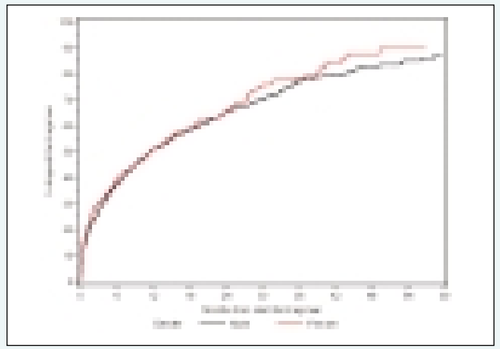


Figure 10.12: Kaplan-Meier plot of time to third change of therapy (duration of third regimen), stratified by gender.

		HR	95% CI
Region of origin	Netherlands	0.78	0.69-0.89
Risk group	Heterosexual	1.0	-
	MSM	1.1	0.91-1.2
	IDU	1.4	1.0-1.8
	Other	0.96	0.77-1.2
Year of start third regimen	≤1996	1.2	0.85-1.6
	1997-1998	1.2	1.1-1.4
	≥1999	1.0	-
Duration of previous regimen (months)	<3	1.3	1.1-1.5
	3-12	1.2	0.99-1.4
	≥12	1.0	-
pVL at start third regimen	Missing	1.1	0.84-1.4
(log copies/ml)	≤4	0.78	0.68-0.89
	4-5	1.0	0.86-1.2
	>5	1.0	-

HR=hazard ratio, CI=confidence interval, pVL=plasma viral load, IDU=intravenous drug user, MSM=men who have sex with men

Table 10.14: Predictors of time to third regimen change

Factors that were predictive of duration of the third regimen are presented in Table 10.14. Again, year of start of the regimen and short duration of the previous regimen (<3 months vs. ≥12 months: HR=1.3, 1.1-1.5) were predictive of a faster regimen change. In addition, a pVL <4 log copies/ml and persons who were born in the Netherlands had a lower hazard of change than those who had a higher pVL at start and were born outside the Netherlands. Finally, the duration of the third regimen was shorter among intravenous drug users than among persons in other risk groups (IDU vs. heterosexual: HR=1.4, 1.0-1.8).

Discussion: Therapy success and failure

After initiation of HAART, the majority of patients rapidly suppressed their pVL to below 500 copies/ml and achieved an increase of 100 or more CD4 cells/mm^3. Time to an increase in the CD4 cell count to levels above 350 cells/mm^3 was considerably longer, especially among patients with low CD4 cell counts at start of HAART. No difference was found in therapy success between men and women. The initial difference in time to suppression of the pVL to below 500 copies/ml could be explained by the differences in socio-demographic background between men and women (see Chapter 5). This lack of a gender effect has been described previously [22].

The observed slower rate of virological and immunological therapy success and more rapid failure among patients of non-Dutch origin may be due to limited adherence to therapy. Differences in adherence between ethnic groups have been reported previously [23,24]. Moreover, adherence to therapy is probably also related to the finding that older patients achieve virological success at a faster rate than younger patients do [1,25,26]. In contrast, CD4 cell reconstitution is slower and less than among young patients [27,28]. Additionally, adherence may be the explanation for the finding that faster virological failure occurs at a faster rate among patients who start therapy at high CD4 cell counts [8].

Finally, the difference found in the rate of success between early and late HAART may be due to a difference in the combinations prescribed. Prior to 1998, the majority of patients start on protease inhibitors (PI), whereas in later years an increasing number of patients start on a combination containing a non-nucleoside reverse transcriptase inhibitor (nNRTi) (see Chapter 9). Combinations that contain a PI are known to have a slower effect on the pVL than combinations that contain an nNRTi [29].

Therapy interruptions

Temporary interruption of HAART was a common phenomenon among naïve patients who initiated therapy without prior antiretroviral treatment. Interruptions occurred more frequently among women than among men, which may result from the fact that women more often interrupt HAART due to toxicity than men [30]. In general, those who interrupted therapy had started HAART earlier and had been in follow-up longer. This suggests that long-term treatment and adherence to the strict dosing protocols may be important reasons for interrupting therapy, although studies show that interruption of treatment does not significantly improve the quality of life [31,32].

Predictors of adverse outcome

Several important predictors of an adverse outcome during the interruption and after reinitiation of HAART were identified. The immunological condition of the patient was the factor that best predicted the overall outcome. Patients who had lower CD4 cell counts at start of therapy and at interruption experienced a faster drop in their CD4 cell count to below 350 during the interruption, were able to remain off therapy for a shorter period, took longer to suppress HIV after reinitiation of HAART, and less frequently achieved a high CD4 cell count after reinitiation.

By contrast, most patients who had high CD4 cell counts quickly re-suppressed HIV and regained the CD4 cells lost during the interruption after they reinitiated HAART. Nevertheless, even for patients with CD4 cell counts still above 500 cells/mm^3 at interruption, the interruption is risky as approximately 20% do not reach CD4 cell counts above 500 cells/mm^3 again after reinitiating therapy. These results are in concordance with the findings of others that discontinuous use of HAART leads a to poorer long-term outcome of therapy, especially among patients who are already in a worse physical condition while on HAART [19,20,21].

In addition to the CD4 cell count, the success of therapy after reinitiation was also dependent on pVL prior and during the interruption. Patients who had a low pVL at start of HAART or at interruption more quickly resuppressed their pVL to below 500 copies/ml after reinitiation. Similarly, the time to immunological success was also shorter among patients with a low pVL prior and during the interruption. Further, we found that the longer the interruption, the slower the gain of CD4 cells, but the faster the resuppression of the pVL. This faster suppression of the pVL might be due to the fact that after short-term interruptions patients resume the drug combination they were taking prior to the interruption, whereas after a long-term interruption patients may be more likely to initiate a different combination.

Change of regimen

Approximately 90% of patients stop their initial regimen, usually within a few months of starting HAART. The median duration of regimens taken as part of HAART therapy was approximately one year, although the median duration of consecutive regimens decreased slightly over the course of therapy. A similar decrease in duration was also described by Palella et al. for the HOPS cohort [33].

Two factors contribute to this finding. First, the association between the duration of successive regimens. We found that patients who changed their current regimen

quickly had a higher risk of quickly changing their next regimen as well. This may be explained by the finding that patients who switched due to toxicity [34]. Further, second-line therapy, in general, is less effective, leading to faster virological failure and potentially more therapy switches [33]. A second factor is the limited maximum duration of follow-up, which implies that only those patients who stopped their first regimen relatively quickly will have had the chance to initiate a second or third regimen before the end of follow-up.

The risk of therapy change was also dependent on several other factors. We found that the duration of regimens started shortly after the introduction of HAART was shorter than regimens started in later years. This effect may be explained by improved effectiveness and a decrease in the number of switches due to toxicity associated with changes in the drug combinations prescribed and in dosing schedules [35].

In addition, we determined that women were at higher risk of switching regimens than men were. This may be due to the fact that women experience toxicity more often than men do [30]. Toxicity may also be the reason for the faster switches among persons who have a high CD4 cell count when starting a next regimen. Possibly, the side effects of HAART and the effect of the dosing protocol on daily life are less acceptable among persons who are in relatively good immunological condition at start of the drug combination. Finally, regimen changes occurred faster among patients with a low pVL at start of the regimen and among patients classified as intravenous drug user, which may explain the higher risk of virological failure among these patients [1].

Limitations

Several limitations of the analyses presented in this chapter should be discussed. First, the analyses do not account for the differences in follow-up frequency, although data on these patients will more accurately reflect the changes in the health status of the patient on therapy. Moreover, in the Cox proportional hazards models the assumption is made that drop-out and censoring are not selective or informative. This may not always be the case. For example, selective drop-out may occur if patients are in such poor physical condition that they are no longer able to attend scheduled appointments. Additionally, in several of the analyses the date of death is considered as the date of censoring. However, deceased patients will have ended their regimen, and, if the death is related to HIV, death is the ultimate sign of therapy failure.

Furthermore, the results of the analyses concerning regimen changes and the differences described in chapter 8 between the effects of different starting regimens imply that future analyses, where possible, should include more information on the use of specific regimens rather than an approach based on an intention-to-treat analysis. Lastly, the development of CD4 cell count and pVL over time has been shown to be a good predictor for morbidity and mortality. Therefore, the analyses, in particular the analyses concerning therapy success and failure, should be expanded to include parameters that better reflect the changes in the immunological and virological status of the patient during therapy.

Conclusion

Successful treatment with HAART was mainly dependent on the immunological status of the patient at start of therapy. Yet, despite the clear benefit of therapy in terms of a quick suppression of the virus and a fast rise in CD4 cell counts, patients frequently interrupt or change their initial regimen within one year of starting HAART. Therapy changes as well as interruptions are associated with a less favourable treatment outcome. Treating physicians should therefore carefully weigh the risks associated with regimen changes and treatment interruptions against the perceived advantages of switching to an alternative regimen.

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AIDS and death

Ongoing decline of HIV-related mortality but not morbidity

Introduction

The beneficial effect of HAART on survival and the development of AIDS has been well established [1,2, 3,4]. Not only has the life expectancy of HIV-infected patients increased, quality of life has also improved [5,6]. In addition, the spectrum of causes of mortality is changing as the number of deaths related to opportunistic infections diminishes [7,8,9]. Similar developments have been observed in the Netherlands [10].

Several studies have assessed prognostic markers related to progression to death or AIDS. Baseline CD4 cell counts are highly predictive of survival and the development of AIDS in both untreated and treated patients, whereas baseline HIV-1 RNA levels have little additional predictive value in treated patients [11,12, 13,14]. Increases in CD4 cell counts during treatment with HAART and reaching undetectable levels of viral load are also significantly associated with a better prognosis [13,15,16].

In our previous study, prognostic markers for survival and progression to AIDS among HIV-infected patients in the ATHENA cohort were identified and included in a multivariate hazards model [10]. This model was used to estimate five-year survival probabilities for patients initiating HAART. In this chapter, we present a model that takes into account the initial virological and immunological response to HAART. It was developed in collaboration with the Verbond van Verzekeraars, the Dutch Association of Insurers. Similar studies were performed by the ART collaboration [17,18].

Population and methods

The study population consisted of 6.703 HIV-1-infected patients who started HAART. Together, these patients accounted for 27.408 person-years of follow-up between initiation of HAART (T^0) and closure of the database (31 July 2003). All deaths and AIDS cases occurring in this population during this period were assessed. AIDS was defined as the first occurrence of a CDC-C event four weeks after start of HAART [19]. It was assumed that AIDS cases during the first four weeks of HAART were most likely the result of the patient's condition prior to start of HAART.

The death cases observed in the population were scored by a panel of three independent physicians (Peter Reiss, Inge Gyssens, Kees Brinkman) as either HIV-related, non-HIV-related (including therapy-related) or unknown [10]. This score was based on clinical data at the time of death as reported by the treating physician and the patient's history of CDC and adverse events. Cases about which the three physicians disagreed were discussed by the panel until a consensus score was reached. A total of 87 death cases was assigned a preliminary score, as they had been included in the database only recently and the three physicians had not yet had an opportunity to assign a score to these cases.

Mortality and AIDS incidence was calculated per 100 person-years of follow-up after start of HAART and are reported with their 95% confidence intervals (CI). Poisson's distribution was used to calculate 95% confidence intervals for rates, and significance of changes over time was assessed by a $\chi 2$-test. Expected death rates were calculated for an age- and gender-matched group from the general Dutch population [20].

For fitting the survival model, only antiretroviral therapy-naïve patients older than 18 years of age at start of HAART, who started HAART in or after 1995, and who had not been infected via intravenous drug use, were selected. In addition, the patients had to have a CD4 measurement at baseline and at 24 weeks after T^0. The baseline CD4 cell count was the CD4 value measured closest to the start of HAART between 24 weeks before start and 1 week thereafter. The CD4 cell count at 24 weeks was the CD4 cell count closest to 24 weeks after T^0 within an interval of 12 weeks before and after that

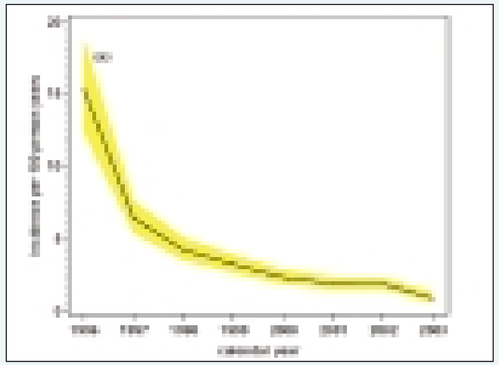

Figure 11a

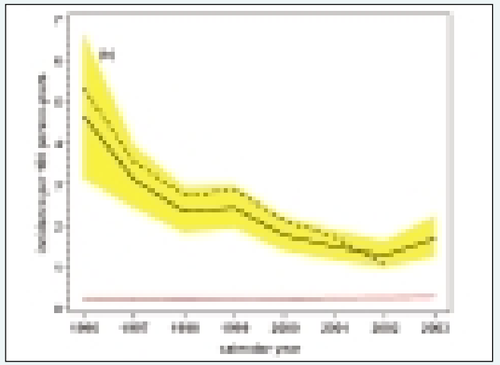

Figure 11b

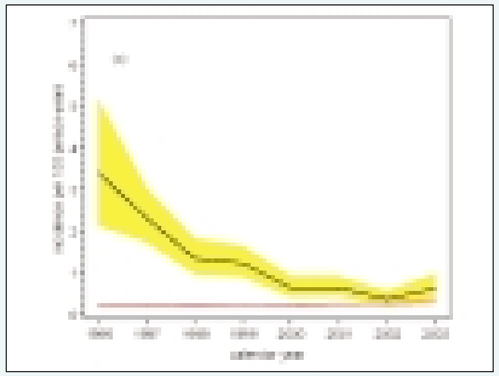

Figure 11c

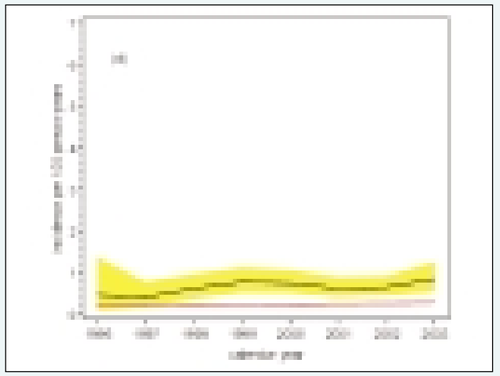

Figure 11d

time. Note that these requirements imply that the patients survived at least the first 24 weeks after start of HAART. HIV-1 RNA levels were defined analogously, although for baseline values the maximum time after T^0 was limited to 0 weeks.

A Cox proportional hazards model was used to find the set of covariates that best predicted the time from 24 weeks after start of HAART to death. Covariates considered for inclusion in the model were disease status at T^0, defined as the most serious CDC-event of category B or C [20] in the year before T^0, age, gender, start of HAART before or after 1998, and CD4 cell counts and HIV-1 RNA levels at start of HAART and at 24 weeks. Covariates were excluded from the model via backward elimination if this did not yield a significantly

worse model (P<0.01, log-likelihood $\chi 2$ test). As it turned out that the resulting baseline hazard was constant over time, an exponential model was used. This model describes the survival probability S(t) of a patient at t years after 24 weeks after T^0 by S(t) = exp[- exp(- Si _i xi) t] where the sum runs over all covariates xi in the model with corresponding hazard ratios exp[-_i].

Results

The total number of CDC-C events registered in the HAART-treated population since 1996 was 741. The incidence of a first CDC-C event per 100 person-years of follow-up steadily declined from 15.3 (95% CI: 12.4--18.7) in 1996 to 1.8 (95% CI: 1.5-2.2) in 2002 (Figure 11.1a). In 1996, the incidence among pre-treated patients was 18.0 (95% CI: 14.4-22.2) compared to 6.31 (95% CI: 2.9-12.0) per 100 person-years in the therapy-naïve population. Thereafter, incidences of AIDS in these two populations were the same.

Mortality rates in the HAART-treated population declined from 4.6 (95% CI: 3.1-6.6) in 1996 to 1.7 (95% CI: 1.3-2.2) per 100 person-years in 2003 (Figure 11.1b). Of the 532 deaths in the HAART-treated population, HIV-related mortality was scored as the most probable cause of death in 257 (48.3%) cases, whereas in 182 (34.2%) cases the cause of death was non-HIV-related. In 93 (17.5%) cases, the cause of death could not be determined. The incidences of HIV-related and non-HIV-related deaths are shown in figures 11.1c and 11.1d. The HIV-related mortality significantly decreased from 3.4 (95% CI: 2.1-5.2) in 1996 to 0.61 (95% CI: 0.36-0.96) in 2003 (P<0.001). Non-HIV-related mortality increased slightly over time, 0.46 (95% CI: 0.10-1.36) in 1996 to 0.84 (95% CI: 0.54-1.24) per 100 person-years in 2003, but this increase was not significant (P=0.6).

In total 3.068 patients were selected for inclusion in the survival model of whom 91 (3.0%) died during follow-up. For 2.718 (88.6%) patients, a viral load measurement was available both at baseline and at 24 weeks after T^0. In this group 67 (2.5%) of the patients progressed to death. At 24 weeks, 2.838 (87.7%) patients had either an undetectable viral load or a load below 500 copies/ml.

covariate	HR 95% CI
log [(CD4+10)/1000] (x 10^6 cells/l)	0.43 (0.33–0.57)
†CD4 at T^0 >100 x 10^6 cells/l	*0.69 (0.52–0.92)
age at T^0 per year	*1.022 (1.002–1.043)
start HAART in or after 1998 vs. before 1998	0.49 (0.32–0.75)

CI: confidence interval; HR: multivariate hazard ratio; †as interaction with previous variable; *hazard ratio statistically not significant

CI: confidence interval; HR: multivariate hazard ratio; †as interaction with previous variable; *hazard ratio statistically not significant

Table 11.1: Effect of baseline variables and CD4 cell counts at 24 weeks on the risk of progression to death

Covariates associated with progression to death are listed in table 11.1. The risk of progression to death for patients starting HAART in or after 1998 was 0.49 times smaller than for patients starting HAART before 1998. Each unit increase in log-transformed CD4 cell count at 24 weeks reduced the risk of progression to death by a factor 0.43. CD4 cell counts at baseline were included as a dichotomous covariate indicating whether or not CD4 cell counts exceeded 100 ´ 10^6 cells/l. The interaction of this variable with the log-transformed CD4 cell count at 24 weeks was borderline significant (P=0.012). An increase of one year in age at initiation of HAART increased the risk of death by a factor 1.022, but this variable was also not significant (P=0.035). Other covariates were not significantly associated with progression to death.

Discussion

AIDS incidences during HAART have dropped significantly since 1996. Since 2001, the incidence seems to have reached a constant level of 1.8 incidences per year. The lower incidence in 2003 should be interpreted with care, as a backlog in the registration of CDC events cannot be excluded.

Analogously, mortality rates declined during the same period. The rise in mortality observed in 2003 compared to 2002 is not significant. It should be noted that the mortality rates might be underestimated, as patients who died before 2002 and did not participate in the ATHENA project were less likely to be included in the database than patients who were still alive at that time. This is because only alive patients were included in the HMF database. On the other hand, during the ATHENA project, patients who died before the start of the project in May 1998, were still included if they had already initiated HAART. For this reason, mortality rates were lower than those reported last year [21].

A similar reduction in morbidity and mortality has been observed in other studies and can largely be explained by the introduction of HAART [1,2,3]. However, part of this decline might be attributed to changes in the treated population during these years, as it shifted towards a population in a less advanced stage of HIV-1 infection at the start of HAART with a growing fraction of therapy-naïve patients.

Non-HIV-related mortality in the HIV-infected population is still two to three times higher than in non-HIV-infected people [8]. A part of this excess can be explained by the presence of intravenous drug users in this population who have a higher risk of dying of non-HIV-related causes. Excluding this group reduces the non-HIV-related mortality rates by 17%. In addition, among the 182 non-HIV-related death cases, ten were definitely therapy-related and approximately 25 were possibly therapy-related.

Although misclassification of causes of death may limit interpretation of the results, the stable incidence of non-HIV-related deaths over the years suggests that toxicity has not yet become a major cause of death. However, this may change in the future when the long-term consequences of HAART become more clearly recognised. Thus, the recognition and careful recording of therapy-related toxicity and death remains of the utmost importance.

Progression to death was largely determined by CD4 cell counts at 24 weeks after starting HAART and only to a small non-significant extent by CD4 cell counts at baseline. Hence, it matters which CD4 cell count a patient has reached after 24 weeks and not where he came from [18]. If, however, age at baseline has been removed from the model – as it is not a significant covariate – CD4 cell counts at baseline become a significant covariate. Nevertheless, it was decided to include age as a predictor in the model because of previous findings and results of the ART collaboration [10,17,18].

No significant association between HIV-1 RNA levels at baseline or at 24 weeks and the risk of progression to death was found. In contrast, the ART collaboration reported that HIV-1 RNA levels at 24 weeks exceeding 100.000 copies/ml were associated with an increased risk of death compared to patients with lower or undetectable HIV-1 RNA levels [18]. This might be due to the lower proportion of patients that were undetectable at 24 weeks (72%) compared to ATHENA-HMF, which is probably due to differences between the two study populations. For example, the ART collaboration did not exclude intravenous drug users. On the other hand, the number of deaths was rather small if only patients with a viral load measurement both at baseline and at 24 weeks were selected, which reduces the significance of covariates included in the model.

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Conclusions and recommendations

The number of patients included in the registration and monitoring database of the Dutch HIV Monitoring Foundation (HMF) has increased from 6.306 patients per October 2002 up to 8.940 patients per 1 November 2003. This substantial increase is achieved by the collaborative effort of treating physicians and data collectors in 24 hospitals of the 22 HIV Treatment Centres in the Netherlands. The number and the length of follow-up of patients have resulted in an enormous rise in the amount of data. Mounting data, together with the highly flexible database that has been developed for the ATHENA project (1998-2000), have stressed the quality and diminished the insight into the quality of the data. This is less a problem for those data and datasets that were uploaded from other well-controlled systems, such as laboratory systems. However, data obtained directly from the medical files of patients are prone to assumptions and interpretations and the quality of those data can only be assured to an acceptable level if a more structured database is used in combination with more rigorous data quality monitoring. With this in mind, the HMF is currently implementing a new database system that has been developed for clinical trials aiming at FDA registration of new drugs. After adjusting it for the follow-up of a prospective observational cohort, and following a pilot performed in the first half of 2003, data entry is now being performed on a regular basis in ten hospitals using the new Oracle database. And although the data entry now requires more time and attention of the data collecting staff, the profit is already becoming clear as well: better structured data and tables, resulting in a lower level of pre-analysis interpretation and subsequently a less laborious adaptation of the data before analysis. Moreover, because all hospitals will enter their data into one database system instead of 24 separate databases, merging of the different datasets is no longer necessary and differences between local and central datasets disappear.

Conclusions

The total number of HIV-infected patients initially included in the 2003 study population is 8.496 patients. In addition to the number of 8.282 HIV-1-infected patients, 28 HIV-2-infected patients have been identified. Of 186 patients, the precise HIV diagnosis remains unclear. The median follow-up period is 5.4 years and the median number of follow-up visits is 3.2 per year, a decline in comparison to the previous reports probably due to the inclusion of a substantial number of non-treated patients who are in a relatively good clinical condition. The large majority of HIV-infected people still live in Amsterdam and in the other larger cities in the Western part of the country. With the data collected up to August 2003, we have tried to answer the questions regarding the changes in the course of the HIV infection.

What are the changes over time of the prevalence of newly diagnosed HIV-infections per year and the predicted number of HIV-infected patients in the Netherlands?

The number of patients included in the HMF is still growing and there is a steady and ongoing increase in the number of newly diagnosed HIV-1 infections per year in both men and women. Based on the figures on newly diagnosed infections per year we predict an increase in new diagnoses from 756 in 2003 to 849 in 2004. Using the figures of newly diagnosed infections, the HIV-1 prevalence reported by the Municipal Health Services of Amsterdam and Rotterdam for the anonymous testing sites, and the figures of the sexually active population (source: CBS 2002) and of the differences between the prevalence of STIs among the tested versus the general population(1,2), we estimate the total infected population in the Netherlands to be between 16.000 and 23.000 individuals.

The relative contribution of Dutch homosexual men to the number of newly diagnosed HIV-1 infections is decreasing, although the majority of the known infected patients still belongs to this group. The absolute number of new diagnoses did increase among older, but not among young homosexual men. Together with the reported growth of other STI diagnoses, this indicates that the sexual behaviour among homosexual men is changing. Furthermore, it may illustrate that the effect of prevention measures taken for this group is decreasing.

The HIV-1-infected heterosexual population is changing as well. The proportion of newly diagnosed Dutch patients in this group decreased from 45% of the total population of patients that acquired HIV heterosexually in 1996 to 21% in 2003, while the proportion Sub-Saharan African patients increased from 33 to 59%. The majority of the heterosexually infected patients in the Netherlands is non-Dutch. Moreover, the majority of the heterosexually infected patients consists of women, especially in the population of Sub-Saharan origin. Patients originating from Sub-Saharan Africa do not contribute to the same degree to the increase in other STDs. This indicates that their HIV infection is not acquired in the Netherlands but has been imported. Based on the total population of first-generation Sub-Saharan Africans living in the Netherlands, the prevalence of HIV-1 is 0.9% for the men and 1.6% for the women. The prevalence in the countries of origin are reportedly higher. Thus, in combination with unawareness about their serostatus, the prevalence among migrant groups from Sub-Saharan Africa may be underestimated.

HIV-1 subtype B is still the most prevalent subtype in all risk groups. Although sexual contact is the main route of transmission of non-B subtypes, the prevalence in the male homosexual population remains very limited.
In the population infected through heterosexual contact the proportion of non-B subtypes increased from 42.5%, as reported in the annual report of 2002, to 50.7% at present. This increase can be attributed to the recent inclusion in the database of already infected patients of non-Dutch origin. The distribution of subtypes across patients from Sub-Saharan Africa corresponded with the endemic distribution observed in this region and confirms that in this population HIV is imported from Sub-Saharan Africa rather than transmitted in the Netherlands, although transmission amongst Sub-Saharan Africans living in the Netherlands cannot be excluded.

Based on the characteristics of a sub-population of pregnant women, it seems that introduction of HAART has boosted the number of pregnancies amongst infected women, although again immigration might play a role in this increase as well. At present less is known about the prevalence of HIV-infected children, mainly due to limitations in database capacity.

A substantial number of people are untreated. HIV was diagnosed in this subgroup between 1999 and 2003 and the median number of CD4 cells was above 500/mm^3. In addition, the median HIV-1 RNA plasma level was relatively low. This may indicate that the large majority of the 1.579 non-treated patients have recently become infected with HIV-1.

What is the prevalence of resistant HIV among newly diagnosed patients without prior antiretroviral treatment and the prevalence among patients failing on HAART?

Transmission of drug-resistant HIV-1 virus strains was observed in 4.8% of the newly diagnosed patients and in 6% of the new infections in the Netherlands. Percentages did not change over time and were lower than those found in a recent study among seroconverters conducted in the Netherlands (3). In other European countries (4) and the US (5), transmission of drug-resistant virus was more frequent. Differences in methods of testing for drug resistance, geographical variation in the accessibility and usage of antiretroviral drugs and variation in risk factors for exposure may explain these differences. In addition, the time between infection and diagnosis was unknown for most patients. Hence, sequences were not necessarily obtained close to seroconversion and rates of transmitted resistance might be underestimated as resistant virus strains may be out-competed by wild-type variants shortly after infection.

The true prevalence of resistance in the HIV-infected population is certainly underestimated as from only less than 10% of the naïve patients failing on therapy HIV-1 RT and/or protease sequences were obtained. Moreover, not all sequences are available for analysis yet. The number of patients failing on different drugs and multiple drug classes rapidly increases after 2001. This suggests that determining resistance profiles in failing patients will become increasingly important for the choices of further treatment. If the prevalence of drug resistance in the HIV-infected population is still small, the transmission of resistant virus strains will be limited as well. Moreover, resistant virus may be transmitted less efficiently than wild-type virus. However, adherence to the antiretroviral drugs used may change and together with changes in sexual behaviour it may add to an increase in the risk of transmission of resistant virus.

What is the efficacy of HAART regimens, i.e. the beneficial effect on immunological and virological parameters versus the effect of toxicity?

Initial PI-containing HAART regimens have a better immunological outcome than those containing an NNRTI. In contrast, the virological outcome of NNRTI-containing HAART is better than of PI-containing HAART. When combining the immunological and virological endpoints, no difference is found between the two most frequently used nRTI backbones AZT+3TC and d4T+3TC and only limited differences are found between HAART regimens including one of these backbones plus one of the more frequently used (boosted) PIs and NNRTIs; combinations with IDV+RTV, SAQ+RTV or EFV are found to be better. The time to interruption or stop because of toxicity was both shorter in patients starting with a HAART regimen including d4T+3TC as compared to AZT+3TC and in patients with HAART including RTV.

Patients on HAART including IDV or NFV showed a steeper and longer-term increase in long-term CD4 cell numbers than patients on HAART including LOP+RTV or NVP or patients starting with ABC (6-8). Time to an increase of 100 CD4 cells/mm^3 from baseline was shortest in patients on initial HAART with LOP+RTV (9); however, the long-term CD4 cell slope was low in these patients. When combining tolerability with virological and immunological endpoints no specific HAART combination including AZT+3TC or d4T+3TC is found to give better results. AZT+3TC is less toxic and together with NFV the long-term immunological response may be favourable.

What are the various HAART outcome patterns, including results of HAART regimen switches and interruption?

The median time to virological success after start of initial HAART in patients without prior antiretroviral treatment is 3.2 months and more than 90% of the treated population reaches a HIV-1 RNA plasma level <500 copies per ml. High HIV-1 RNA levels at start of therapy are associated with a longer time to plasma levels <500. Patients of non-Dutch origin are at higher risk of staying >500 HIV-1 RNA copies/ml than Dutch patients. Immunological success is also achieved in more than 90% of the patients and an increase of 100 CD4 cells/mm^3 is reached in a median four months. Non-Dutch origin is a risk factor for needing a longer time to reach a 100 cells/mm^3 higher CD4 cell count. Long-term success of HAART depends mainly on the immunological status of a patient at start of therapy. An increase to a CD4 cell count of >350 cells/mm^3 is achieved after a median 8.6 months and depends on the CD4 cell number at baseline. Again a difference is found between Dutch patients and non-Dutch patients. Poorer adherence to the antiretroviral drugs prescribed may explain the differences between Dutch and non-Dutch patients, although differences in the effect of HAART on various HIV-1 subtypes cannot be totally excluded.

After 66 months of initial success, around 40% of the patients again have HIV-1 RNA levels >500 copies/ml, most of them under HAART treatment. Non-Dutch patients and patients who started HAART treatment in 1996-1998 are at higher risk. More than half of the patients show immunological deterioration, i.e. CD4 cells <350, after 66 months of initial success. Subsequent virological success after the first failure is achieved after six months in half of the patients, similar to the first virological success. However, in 25% of the patients HIV-1 RNA levels increased again to >500 copies/ml 22 months after the second success.

Temporary interruption of HAART is a common phenomenon. Interruptions occur more frequently among women than among men and also among those who started HAART between 1996 and 1998 and have therefore had a longer follow-up. The latter may be associated with the chronic nature of anti-HIV treatment, although interruption of treatment does not significantly improve the quality of life (10,11). The effect of an interruption as well as of reinitiated HAART depends largely on the immunological status of a patient at start of the interruption and the duration of the interruption (12,13). A lower CD4 cell count at start of the interruption is associated with a more rapid decline in CD4 cells during interruption and a slower restoration after reinitiating therapy. When in a good immunological condition, the risk of interrupting HAART is still substantial as approximately 20% of the patients do not regain CD4 cell counts >500 cells per mm^3 after reinitiating therapy.

In approximately 90% of the patients the initial HAART regimen is changed for another, mostly within a few months. The median duration of the first HAART regimen is approximately one year; the duration of the consecutive regimens decreases slightly over the course of treatment. If the first regimen is rapidly changed due to toxicity, patients will change their next HAART regimen after an even shorter period of time. This may be caused by an increased risk of toxicity of the subsequent regimens (14). In addition, second-line HAART is in general less effective and results in virological failure after a shorter period of treatment as compared to first-line HAART (15). Another factor that increases the risk of therapy change is the start of treatment shortly after the introduction of HAART in 1996. This may be explained by improved effectiveness and a decrease in the number of switches due to toxicity associated with changes in the drug combinations prescribed and in dosing schedules (16). Women are at higher risk of switching regimens than men, probably as a result of a higher risk of toxicity (17).

What are the changes in HIV-related morbidity and mortality?

AIDS incidences have dropped significantly since the introduction of HAART in 1996 (18-20), but in the last years the incidence seems to have reached a constant level of 1.8 per year. Mortality rates have declined during the same period. The rise in mortality observed in 2003 compared to 2002 is not significant.

Part of the decline may be attributed to changes in the infected and treated population during these years, as it has shifted towards a population with a less advanced stage of HIV-1 infection at the start of HAART and a growing fraction of therapy-naïve patients.

Non-HIV-related mortality is still two to three times higher for HIV-infected people than for non-HIV-infected people (21). This can partly be explained by the presence of intravenous drug users in the HIV-infected population who have a higher risk of dying of non-HIV-related causes. Excluding this group reduces the non-HIV-related mortality rates by 17%. In addition, among the 182 non-HIV-related death cases, ten were definitely and approximately 25 were possibly therapy-related, but toxicity has not yet become a major cause of death. However, this may change in the future when the long-term consequences of HAART become more clearly recognised.

Recommendations

With respect to the data collection, it is of importance to customise the data items to the needs of the applied and clinical research programmes that are approved by the HMF. In addition, it is recommended to customise the quality control of the data that are entered in the monitoring database as well in order to improve the power of the analysis for specific research questions. To improve the scientific output of specific research programmes for which data are used that are collected through the HMF monitoring system, regular meetings of principal investigators should be organised.

Based on the findings that are described and discussed in this report the following recommendations are made.

In order to better focus the prevention strategies, further research into the changes of the risk of infection in the group of older homosexual men is needed, taking into account the possible change in behaviour of the already infected but chronically HAART-treated group.

A relatively large proportion of migrant subgroups and especially young women are found among the patients who acquired HIV-1 heterosexually. Patients in this group are diagnosed with HIV at a relatively late stage of infection. From both a clinical and a public health perspective, it might be of importance to develop a special research programme supporting specific information, awareness and prevention programmes aiming at this group.

A more accurate knowledge of transmission patterns among migrants, using results of HIV-1 subtyping, will help to develop prevention strategies focussed on population-specific transmission characteristics. Presently, migrants are underrepresented in the sequenced population due to the way the sequences are obtained. Consequently, the introduction of non-B subtypes is currently underestimated. This, together with the variation in susceptibility to antiretroviral drugs of some non-B subtypes, leads to the recommendation to put more emphasis on the molecular epidemiology of HIV among infected non-Dutch patients living in the Netherlands.

Long-term success of HAART is to a lesser extent achieved by non-Dutch patients and non-Dutch patients are at higher risk of virological failure. With an increasing number of non-Dutch patients receiving HAART it is clinically of importance to further investigate adherence to HAART regimens in these specific groups. And as women are at higher risk of switching HAART regimens than men, combined research on adherence with therapeutic drug monitoring and research on toxicity is needed.

To monitor whether resistance will increase among the treated population and subsequently be transmitted to a higher extent, measurement of resistance at baseline and at therapy failure is needed. In addition, resistance should be measured in all new primary infections. Moreover, more insight is needed into changing adherence patterns of HIV-infected patients on treatment. Adherence and resistance data used together in the mathematical modelling of resistance would allow for an estimate of the transmission probability of resistant virus.

Analysis of the differences in efficacy between the various HAART regimens is still restricted to initial combinations of antiretroviral drugs. Similar analyses should be done for second and third regimens, taking the efficacy of prior HAART combinations into account. When analysing the effects of several regimens together, a large number of variables will be involved and will require substantial computer time, which is not available as yet. Moreover, a larger dataset is needed for a thorough statistical analysis. Collaboration with other research groups with the aim to achieve those larger datasets but also to develop analytical models and computer programmes that can handle large datasets and numbers of variables is needed to achieve more insight in the efficacy of various subsequent HAART regimens.

Registration of mortality and especially the causes of death should be improved to better understand the HIV- and antiretroviral drug-relatedness. The same holds true for the registration of morbidity where an improvement of the registration of both toxicity-related clinical signs and symptoms as well as laboratory results is needed.

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Research

Overview of ongoing research projects

Incidence of solid tumours among HIV-1 infected patients treated with HAART

Incidentie van solide tumoren bij HIV-geinfecteerde patiënten met HAART

Auteurs: Gitte van Twillert, afdeling Interne Geneeskunde, AMC, Amsterdam; Elly Hassink, IATEC, Amsterdam; Gerrit Jan Weverling, afdeling Klinische Epidemiologie en Biostatistiek; AMC, Amsterdam; Frank de Wolf, Stichting HIV Monitoring, Amsterdam; Annelies Verbon, afdeling Medische Microbiologie, AZM, Maastricht.

Goedkeuring Adviesraad d.d.: 24-05-2002

Inleiding

Onbehandeld kan HIV- infectie leiden tot een ernstige imuundeficientie en verschijning van 'AIDS-definierende ziekten', zoals tumoren als Kaposi's sarcoma, non-Hodgkin lymfomen, cervix en anuscarcinomen. Ook een verhoogde incidentie van niet HIV-gerelateerde maligniteiten zoals M.Hodgkin, longcarcinomen, testis carcinomen en lipcarcinomen is al beschreven. Echter, andere studies toonden een vergelijkbare incidentie van deze tumoren in de HIV populatie en de algemene populatie. De invloed van antiretrovirale therapie (HAART) op het voorkomen van maligniteiten is ook niet eenduidig. Hier beschrijven wij de incidentie van niet HIV-gerelateerde tumoren van patienten uit het ATHENA cohort die HAART gebruiken en vergeleken deze met die van de algemene Nederlandse populatie.

Materiaal en methoden

Alle solide tumoren in het Athena bestand tot en met november 2001 werden geselecteerd. Vervolgens werden alle HIV-gerelateerde tumoren geëxcludeerd en alle tumoren opgetreden voor de start van HAART. Berekend werd het aantal observatiejaren in ATHENA en een gestandaardiseerde morbidity ratio (SMR) werd berekend met gegevens van het CBS over de incidentie van kanker per 100.000 persoonsjaren (HIV-gerelateerde tumoren werden uitgesloten. De gegevens uit de Athena database werden steeksproefgewijs gecontroleerd met de gegevens van het IKA door een match te maken van alle Athena patiënten met data van patienten uit Noord Holland op basis van initialen, geboortedatum, geslacht, datum van overlijden en land van herkomst. Daarna werden de gegevens uit het gekoppelde bestand van Athena en IKA met elkaar vergeleken. Tevens kregen alle behandelaren van patiënten uit het Athena bestand met een tumor een vragenlijst toegestuurd voor aanvullende informatie over de aard en de behandeling van de tumor.

Resultaten

Het totaal aantal tumoren in het Athena bestand was 33 in 15.383 persoonsjaren, terwijl op basis van de gegevens van het CBS 37 maligniteiten werden verwacht, SMR 95% CI: 0.89 (0.61-1.25). Het aantal verschillende tumoren bedroeg 8. Uitgesplitst naar geslacht werden er bij mannen 32 tumoren gevonden tegen 33 verwacht, voor de vrouwen was dit 1 tumor tegen 4 verwacht. De bijbehorende SMR (95% CI) voor mannen was 0.97 (0.66- 1.37) en 0.8 (0.52/1.16) voor vrouwen. De mediane leeftijd ten tijde van de diagnose was 47.3 jaar (36.2-56.0). Het mediane aantal weken tussen start van HAART en 1e diagnose maligniteit was 81.7 weken (49.5-158.8). Het laatste CD4 getal voor de diagnose maligniteit was 371 (255-477), de CD4 nadir voor de 1e diagnose maligniteit was 150 (67-477). Ter controle werd er gekeken of de patiënten met tumoren in het Athena cohort gelijk in aantal waren aan die van het IKA bestand. Er blijken meer patiënten met een solide tumor in het IKA bestand te staan dan in het ATHENA data bestand (64 in IKA, 30 in Athena). Tevens blijken de tumoren uit het ATHENA bestand niet altijd terecht te zijn ingevoerd.

Conclusie

Deze data lijken er op te wijzen dat er geen verhoogde incidentie van solide tumoren bij HIV patienten met HAART is. Het blijkt echter dat het Athena bestand niet goed geschikt is om een betrouwbare uitspraak te doen over het voorkomen van solide tumoren in de HIV populatie. Er is lijkt sprake van onderrapportage en foutrapportage in het ATHENA data bestand.

Verdraagzaamheid, veiligheid en werkzaamheid van antiretrovirale therapie in HIV-1-geïnfecteerde vrouwen in Nederland gedurende 6 jaar

Tolerance, safety and efficacy of antiretroviral combination therapy in HIV-infected women

Auteurs: Claire Tempelman[1], Sarah Timmermans[1], Jeanne Dieleman[1], Mieke H Godfried[2], Jeannine FJB Nellen[2], Herman G Sprenger[3], Margriet M.E. Schneider[4], Robert H Kauffmann[5], Frank de Wolf[6], Kees Boer[2], Marchina E van der Ende[1] — [1]Erasmus MC. [2]AMC. [3]AZG. [4]UMCU. [5]Ziekenhuis Leyenburg, [6]Stichting HIV Monitoring.

goedkeuring adviesraad d.d.: 16-01-2003:

Achtergrond

Verticale transmissie van HIV is significant verminderd sinds het gebruik van antiretrovirale therapie (ART). Het percentage besmettingen is minder dan 1%. Mede door het succes van de huidige antiretrovirale therapie, kiezen veel HIV-geïnfecteerde vrouwen er bewust voor om zwanger te worden, dan wel een zwangerschap niet meer af te breken. Er is echter nog weinig bekend over de veiligheid van deze middelen tijdens de zwangerschap.

Doel

Vaststellen van verdraagzaamheid, veiligheid en werkzaamheid van ART in een cohort HIV-geïnfecteerde zwangere vrouwen in Nederland.

Methode

In een retrospectief onderzoek werd in 15 HIV-gespecialiseerde centra status onderzoek verricht van HIV-geïnfecteerde vrouwen die tijdens de zwangerschap (1 januari 1997 tot 1 juni 2003) ART gebruikten. Er werden gegevens verzameld van patiënt-karakteristieken, de duur en de samenstelling van de voorgeschreven ART, het optreden van bijwerkingen, de viral load respons, de wijze van bevalling en de HIV-status van het kind. De verkregen data werden statistisch bewerkt met een Pearson Chi-squared test.

Resultaten

267/420 geïdentificeerde zwangere vrouwen werden geincludeerd. De gemiddelde leeftijd bedroeg 28 jaar. Een kwart van de vrouwen gebruikte ART tijdens de conceptie, 75% was ART naïef. Het merendeel van de ART-naieve vrouwen startten ART tussen de 21ste en 28ste week van de zwangerschap, en gebruikten dit gemiddeld gedurende 13.3 weken (1-29).
De twee meest gebruikte ART regimes bevatten Nelfinavir (NFV,57%) of Nevirapine (NVP,31%). Een of meer gastro-intestinale bijwerkingen werden significant vaker in NFV groep (20% versus 2%) geobserveerd. Huiduitslag trad op bij 6 van de 58 naieve NVP gebruiksters (10%), terwijl geen van de 128 naieve NFV gebruiksters dit rapporteerden. Leverfunctiestoornissen werden vaker in de NVP groep(22%) dan in de NFV groep (5%) geobserveerd, en vaker in ART-naïeve dan in voorbehandelde patiënten (20% vs 9%). Het stoppen en switchen van ART tgv bijwerkingen bleek vaker noodzakelijk in de NVP groep (14%) dan in de NFV groep (5%). Er was geen verschil tussen de NFV en de NVP groep in het percentage vrouwen (83,5%) dat vóór de bevalling een plasma HIV-RNA <500 c/ml had. Ondanks dat hoge percentage werd er in 47% van de bevallingen een sectio verricht. De percentages prematuriteit, small en very small for gestational age bedroegen 13,9%, 6,7% en 4%. Hierbij was er geen verschil tussen de NVP en de NFV groep. Twee kinderen (0,7%) bleken HIV geïnfecteerd te zijn. Drie zwangerschappen eindigden met een intrauterine

vruchtdood, twee kinderen overleden kort na de geboorte, waarvan één kind ten gevolge van congenitale afwijkingen, mogelijk geassocieerd met ART.

Conclusie

Het gebruik van NVP en NFV in ART-regiems wordt door HIV-geïnfecteerde zwangere vrouwen goed verdragen, is veilig en effectief. Hierbij wordt regelmatige controle van de leverfuncties geadviseerd. Het percentage verticale transmissie is <1%. Het percentage prematuriteit, small en very small for gestational age verschilt niet tussen de NVP en de NFV groep.

Prevalentie van resistentie onder nieuwe patiënten met de diagnose HIV infectie die via SHM worden gemonitord en naar het effect van resistentie bij aanvang van antiretrovirale therapie op het uiteindelijke behandelresultaat

Auteurs: F, de Wolf, Stichting HIV Monitoring, R. Schuurman UMC Utrecht

Goedkeuring adviesraad d.d.: 16-01-2003, uitvoering i.o.m. wg virologie

Conclusions of the 090903 meeting on studies to predict the distribution of HAART outcomes in populations of HIV-infected patients based on analysis of data obtained in ATHENA/HMF

Attendees

Jan Prins, Academic Medical Centre, Dept Internal Medicine, Amsterdam. Marijn de Bruin, Gezondheidswetenschappen, University of Maastricht. Joep Lange, Academic Medical Centre, Dept Internal Medicine, Amsterdam. Suzanne Juriaans, Academic Medical Centre, Dept Human Retrovirology, Amsterdam. Pythia Nieuwkerk, Academic Medical Centre, Dept Medical Psychology, Amsterdam. Marieke Tollenaar, Academic Medical Centre, Dept Medical Psychology, Amsterdam. David Burger, Dept of Clinical Pharmacology, University Medical Centre St Radboud, Nijmegen. Azra Ghani, Imperial College, Dept of Infectious Disease Epidemiology, London. Grace Kwong, Imperial College, Dept of Infectious Disease Epidemiology, London. Luuk Gras, HIV Monitoring Foundation, Amsterdam. Irene van Valkengoed, HIV Monitoring Foundation, Amsterdam. Ard van Sighem, HIV Monitoring Foundation, Amsterdam. Frank de Wolf, HIV Monitoring Foundation, Amsterdam.

1. Suzanne Jurriaans: Measurement of resistance of HIV to RT and protease inhibitors by using sequence analysis of the RT and protease gene is clinically available in the AMC. Measurement in the first sample taken from a new HIV positive patient is currently a standard procedure. Results over the first half of 2003 were presented showing 8% of the newly diagnose patients harbouring potentially resistant strains and >30% of the patients being infected with a non-B HIV-1 subtype.
2. Jan Prins: Measurement on (non-)adherence by using mems-cap appears is considered to be a relatively easy tool to monitor changes in drug intake. In the outpatient HIV clinic introduction of memscap for every new HIV positive patients will be prepared.
3. David Burger: Therapeutic drug monitoring is a relative simple and accurate tool for measurement of adherence as well, providing more objective information on reported drug intake and actual drug level. Is widely used clinically and provides direct information on the cause of therapy failure.
4. Azra Ghani: Memscap data are used for the modelling of the effect of adherence on therapy effect and for the determination of adherence patterns in a population. Therapeutic drug monitoring could provide the information needed to improve the accuracy of those adherence models.
5. Pythia Nieuwkerk: Measuring adherence by using (self-reporting) questionnaires is probably less useful for large scale population based research on the predictive value of various adherence patterns on therapy outcome in terms of suppression of viral replication and development of resistance.
6. Practically: data obtained by the HMF and the TDM data can be linked to each other.

Two projects will be initiated

a. A retrospective study on adherence and TDM, connecting the ongoing study of Pythia Nieuwkerk among the 600 ATHENA group of patients with the TDM work of David Burger. This study furthers to the first and similar study reported in the ATHENA final report as well as in Nieuwkerk PT, et al. Limited patient adherence to highly active antiretroviral therapy for HIV-1 infection in an observational cohort study. Arch Intern Med. 2001;161(16):1962-8. End-point data of the 600 group will be added to analyse the possible relationship between adherence measures, TDM measures and suppression of virus replication and development of resistance. Moreover, that dataset might be useful for parameterisation of mathematical models of development of resistance over time.
Pythia Nieuwkerk and David Burger will take the initiative to further develop a proposal. People involved are Suzanne Jurriaans for additional (already available) resistance data and Ard van Sighem and Azra Ghani for the m resistance modelling.

b. A prospective longitudinal study on the predictive value of adherence measures for therapy outcome. Is an initiative following the announcement of Jan Prins to introduce memscap as 'standard of care' in the HIV outpatient clinic of the AMC. Aim is to study adherence patterns and their predictive value for therapy outcome determined by level of virus suppression and development of resistance. In addition to memscap data obtained through TDM will be used as well. Jan Prins and Frank de Wolf will prepare a ZON-MW grant application. Pythia Nieuwkerk, David Burger, Suzanne Jurriaans, Ard van Sighem and Azra Ghani as well as Marijn de Bruin are involved in this study.

Finally, it was agreed to meet another time to follow-up progress in the preparation and execution of the two studies. Frank de Wolf will arrange and prepare that second meeting.

Verschillen in CD4+ T-lymfocyten respons bij patiënten op eerstelijns HAART therapie met een protease remmer of nevirapine

Differential CD4+ T cell response in HIV-1 infected patients using protease inhibitor or nevirapine based highly active antiretroviral therapy.

Auteurs: Frank van Leth[1], Ferdinand WNM Wit[1,2], Peter Reiss[1,2], JKM Eeftinck Schattenkerk[2], Marchina E van der Ende[3], Margriet ME Schneider[4], Jan W Mulder[5], PH Jos Frissen[6], Frank de Wolf[7], Joep MA Lange[1,2,8] — [1]International Antiviral Therapy Evaluation Center (IATEC), Amsterdam, The Netherlands. [2]Division of Infectious Diseases, Tropical Medicine, and AIDS, Department of Internal Medicine, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands. [3]Department of Internal Medicine, Erasmus Medical Center, University of Rotterdam, Rotterdam, The Netherlands. [4]Department of Acute Internal Medicine and Infectious Diseases, University Medical Center, University of Utrecht, Utrecht, The Netherlands. [5]Department of Internal Medicine, Slotervaart Ziekenhuis, Amsterdam, The Netherlands. [6]Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands. [7]HIV Monitoring Foundation, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands. [8]Department of Human Retrovirology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.

Goedkeuring adviesraad d.d.: 16-01-2003:

Objective

To study the dynamics of CD4+ T-lymphocyte counts (CD4 counts) after the initiation of either protease inhibitor (PI) or nevirapine (NVP) based first-line highly active antiretroviral therapy (HAART).

Design and methods

Retrospective cohort study of 1029 HIV-infected antiretroviral therapy-naive patients initiating either PI or NVP based HAART. Patients were censored as soon as they experienced virologic failure, or changed their original antiretroviral regimen for any reason.

Results

920 and 109 patients initiated PI or NVP based HAART, respectively. The patients in the PI group more often had AIDS (15% vs 6% in the NVP group), a lower median baseline CD4 count (234 vs 250 cells/mm^3 in the NVP group) and higher median baseline plasma HIV-1 RNA levels (pVL) (5.0 vs 4.7 log^{10} copies/mL in the NVP group). After 96 weeks of follow-up, the mean increase from baseline in the CD4 count, adjusted for baseline CD4 count, age, gender and baseline pVL was 310 cells/mm^3 in the PI group and 212 cells/mm^3 in the NVP group (p= 0.003). This difference was driven by the patients from the NVP group initiating HAART with a baseline CD4 count below 200 cells/mm^3. There were no differences between the PI and NVP groups with respect to the change in CD4 cells as a proportion of the total number of lymphocytes.

Conclusion

Patients successfully treated with NVP based HAART have a smaller increase in absolute CD4 cells than those treated with PI based HAART.

Behandelresultaten van patiënten bij wie behandeling wordt gestart tijdens een primo-HIV infectie

Auteurs: J.M. Prins, Academisch Medisch Centrum, afdeling Inwendige Geneeskunde, F.P. Kroon, LUMC, afdeling Infectieziekten

Goedkeuring adviesraad d.d.: 15-04-2003

Op aangeven van de behandelaren zelf en middels selectie op SHM database gegevens is een voorlopige dataset gecreëerd. Na een initiële survey van deze data en logistiek regelen van eea. is sinds augustus dit jaar begonnen met de eerste stap waarmee zo goed mogelijk getoetst wordt welke patiënten aan de inclusiecriteria voldoen. Het gaat hierbij om onzekerheden in de datum van laatste HIV-negative test en eerste HIV-positieve test weg te nemen of te bevestigen. Voor ruim 200 patiënten is inclusie hierdoor nog onzeker. Een groep patiënten ter grootte van 280 mensen kon op basis van de reeds beschikbare gegevens al worden geïncludeerd.

Naar verwachting zal het controleren van patiëntengegevens en daarmee samenhangend de in-, en exclusie van patiënten in het 4e kwartaal 2003 worden voltooid. Vervolgens zal statusonderzoek plaatsvinden, omdat een aantal relevante gegevens niet door SHM verzameld wordt. Analyse van de definitieve dataset, en de eerste resultaten worden 2e kwartaal 2004 verwacht.

A non-randomized, single-arm, prospective, observational study to evaluate the efficacy and safety of discontinuing successful antiretroviral combination therapy in patients who initiated antiretroviral therapy with CD4+ T-cell counts above 350 cells/mm^3

Auteurs: K. Pogany, IATEC, J.M. Prins, Academisch Medisch Centrum, afdeling Inwendige Geneeskunde

Goedkeuring adviesraad d.d.: 16-01-2003

De Triestan studie is een niet-gerandomiseerde, tweearmige, prospectieve, observationele studie ter evaluatie van effectiviteit en veiligheid van het staken van succesvolle antiretrovirale therapie (HAART) bij patiënten die met CD4+ T-cel aantallen hoger dan 350 cellen/mm^3 gestart zijn met antiretrovirale therapie.

De eerste arm bestaat uit de patiënten die voldoen aan de inclusie criteria en stoppen met HAART. De tweede arm fungeert als controle groep en bestaat uit de patiënten die ook voldoen aan de inclusie criteria maar besluiten HAART te continueren. De eerste groep wordt vervolgd gedurende de tijd dat het mogelijk is de therapie te discontinueren. Indien opnieuw HAART gestart moet wordt, worden zij vervolgd

worden tot hun HIV-RNA weer ondetecteerbaar is. De tweede groep wordt gedurende 1 jaar vervolgd.

Op dit moment zijn er 8 centra gestart met het includeren van patiënten en bij 6 centra ligt de aanvraag bij de MEC. Vanaf april 2003 tot eind september hebben wij 23 patiënten geincludeerd. Hiervan zijn 18 patiënt gestopt met hun medicatie. Tot nu toe heeft geen een patiënt de medicatie moeten hervatten.

Prognosis of HIV-1-infected patients starting highly active antiretroviral therapy: a collaborative analysis of prospective studies

Auteurs: Matthias Egger[a], Margaret May[b], Geneviève Chêne[c], Andrew N Phillips[d], Bruno Ledergerber[e], François Dabis[c], Dominique Costagliola[f], Antonella D 'Arminio Monforte[g], Frank de Wolf[h], Peter Reiss[h], Jens D Lundgren[i], Amy C Justice[k], Schlomo Staszewski[l], Catherine Leport[m], Robert S Hogg[n], Caroline A Sabin[d], M John Gill[o], Bernd Salzberger[p], Jonathan A C Stern[e] and ART Cohort Collaboration1[b]

Goedkeuring adviesraad d.d.: 16-01-2003

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Background

Insufficient data are available from single cohort studies to allow estimation of the prognosis of HIV-1 infected, treatment-naive patients who start highly active antiretroviral therapy (HAART). The ART Cohort Collaboration, which includes 13 cohort studies from Europe and North America, was established to fill this knowledge gap.

Methods

We analysed data on 12574 adult patients starting HAART with a combination of at least three drugs. Data were analysed by intention-to-continue-treatment, ignoring treatment changes and interruptions. We considered progression to a combined endpoint of a new AIDS-defining disease or death, and to death alone. The prognostic model that generalised best was a Weibull model, stratified by baseline CD4 cell count and transmission group.
Findings During 24310 person-years of follow up, 1094 patients developed AIDS or died and 344 patients died. Baseline CD4 cell count was strongly associated with the probability of progression to AIDS or death: compared with patients starting HAART with less than 50 CD4 cells/L, adjusted hazard ratios were 0·74 (95% CI 0·62–0·89) for 50–99 cells/L, 0·52 (0·44–0·63) for 100–199 cells/L, 0·24 (0·20–0·30) for 200–349 cells/L, and 0·18 (0·14–0·22)

for 350 or more CD4 cells/L. Baseline HIV-1 viral load was associated with a higher probability of progression only if 100000 copies/L or above. Other independent predictors of poorer outcome were advanced age, infection through injection-drug use, and a previous diagnosis of AIDS. The probability of progression to AIDS or death at 3 years ranged from 3·4% (2·8–4·1) in patients in the lowest-risk stratum for each prognostic variable, to 50% (43–58) in patients in the highest-risk strata.

Interpretation The CD4 cell count at initiation was the dominant prognostic factor in patients starting HAART. Our findings have important implications for clinical management and should be taken into account in future treatment guideline.

Prognostic importance of initial response in HIV-1 infected patients starting potent antiretroviral therapy: analysis of prospective studies

Auteurs: Matthias Egger, and The Antiretroviral Therapy (ART) Cohort Collaboration (zie boven)

Goedkeuring adviesraad d.d.: 16-01-2003

Background

We examined whether the initial virological and immunological response to highly active antiretroviral treatment (HAART) is prognostic in patients with HIV-1 who start HAART.

Methods

We analysed 13 cohort studies from Europe and North America including 9323 adult treatment-naive patients who were starting HAART with a combination of at least three drugs. We modelled clinical progression from month 6 after starting HAART, taking into account CD4 count and HIV-1 RNA measured at baseline and 6 months.

Findings

During 13408 years of follow-up 152 patients died and 874 developed AIDS or died. Compared with patients who had a 6-month CD4 count of fewer than 25 cells/L, adjusted hazard ratios for AIDS or death were 0·55 (95%CI 0·32–0·96) for 25–49 cells/L, 0·62 (0·40–0·96) for 50–99 cells/L, 0·42 (0·28–0·64) for 100–199 cells/L, 0·25 (0·16–0·38) for 200–349 cells/L, and 0·18 (0·11–0·29) for 350 or more cells/L at 6 months. Compared with patients who had a 6-month HIV-1 RNA of 100000 copies/mL or greater, adjusted hazard ratios for AIDS or death were 0·59 (0·41–0·86) for 10000–99999 copies/mL, 0·42 (0·29–0·61) for 500–9999 copies/mL, and 0·29 (0·21–0·39) for 6-month HIV-1 RNA of 500 copies/ mL or fewer. Baseline CD4 and HIV-1 RNA were not associated with progression after controlling for 6-month concentrations. The probability of progression at 3 years ranged from 2·4% in the patients in the lowest-risk stratum to 83% in patients in the highest-risk stratum.

Interpretation

At 6 months after starting HAART, the current CD4 cell count and viral load, but not values at baseline, are strongly associated with subsequent disease progression. Our findings should inform guidelines on when to modify HAART.

Verschillen in het beloop van de HIV infectie en de behandelresultaten van allochtone patiënten en autochtone patiënten

Auteurs: M.M.E. Schneider, UMC Utrecht, Sectie Infectieziekten en AIDS

Goedkeuring adviesraad d.d.: 15-04-2003

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Onderzoek naar transmissie van resistentie en non-B subtypen

Auteurs: R. Coutinho, GGGD Amsterdam, F. de Wolf, Stichting HIV Monitoring

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Verschillen in therapie respons bij patiënten op AZT of d4T bevattende eerste-lijns HAART regimes

Auteurs: F. Wit, J. Lange, International Antiviral Therapy Evaluation Center (IATEC), Amsterdam

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