Table of Contents

HIV treatment centres

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Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, Locatie Jan van Goyen Kliniek

Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, Locatie Oosterpark

Onze Lieve Vrouwe Gasthuis (OLVG), Amsterdam, Locatie Prinsengracht

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Sint Lucas Andreas Ziekenhuis, Amsterdam

VU Medisch Centrum, Amsterdam

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Universitair Medisch Centrum Groningen (UMCG), Groningen

Kennemer Gasthuis, Haarlem, Locatie EG

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Introd

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Frank de Wolf

This scientific report for 2005 is the fourth annual update on HIV and AIDS in the Netherlands to appear since the HIV Monitoring Foundation (HMF) was appointed by the Dutch Minister of Health, Welfare and Sport in 2002. As the executive organization for the monitoring of HIV in the Netherlands, HMF has 23 collaborative HIV Treatment Centres throughout the country and collects data from HIV-infected patients that are seen regularly by HIV/AIDS-treating physicians.

HMF's mission is to study the natural history of HIV infection and the effects of treatment and to further knowledge and understanding of HIV epidemiology and the course of HIV infection in both treated and untreated patients.

A primary activity through which HMF seeks to achieve this goal is to make data available to other groups involved in HIV-related research. Consequently, an accurate and periodically updated description of the HIV-infected population from which HMF collects data is of great importance. This annual report provides that comprehensive description. Since the population under study is not static, the report also addresses the dynamics of change in the course of the infection and epidemic that result from the large-scale, lifetime treatment of HIV.

Treatment with highly active antiretroviral therapy (HAART) of large groups of infected individuals started in the Netherlands in 1996, when inhibitors of the HIV protease gene became available for routine clinical use. Since then, the number of drugs used to suppress virus production to very low levels has increased, although the number of drug classes remains limited. HAART has an impressive impact on the course of both individual infection and the epidemic. Fewer infected people suffer disease or death from AIDS when effective treatment begins before deterioration of the immune system occurs. Mortality and morbidity amongst all groups of HIV-infected individuals have decreased, and transmission of HIV has slowed down.

However, the downside of HAART is the existence of large and ever-growing groups of chronically infected patients who need lifetime treatment with antiretroviral drugs and are, consequently, under the continuous threat of developing serious side effects of treatment as well as resistance to the drugs. In the long run, the success of HAART will result in a larger group of HIV-infected people that live longer and might again increase the transmission of HIV, despite the low levels of virus particles circulating in treated individuals.

In the present monitoring report, we discuss HAART-related issues including:
- The long-term effect of HAART - Chapter 10;
- The effect of particular HAART regimens on markers for cardiovascular complications of treatment, such as cholesterol and triglyceride plasma levels - Chapter 11;
- Regimen change after successful initial HAART to more simple and probably less toxic combinations of three nucleoside reverse transcriptase inhibitors (NRTI) - Chapter 12;
- The importance of transient low-level virus production under HAART for the outcome of HIV infection - Chapter 13;
- The prevalence and incidence of infection with strains of HIV which are resistant to one or more classes of antiretroviral drugs - Chapter 15.

The report also offers an updated description of the HIV-infected population in the Netherlands, presenting new data on:
- Changes over time in the HIV-infected subpopulation of immigrants and especially the four large groups originating from the Netherlands Antilles, Suriname, Ghana, and Cape Verde - Chapter 7;
- The population of infected patients that have survived despite being infected with HIV for a long period of

time, in some cases more that 20 years - Chapter 8;
- The baseline characteristics of the population of HIV-infected children in the Netherlands - Chapter 9.

A crucial prerequisite for the analyses of the data of the ATHENA national observational cohort is to maximize the quality of the data collected on individual patients by individual physicians in our many HIV Treatment Centres[1-5]. This report therefore begins with a chapter on the quality control of HMF data (Chapter 4). With the growing number of patients included and the resulting steady increase in data, comparison of all collected data against the source documents is not feasible. However, evaluation of data entry errors can provide further insight into the quality of collected data and the pitfalls of data entry procedures[4, 5]. Optimisation of these procedures is of great importance in order to achieve and maintain high data quality[1, 4]. An example, described in Chapter 4, is the direct importation of authorized laboratory data from laboratory databases, which already has replaced manual entry at one of our Centres.

The effect of patient characteristics on the frequency of follow-up visits and measurements of CD4 cell count and virus load is addressed in Chapter 6. Frequency is an issue that must be considered when analysing observational data, especially when end-points are used that predict more definitive outcomes such as AIDS and death. Measurement frequencies may influence the outcome substantially and, since we deal with data that are collected as part of patient care, frequencies will differ amongst patients, treating physicians, and HIV treatment centres. Chapter 6 discusses the effect of patient characteristics on follow-up and measurement frequencies.

The HMF participates in the Anti-Retroviral Therapy Cohort Collaboration (ART-CC), which encompasses more than a dozen observational cohorts from various European countries, the US, and Canada. The data used are obtained from patients starting HAART without any previous experience with antiretroviral drugs. The aim of ART-CC is to investigate early markers for the effect of HAART, an effort that requires large numbers of patients, especially when long-term follow-up is not available. An ART-CC collaborator recently showed that the substantial post-HAART decrease in AIDS-defining events was most pronounced for events with a viral aetiology and less so for those with a bacterial and especially a fungal aetiology[6].

HMF participates in a number of studies in addition to those connected to ART-CC. Currently the most important is the Data Collection on Adverse Events of Anti-HIV Drugs (DAD), a study on the cardiovascular complications that might be related to the use of combinations of antiretroviral drugs. Lastly, there is the long-standing collaboration with the Department of Infectious Disease Epidemiology of the Medical Faculty of Imperial College in London. Its focal point is the development of new analytical and mathematical models to apply to observational data and thereby to sharpen analysis of the impact of antiretroviral treatment on the epidemic of HIV in Western Europe.

The work of the HMF basically depends on the collaboration between AIDS-treating physicians in the HIV Treatment Centres throughout the Netherlands and the HMF staff employed specifically to collect the data. These so-called data collectors are on site at the Centres and transmit data to the national HMF database. The quality of the data is controlled for by data monitors. The HMF analysis unit is essential in the execution of its registration and research programmes and its support of groups who have approval to use data from the ATHENA-HMF dataset. The clinical and the virological working groups of the HMF meet regularly and, together with its Advisory Board, they guide the HMF director and governing board on policy matters as well as the usage of the data collected.

In addition to participating in the monitoring program, the groups providing data to HMF also conduct clinical research. For example, the effect of antiretroviral therapy is studied in specific populations, such as HIV-2-infected patients[7] and HIV-1-infected pregnant women[8]. Studies are in progress on TBC co-infection with HIV, differences in response to HAART between indigenous and non-indigenous patients in the Netherlands, the effect of antiretroviral treatment on primary HIV infection, the role of triple NRTI in first-line treatment, the effects of treatment interruption, and the characteristics of different HAART combinations.

As of 1 June 2005, the total number of HIV-infected patients included in the HMF programme is 10,854. The number is still increasing although the pace is slowing. HIV-infected children are now actively monitored. Almost 80 percent of all HMF-registered patients are treated with HAART.

Despite this progress, three areas of HIV monitoring still need a lot of attention. The high percentage of patients that are treated with HAART is not matched by the reporting of resistance data. Underreporting of data that should be collected can cause individual patients to commence therapies that might be contraindicated by such data. Substantial underreporting can also result in less reliable population-wide resistance figures.

The registration of death and especially the causes of death likewise needs to improve, such that HIV-related causes can be more accurately distinguished from other causes. A protocol has been developed, and its implementation will start in the beginning of 2006.

Finally, there is a need to know more about the genetic background of HIV-infected patients in order to explain not only differences in the immune response to HIV but also differences in the response to antiretroviral therapy. National and international initiatives to study host genetics in HIV patients are currently being developed.

Sum

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Frank de Wolf

Baselines

Patient numbers, median follow-up, and geographic distribution

As of 1 June 2005, the HIV Monitoring foundation had monitored in total 10,854 patients with 69,771 person-years of follow-up. Together they form the ATHENA national observational cohort on HIV, encompassing 8326 men (76.7%) and 2432 women (22.4%) 13 years of age or older as of 1 June 2005; 96 of the patients (0.9%) are younger than 13 years. Of the total population, 96.9% is infected with HIV-1.

Of adult women, 66% were diagnosed with HIV at an age between 18 and 34 years; 70.2% of the adult men were diagnosed between 25 and 44 years. Women were diagnosed with HIV at the median age of 30 years and were significantly ($p<0.0001$) younger than men at diagnosis, whose median age was 35.9.

The median follow-up of the study population was 5.4 years: for men 5.8 and for women 4.2 years. The median time between healthcare visits was 91 days; between plasma viral load and CD4 measurements, the median was 92 days. Visits and measurements became less frequent after 1998 and differed amongst transmission risk groups, the intervals being longer for drug users than for homosexual men. In addition, frequency was associated with new CDC-C events and with the results of previous CD4 cell and HIV-RNA measurements. Finally, frequencies differed amongst HIV treatment centres.

The western part of the Netherlands, including Amsterdam, Rotterdam, Utrecht, and The Hague, still harboured the majority of the known HIV-infected population in the Netherlands: currently 75.6 percent.

Since 2002, the number of new HIV diagnoses seems to have stabilised at around 800 per year; the number for 2005 is still incomplete, due to a backlog in HMF registration. The relative distribution of HIV-infected men and women per year of diagnosis has changed from 85% men and 15% women in 1990 to 70% men and 30% women in 2003. Interestingly, gender distribution changed again after 2003: 75% of the new HIV diagnoses were men in 2004, and 77% in 2005.

The median HIV-RNA plasma level at diagnosis was 4.8 log copies/ml. Per year of diagnosis, a steady decline was found, with 1996 levels being 4.8 log copies/ml and 2005 levels being 4.6. The levels measured in women, at median 4.4 log copies/ml, were significantly ($p<0.0001$) lower than levels in men, at median 4.9.

The median CD4 cell number at diagnosis was 290 cells/mm^3. For women, it was 300 and for men, 288. Median CD4 cell count at diagnosis improved over time, from 260 cells/mm^3 in 1996 to 310 cells/mm^3 in 2005.

HIV-infected children

HMF registration of children – patients below 13 years of age at diagnosis – began in 2004, and 96 such patients are now included. Their median age at HIV diagnosis was 0.8 years. The median current age was 6.5 years. Median HIV-RNA plasma levels at diagnosis were 5.4 log copies/ml, which is high compared to adults. Median CD4 cell count in children at diagnosis was 1010 cells/mm^3.

Pregnant women

Amongst 661 of the women diagnosed with HIV, 847 pregnancies were registered. Of the pregnant women, 97% were diagnosed before their first pregnancy or a maximum of 3 months into that pregnancy. In the remaining 3%, HIV was diagnosed more than 9 months after the date pregnancy was first registered. The pregnant women had a median age of 26 at HIV diagnosis, a median HIV-RNA level of 4.0 log copies/ml, and a median CD4 cell count of 340 cells/mm^3. HAART was

initiated before the first registered pregnancy in 26%, during pregnancy in 44%, and after the first pregnancy in 23%. In 16% of the total (661), the duration of at least one pregnancy was less than 26 weeks. Amongst pregnant women, transmission of HIV was predominantly heterosexual (93%), and the majority were from sub-Saharan Africa (61%).

Antiretroviral treatment: HAART and pre-HAART

In the ATHENA observational cohort, 80.2% of the patients are currently registered as being treated with HAART. Of these, 21% have pre-HAART antiretroviral drug experience and 59.2% do not. A small fraction of 1.3% is still using ART drug combinations that do not fit the HAART definition. The remaining 18.5% of the patients are not treated with any antiretroviral drug.

Those receiving no antiretroviral treatment were clinically well. Compared to CD4 cell numbers and RNA levels found at diagnosis amongst the HAART- and ART-treated patients, the non-treated patients had high CD4 cell numbers and low HIV-RNA levels at diagnosis. This indicates that they were infected more recently and were thus ineligible for HAART, according to current national guidelines.

Zidovudine in combination with lamivudine was still the most frequently used NRTI backbone. It was used in the first HAART combination given to ART-naïve patients, of whom 52.4% received this combination as part of their initial treatment. Lopinavir boosted with ritonavir and efavirens have been the most frequent addition to this backbone. Since 2003-2004, the combination of tenofovir and lamivudine has slowly increased to 29.4% of the initially prescribed HAART regimens in 2004-2005. Emtricitabine together with tenofovir is emerging rapidly and now figures in 6.9% of the HAART regimens used.

HCV co-infection with HIV

The HCV status was known for 7951 patients (75.6%), of whom 839 (10.6%) were HCV-positive. HCV prevalence was highest amongst intravenous drug users – 94.9% of 435 patients ($p<0.001$) – and did not differ between male and female drug users. In the population infected with HIV through heterosexual contact, the HCV prevalence was 5.1% in both men and women. Their HCV prevalence was higher than amongst homosexual men, of whom only 3.0% of 4274 patients were HCV-positive. HCV was more prevalent amongst men infected with HIV through blood-blood contact (42.7%) and amongst men and women for whom the infection route was unknown: 16.1% for men and 61.0% for women, respectively.

Trends over time

Homosexual men

Between 2000 and 2004, the number of homosexual men newly diagnosed with HIV increased from 326 per year to 455 per year ($p<0.0001$). The majority of these homosexually-infected men, 4080 (74.1%), were of Dutch origin. Median CD4 cell counts found in the newly infected patients, per year of diagnosis, increased from 250 in 1996 to 370 in 2005 ($p<0.0001$), whilst RNA levels slightly decreased ($p=0.007$) from 4.8 in 1996 to 4.7 in 2005.

In patients of Dutch origin, the median age at diagnosis, 38.7 years, was higher than in homosexual patients from other regions, 33.8 years ($p<0.0001$). It increased over time from 36.3 years in 1996 to 38.8 years in 2005 ($p=0.002$).

For 1322 men (24.0%) in the study population, the HIV subtype could be determined. Of these, 97.4% were infected with subtype B. The annual proportion of homosexuals diagnosed with a subtype B virus did not change between 1996 and 2005.

Of men infected through homosexual contact, a majority (88%) was infected in the Netherlands. Of those born in the Netherlands, 96.7% were infected in the Netherlands, whilst the remaining patients were infected

largely in other Western European countries, in South/Southeast Asia, or in North America. Of the patients born outside the Netherlands, 58.8% were infected in the Netherlands and 35.9% in the region from which they originated. The proportion of patients born and/or infected in the Netherlands versus elsewhere did not change with time. Of the patients from the Antilles, 17.4% were infected there and 73.9% infected in the Netherlands; of the patients from Suriname, 14.9% got their HIV-infection in Suriname and 85.1% in the Netherlands.

Intravenous drug users (IDUs)

The group of patients infected by intravenous drug use consisted of 409 men and 152 women. Of the total, the majority (64.7%), was diagnosed in or before 1995; only 70 IDUs were diagnosed between 2000 and 2004. Most of the IDU population originated from the Netherlands (66.7%), other Western European countries (17.6%), Latin America (3.9%), and the Caribbean (0.9%). All the patients from the Caribbean originated from the Antilles, whilst 86% of the patients from Latin America were of Surinamese origin. No patients from Cape Verde or Ghana were registered in the HMF as being infected through drug use.

The majority of the patients infected through intravenous drug use were infected in the Netherlands (87.3%) or in other Western European countries (7.6%).

Of the IDU population, 3.2% were born in Central and Eastern Europe. The number of non-B subtypes in the IDU population remained very limited.

Heterosexually infected men and women

Of 3361 patients infected by heterosexual contact, 1373 were men (13.2% of the total infected population, 40.9% of the heterosexual subgroup), and 1988 were women (19.2% of the total and 59.1% of heterosexuals). Most patients were diagnosed in or after 1996. Between 2000 and 2004, the mean number of diagnoses was 146 for men and 226 for women, without a significant change over time.

The majority of the male population originated from the Netherlands (37.0%) or sub-Saharan Africa (35.9%), whilst 10.1% originated from Latin America and 5.5% from the Caribbean. In the female population, the most frequent region of origin was sub-Saharan Africa (49.0%). Only 24.8% originated from the Netherlands. The proportions of female patients from Latin America and the Caribbean were similar to those of male patients, being 9.5% and 5.8%, respectively.

Between 1996 and 2002, the proportion of annually diagnosed heterosexual patients originating from sub-Saharan Africa increased from 34.2% to 59.2% ($p<0.0001$). Thereafter, this proportion declined to 40.2% in 2005 ($p<0.0001$). In contrast, the proportion of patients originating from the Netherlands decreased from 39.2% in 1996 to 19.7% in 2002 ($p<0.0001$) and rebounded to 27.2% in 2005 ($p=0.03$).

Of the 2754 heterosexual patients diagnosed in or after 1996, 17.5% had an AIDS-defining (CDC-C) event at diagnosis. The proportion of patients presenting with AIDS declined from 22.8% in 1996 to 14.1% in 2005 ($p=0.003$).

The majority of the heterosexual patients (60.0%) was infected outside the Netherlands. Only 42.3% of the men and 38.5% of the women were infected within the Netherlands. Of those born elsewhere, 70.0% of the men and 75.5% of the women were infected in the region from which they originated. Of the combined male and female patients from the Netherlands Antilles and Aruba, 55.5% were infected in the home country, as were 32.1% of the patients from Suriname, 79.7% from Ghana, and 16.7% from Cape Verde. Of patients from these regions infected in the Netherlands, there were

39.1% from the Antilles/Aruba, 64.7% from Suriname, 20.3% from Ghana, and 83.3% from Cape Verde.

In the HIV-infected heterosexual male population originating from the Netherlands (371 patients), 67.9% were infected in the Netherlands, 11.3% in sub-Saharan Africa, and 13.5% in South/Southeast Asia. Of the 400 women originating from the Netherlands, 85.8% were infected in the Netherlands, whilst 6.8% were infected in sub-Saharan Africa.

Although subtype B is the most prevalent countrywide, it was found in only 4% of the infections amongst the heterosexually infected patients from sub-Saharan Africa living in the Netherlands. The most prevalent subtypes in that subgroup were C (28%), AG (30%), and A (12%).

Long-term survivors

Of the total patients included in the HMF registration, 7622 were diagnosed with HIV before 1 January 2003 and were still alive on that date. Four groups were defined according to calendar year of diagnosis: 481 (6.3%) diagnosed before 1987, 2278 (29.9%) between 1988 and 1995, 3128 (41.0%) between 1996 and 2000, and 1735 (22.8%) after 2000.
Of patients diagnosed in or before 1987, 37.0% had experienced an AIDS- defining event. This proportion was 20.2% in the group of most recently diagnosed patients.

Amongst all patients still alive on 1 January 2003, 285 AIDS-defining events were recorded after 1 January 2003 during 14,784 person-years of follow-up, corresponding with an incidence of 1.93 events per 100 person-years. The incidence did not vary across the four diagnosis groups. Mortality after 1 January 2003 declined from 3.83 per 100 person-years in the group of patients diagnosed in or before 1987 to 0.95 per 100 person-years in the group of most recently diagnosed patients ($p<0.0001$).

When correction was made for age, mode of transmission, having experienced a CDC-C event before baseline, CD4 count, and RNA level, the progression to AIDS or death did not differ amongst the four diagnosis groups. Of the deaths recorded after 1 January 2003, 51% were scored as non-HIV-related and 32% as HIV-related; data was unavailable for the remainder. For patients diagnosed before 2000, 34% of deaths occurring after 1 January 2003 were HIV-related, in cases that could be scored. There was no difference in this proportion amongst the three main risk groups. Amongst patients most recently diagnosed, 70% deaths were HIV-related, a proportion significantly different from that in the other diagnosis groups ($p=0.001$). When considering progression to HIV-related death (i.e., by censoring deaths due to unknown or non-HIV-related causes), the four diagnosis groups did not differ.

Effect of HAART

Between 1 July 1996 and 31 December 2004, 7986 HIV-1-infected patients started HAART, of whom 1986 (25%) had received prior antiretroviral therapy. The probability of progression to death 8 years after the start of HAART in all patients was 13.0%, but it differed between pre-treated patients and therapy-naïve patients, being 19.0% and 9.3% ($p<0.0001$), respectively. The risk of an AIDS-defining event occurring within 8 years after the start of HAART was 16.4% and, like mortality, was significantly higher in pre-treated patients, being 20.1% as compared to the 14.2% in therapy-naïve patients ($p<0.0001$).

Death

Amongst therapy-naïve patients, 314 died during 24,074 person-years of follow-up. In multivariate analyses of time to death within 3 years after HAART initiation (14,271 person-years of follow-up, 208 deaths), patients initiating HAART with a CD4 cell count between 50-200 cells/mm^3 had a hazard ratio of 2.12 ($p=0.005$) as compared to patients with 200-350 cells/mm^3. There were no significant differences amongst patients with a baseline CD4 cell

count of 200-350 cells/mm^3, 350-500 cells/mm^3, and >500 cells/mm^3. Patients without a baseline CD4 cell count measurement were at an increased risk of death (p=0.01), as were patients without a baseline HIV-RNA measurement (p=0.03). There were no significant differences amongst the other strata of baseline HIV-RNA plasma levels. Older age, a CDC-C event prior to starting HAART, intravenous drug use as the HIV transmission route, and initiation of HAART in later calendar years were all associated with death. From 1996 to 2000, hazard ratios for death decreased, but they increased and were highest in 2003-2004. Inspection of the hazard of death over time per calendar year of starting HAART revealed that the differences in hazards were greatest in the first year after HAART initiation. Hazards were similar between 1 and 3 years after initiation.

CDC-C events

During follow-up, at least one new AIDS-defining event occurred in 546 therapy-naïve patients after they started HAART. Baseline characteristics which were univariately associated with a shorter time to a new AIDS-defining event after starting HAART were a low baseline CD4 count, a CDC-C event before HAART initiation, being infected through drug use, and originating from countries other than the Netherlands. All the variables univariately associated with the risk of AIDS remained significant in multivariate analyses of time to a new AIDS-defining event within 3 years after the start of HAART. The calendar year of HAART initiation was not significantly associated with the time to a new AIDS-defining event.

Markers of disease progression over time

In 5393 patients for whom the CD4 cell count was measured when HAART was started, the median CD4 cell count increased from 195 cells/mm^3 at the start of HAART to 360 cells/mm^3 at 48 weeks afterward. Five years after starting HAART, the median cell CD4 count was 500 cells/mm^3. The largest changes from baseline CD4 cell count were seen in those patients with a baseline value of <50 cells/mm^3. The median increase from baseline in these patients was 310 cells/mm^3. The changes in CD4 cell count from baseline that were observed at week 240 were smallest in those patients initiating HAART with ≥500 cells/mm^3; the median was 160 cells, a level not significantly different from the median count reached at week 96. Apart from the patients with baseline CD4 cell counts of 50-200 or 200-350 cells/mm^3, increases in CD4 cell count observed at week 240 differed significantly amongst the CD4 strata.

A significantly higher percentage of patients having baseline HIV-RNA concentrations of >100,000 copies/ml reached levels <50 copies/ml at week 240 than patients with concentrations of <10,000 copies/ml (81.5% versus 66.0%, p<0.0001). Amongst the 2558 patients who started with HAART before 30 June 2000 and achieved suppression of HIV-RNA levels to <500 copies/ml, 59.9% maintained HIV-RNA levels of <500 copies/ml during the first five years of follow-up. Again, this percentage was higher in those patients having higher baseline HIV-RNA plasma levels, being 62.1% in patients with >100,000 copies/ml and 58.1% in patients with 10,000-100,000 copies/ml at baseline, compared to 51.9% in patients with <10,000 copies/ml (p=0.07 and p=0.003, respectively).

Transient viraemia

In total, 4838 patients who started HAART had an initial therapy success, defined by two sequential HIV-RNA results <50 copies/ml. The total follow-up after success until the most recent RNA measurement was 11,856 person-years, including 2986 person-years for the 956 pre-treated patients (19.8%) and 8870 person-years for the 3882 treatment-naïve patients (80.2%).

During follow-up, 40,946 plasma viral load measurements were performed, corresponding with an average of 3.45 measurements per person-year of follow-up. In the treatment-naïve population, the incidence of viral

load measurements in the range of 50 to 1000 copies/ml was 0.22 per person-year; the incidence of measurements above 1000 copies/ml was 0.076 per person-year. In the pre-treated population, these incidences were higher ($p<0.0001$), being 0.33 and 0.10 per person-year, respectively.

Of the 40,946 RNA measurements, 9.5% were above 50 copies/ml, of which 7.1% were between 50 and 1000 copies/ml and 2.4% were above 1000 copies/ml. In total, 3303 patients (68.3%) persistently had a viral load below 50 copies/ml, whilst 1220 (25.2%) had one or more viral load measurements between 50 and 1000 copies/ml but never exceeding 1000 copies/ml, and 315 (6.5%) had at least one measurement exceeding 1000 copies/ml.

In the total population, there were 8974 periods of failure or success. The majority of the periods, 6730 (75.0%), were periods of success, whilst 1896 (21.1%) were marked with a mean viral load between 50 and 1000 copies/ml, and 348 (3.9%) had a viral load above 1000 copies/ml. Using the number of viral load measurements in each period of failure or success as markers of the duration of the period, we found that mean CD4 counts during periods of low-level viraemia that extended over three or more consecutive viral load measurements were lower than CD4 counts during periods of success ($p=0.01$). However, CD4 count was not affected during shorter periods of viral failure, commonly called "viral blips".

Mortality and morbidity

The average mortality was 1.83 deaths per 100 person-years. The mortality rate declined from 4.62 in 1996 to a level of 1.55 per 100 person-years after 2000. Thereafter, mortality did not change significantly over calendar time. In the therapy-naïve population, mortality was lower than in the pre-treated population, being 1.16 compared to 2.50 per 100 person-years after 2000.

In the total group, 957 AIDS diagnoses were registered after the start of HAART during 36,657 person-years of follow-up. From 1996 onwards, there was a monotonous decline from 15.4 AIDS diagnoses per 100 person-years in 1996 to 2.16 in 2000 and 1.43 in 2004. After 2000, AIDS incidence did not change significantly over calendar time. In the therapy-naïve population (23,538 person-years of follow-up), the incidence of AIDS after 2000 was similar to that in the pre-treated population (13,119 person-years of follow-up), being 1.84 and 1.69 per 100 person-years, respectively.

Transmission of drug-resistant virus

HIV-RNA was obtained from plasma samples taken from 251 patients shortly after the onset of primary infection, and the RT and protease genes were sequenced. Amongst these 251 so-called "recently infected" patients, resistance-associated mutations were found in 8.4%. For all HIV transmissions, the percentage of resistant virus strains per year of infection dropped from 24% in 1994 to 6% in 1996. Due to a limited number of recent infections, the percentage fluctuated thereafter between 0% and 15%. Overall, the percentage was 18% in patients infected in or before 1996 and 6.0% in patients infected thereafter.

For the first time in the ATHENA cohort, a recently infected patient was found to harbour a virus strain that was resistant to more than one drug-class. Infected in 2004, this patient harboured resistance mutations to all three drug-classes.

HIV-RT and protease sequences were obtained from viral RNA isolated from plasma sampled at HIV diagnosis in 644 patients. In these cases of new diagnosis, resistance was found in 5.9%. The majority of the resistant sequences were obtained in or after 2002. The annual percentage of transmissions of resistant virus strains varied between 0% and 8%. In 2003 and 2004, 25 (6.8%) transmissions of resistant virus were observed amongst the 366 new diagnoses of those two years. Resistance

was found more frequently amongst newly diagnosed homosexual men (8.4%) than amongst heterosexually infected men and women (3.3%; p=0.02). In one newly diagnosed patient, mutations conferring resistance to all three drug classes were found.

Resistance arising during treatment

The fraction of pre-treated patients on HAART who failed virologically declined from 39% in 1996 to 18% in 2005. During the same period, the failures amongst therapy-naïve patients on HAART increased from 7% in 1997 to 10% in 2005. In the group of pre-treated patients, the fraction of failing patients from whom a sequence was obtained increased from 11% in 1996 to 28% in 2003. More than 90% of these sequences harboured one or more resistance-associated mutations. In the therapy-naïve group, the failing patients for whom sequences were available increased from a few percent before 1998 to 24% in 2003. In the years after 2000, 80% to 85% of the sequences obtained from therapy-naïve patients harboured mutations.

As of 1 June 2005, a total of 9019 ATHENA patients were still in follow-up. In the case of 1025 (11.4%), a sequence had been obtained in which resistance-associated mutations were found. The number of patients found with resistance to only one drug class was 319 (35.4%). Resistance to two drug classes was found in 487 (54.0%), whilst 219 (24.3%) turned out to be resistant to three drug classes.

Samen

vatting

Frank de Wolf

Uitgangswaarden

Patiëntenaantallen, mediane follow-up en geografische spreiding

Per 1 juni 2005 heeft Stichting HIV Monitoring in totaal 10.854 patiënten gemonitord, die zijn geïnfecteerd met het humaan immuundeficiëntie virus (HIV), de verwekker van AIDS. Deze patiënten, met in totaal 69.771 persoonsjaren follow-up, zijn onderdeel van het nationale observationele ATHENA cohort voor de monitoring van HIV. Er worden in dit cohort 8326 mannen (76,7%) en 2432 vrouwen (22,4%) van 13 jaar of ouder gevolgd; 96 (0,9%) patiënten zijn jonger dan 13 jaar. Van de totale in ATHENA gevolgde populatie, is 96,9% geïnfecteerd met HIV type 1.

Zesenzestig procent van de volwassen vrouwen was tussen de 18 en 34 jaar op het moment dat de HIV-diagnose werd vastgesteld; 70,2% van de mannen was op dat moment tussen de 25 en 44 jaar. Vrouwen waren op het moment van de HIV diagnose 6 jaar jonger ($p<0,0001$) dan mannen.

De mediane follow-up van de studiepopulatie was 5,4 jaar; voor mannen 5,8 en voor vrouwen 4,2 jaar. Het aantal dagen tussen de polikliniekbezoeken was mediaan 91 en tussen plasma virusconcentratie en CD4 metingen 92 dagen. De bezoek- en meetfrequentie daalde sinds 1998 en verschilde per transmissierisicogroep. Vergeleken met homoseksuele mannen was de frequentie lager onder drugsgebruikers. Frequentieverschillen bleken geassocieerd met AIDS en met de resultaten van de voorafgaande CD4 cel en HIV-RNA metingen. Bovendien waren er frequentieverschillen tussen de HIV-behandelcentra.

De meeste HIV-geïnfecteerde patiënten wonen nog steeds in het westen van het land: 75,6 procent van de patiënten werd gemonitord in een van de HIV behandelcentra in Amsterdam, Rotterdam, Utrecht en Den Haag.

Sinds 2002 lijkt het aantal nieuwe HIV-diagnoses te zijn gestabiliseerd op 800 per jaar; het aantal registraties voor 2005 is nog onvolledig, ten gevolge van een achterstand in de registratie. De relatieve verdeling van HIV-geïnfecteerde mannen en vrouwen per diagnosejaar is veranderd van 85% mannen en 15% vrouwen in 1996 naar 70% mannen en 30% vrouwen in 2000. Interessant is dat de man-vrouw verdeling opnieuw veranderde na 2003. In 2004 was 75% van de nieuwe HIV-diagnoses man, toenemend tot 77% in 2005.

De hoeveelheid HIV-RNA in plasma bij diagnose was mediaan 4,8 log kopieën/ml. Geleidelijk aan nam per jaar van HIV diagnose de HIV-RNA concentratie af van 4,8 log kopieën/ml in 1996 tot 4,6 log kopieën/ml in 2005. De HIV-RNA concentraties in vrouwen waren mediaan 4,4 log kopieën/ml en significant ($p<0,0001$) lager dan die in mannen (mediaan 4,9).

Bij diagnose werden mediaan 290 CD4 cellen/mm^3 gemeten. Voor vrouwen was dit aantal 300 en voor mannen 288. Het CD4 cel aantal bij diagnose steeg over de jaren van 260 cellen/mm^3 in 1996 tot 300 cellen/mm^3 in 2005.

HIV-geïnfecteerde kinderen

De registratie van kinderen - patiënten jonger dan 13 jaar op het moment van de HIV-diagnose - begon in 2004 en momenteel zijn gegevens van 96 patiënten uit deze leeftijdsgroep in de database opgenomen. De leeftijd van deze kinderen op het moment van het stellen van de HIV diagnose was mediaan 0,8 jaar. Op dit moment is mediane leeftijd 6,5 jaar. De HIV-RNA plasma-concentratie bij diagnose waren hoog vergeleken bij die van de volwassenen: 5,4 log kopieën/ml. Het aantal CD4 cellen bij diagnose was 1010 cellen/mm^3.

Zwangere vrouwen

Er werden 847 zwangerschappen geregistreerd bij 661 HIV-geïnfecteerde vrouwen. Bij 97% werd de diagnose

HIV gesteld voor de eerste zwangerschap of maximaal drie maanden in de zwangerschap. In de resterende 3% werd de infectie met HIV meer dan 9 maanden na de datum van registratie van de zwangerschap vastgesteld. De zwangere vrouwen waren bij HIV-diagnose mediaan 26 jaar, met een HIV-RNA plasmaconcentratie van 4,0 log kopieën/ml en een CD4 cel aantal van 340 cellen/mm^3. HAART werd vòòr de eerste zwangerschap gestart in 26%, tijdens de zwangerschap in 44% en na de eerste zwangerschap in 23%. In 16% was de duur van tenminste één zwangerschap minder dan 26 weken. De transmissieroute bij zwangere vrouwen was overwegend (93%) heteroseksueel en 61% was afkomstig uit een Afrikaans land beneden de Sahara.

Antiretrovirale behandeling: HAART and pre-HAART

Tot medio 2005 werd in totaal 80,2% van de patiënten in het ATHENA observationele klinische cohort behandeld met HAART: 21% was voor de start van HAART al behandeld met antivirale middelen en 59,2% startte HAART zonder eerder te zijn behandeld. Behandeling met een combinatie van antivirale middelen die niet voldoet aan de definitie voor HAART, werd bij 1,3% van de patiënten toegepast. De overige 18,5% van de patiënten werd niet behandeld.

Die patiënten zonder antivirale behandeling waren klinisch gezond en hadden op het moment van HIV-diagnose, vergeleken met de met HAART of ART behandelde patiënten, een hoger CD4 cel aantal en een lage HIV-RNA plasma concentratie. Dit duidt er mogelijk op dat niet behandelde patiënten vrij recent zijn geïnfecteerd en – conform de huidige richtlijnen – nog niet in aanmerking komen voor behandeling met HAART.

Zidovudine plus lamivudine was nog steeds de meest gebruikte NRTI basis in de HAART combinatie van antiretrovirale middelen. Het werd gebruikt in de eerste HAART bij 52,4% van de antiretrovirale therapie-naïeve patiënten. Lopinavir plus ritonavir en efavirenz zijn de meest frequente toevoegingen aan de basis NRTI combinatie. Sinds 2003-2004 neemt de combinatie tenofovir en lamivudine als onderdeel van de eerst voorgeschreven HAART-regiems toe tot 29,4% in 2004-2005. Emtricitabine plus tenofovir neemt snel toe en maakt momenteel deel uit van 6,9% van de gebruikte HAART-regiems.

Co-infecties met HIV

Bij 7951 patiënten (75,6%) waren gegevens beschikbaar over de aanwezigheid van een co-infectie met hepatitis C virus (HCV); 839 (10,6%) daarvan bleken HCV-positief. De HCV-prevalentie was het hoogst onder intraveneuze drugsgebruikers (IVD) – 94,9% van 435 patiënten ($p<0,001$) – en er was geen verschil tussen mannelijke en vrouwelijke IVD-ers. In de door heteroseksueel contact met HIV geïnfecteerde populatie was de HCV-prevalentie voor zowel mannen als vrouwen 5,1 %. Deze prevalentie was hoger dan onder de homoseksuele mannen, van wie slechts 3,0% van 4274 patiënten HCV-positief was. HCV bleek meer voor te komen onder mannen die via bloed-bloed contact met HIV waren geïnfecteerd (42,7%) en onder mannen (16,1%) en vrouwen (16%) van wie de transmissieroute van HIV onbekend was.

Ontwikkelingen over tijd

Homoseksuele mannen

De meerderheid (74,1%) van de via homoseksueel contact geïnfecteerde mannen was van Nederlandse afkomst. Tussen 2000 en 2004 nam het aantal homoseksuele mannen waarbij HIV voor het eerst werd vastgesteld toe van 326 tot 455 per jaar ($p<0,0001$). Het aantal CD4 cellen gemeten op het moment van de HIV-diagnose nam per jaar toe van mediaan 250 in 1996 tot 370 in 2005 ($p<0,0001$). HIV-RNA plasma spiegels namen enigszins af van 4,8 in 1996 tot 4,7 in 2005 ($p=0,007$).

Homoseksuele Nederlandse mannen waren op het moment van de HIV diagnose mediaan 38,7 jaar en ouder

dan patiënten uit andere regio's, met een mediane leeftijd van 33,8 jaar ($p<0,0001$). In de loop der jaren steeg de leeftijd bij diagnose van 36,3 jaar in 1996 tot 38,8 jaar in 2005 ($p=0,002$).

Bij 1322 mannen (24,0%) werd het HIV-subtype bepaald en 97,4% van hen was geïnfecteerd met subtype B. Dat percentage veranderde niet tussen 1996 en 2005.

In meerderheid werden homoseksuele mannen geïnfecteerd in Nederland: 88,8%. Van de in Nederland geboren mannen werd 96,7% geïnfecteerd in Nederland. De overige patiënten werden geïnfecteerd in voornamelijk andere West-Europese landen, Zuidoost Azië, of in Noord-Amerika. Van de niet in Nederland geboren homoseksuele mannen werd 58,8% geïnfecteerd in Nederland en 35,9% in de regio van afkomst. In de loop der jaren veranderderde de verhouding van het aantal in Nederland geboren en/of geïnfecteerde mannen versus het aantal niet in Nederland geboren en/of geïnfecteerde mannen niet. Van de mannen uit de Nederlandse Antillen bleek 17,4% aldaar geïnfecteerd en was 73,9% geïnfecteerd in Nederland, terwijl van de mannen uit Suriname 14,9% werd geïnfecteerd in Suriname en 85,1% in Nederland.

Intraveneuze drugsgebruikers

De groep patiënten die door intraveneus drugsgebruik (IVD) werd geïnfecteerd, bestond uit 409 mannen en 152 vrouwen. Waarvan 64,7% in of voor 1995 bleek te zijn gediagnosticeerd. Slechts 70 IVD-ers werden gediagnosticeerd tussen 2000 en 2004. Het merendeel van de HIV-positieve IVD groep komt uit Nederland (66,7%) en andere West-Europese landen (17,6%); 3,9% komt uit Latijns Amerika en 0,9% uit het Caribische gebied. Alle patiënten uit het Caribische gebied waren Antillianen en 86% van de patiënten uit Latijns Amerika waren afkomstig uit Suriname. Geen van de uit Kaapverdië of Ghana afkomstige patiënten bleek geïnfecteerd via intraveneus drugsgebruik.

Regio of land van infectie was voor 87,3% Nederland en 7,6% een van de andere West-Europese landen.

Van de IVD-ers werd 3,2% geboren in Centraal of Oost-Europa. Het aantal non-B subtypes in de IVD-populatie bleef beperkt.

Heteroseksueel geïnfecteerde mannen en vrouwen

Van de 3361 door heteroseksueel contact geïnfecteerde patiënten waren er 1373 man (13,2% van de totaal geïnfecteerde populatie, 40,9% van de heteroseksuele subgroep) en 1988 vrouw (19,2% van het totaal en 59,1% van de heteroseksuele subgroep). De meeste patiënten werden gediagnosticeerd in of na 1996. Gemiddeld werd tussen 2000 en 2004 bij 146 mannen en 226 vrouwen HIV aangetoond. Er werd geen significante trend aangetoond over deze periode.

Van de mannelijke populatie was 37% afkomstig uit Nederland en 35,9% uit Afrikaanse landen beneden de Sahara; 10,1% was afkomstig uit Latijns Amerika en 5,5% uit het Caribische gebied. Van de vrouwen was 49,0% afkomstig uit een van de beneden de Sahara gelegen Afrikaanse landen. Slechts 24,8% was geboren in Nederland. Het percentage vrouwen uit Latijns Amerika en het Caribische gebied was vergelijkbaar met dat van bij de mannen, namelijk 9,5% en 5,8%.

Tussen 1996 en 2002 nam het percentage nieuwe HIV-diagnoses bij via heteroseksueel contact geïnfecteerde patiënten afkomstig uit Midden en Zuidelijk Afrika toe van 34,2% tot 59,2% ($p<0,0001$). Vanaf 2002 nam dit aandeel af tot 40,2% in 2005 ($p<0,0001$). Omgekeerd nam het percentage in Nederland geboren via heteroseksueel contact geïnfecteerde patiënten af van 39,2% in 1996 tot 19,7% in 2002 ($p<0,0001$) en vervolgens weer toe tot 27,2% in 2005 ($p=0,03$).

Van de 2754 in of na 1996 gediagnosticeerde heteroseksuele patiënten had 17,5% AIDS op het moment van

diagnose. Dat percentage patiënten met AIDS nam af van 22,8% in 1996 tot 14,1% in 2005 (p=0,003).

Zestig procent van de heteroseksueel besmette patiënten werd geïnfecteerd buiten Nederland. Slechts 42,3% van de mannen en 38,5 % van de vrouwen werd geïnfecteerd in Nederland. Van diegenen die buiten Nederland werden geboren, werd 70,0% van de mannen en 75,5% van de vrouwen geïnfecteerd in de regio van herkomst. Van de samengevoegde groep mannelijke en vrouwelijke patiënten afkomstig van de Nederlandse Antillen en Aruba werd 55,5% geïnfecteerd in de Antillen. Hetzelfde gold voor 32,1% van de patiënten uit Suriname, 79,7% uit Ghana, en 16,7% uit Kaapverdië. Van de in Nederland geïnfecteerde patiënten was 39,1% afkomstig van de Antillen of Aruba, 64,7% uit Suriname, 20,3% uit Ghana, en 83,3% uit Kaapverdië.

Van de in Nederland geboren 371 mannen die via heteroseksueel contact waren besmet werd 67,9% geïnfecteerd in Nederland, 11,3% in Midden en Zuidelijk Afrika en 13,5% in Zuid/Zuid-Oost Azië. Van de 400 in Nederland geboren vrouwen werd 85,8% geïnfecteerd in Nederland en 6,8% in Midden en Zuidelijk Afrika.

HIV-subtype B werd in slechts 4% van de via de heteroseksueel contact geïnfecteerde, in Nederland wonende patiënten afkomstig uit Midden en Zuidelijk Afrika gevonden. Meest prevalent in deze subgroep waren HIV-subtype C (28,8%), AG (30%) en A (12%).

Long-term survivors

Van de totale gemonitorde HIV-positieve populatie waren 7622 patiënten op 1 januari 2003 in leven en gegevens van deze groep werden gebruikt voor een eerste oriënterende studie naar de karakteristieken van die patiënten die al geruime tijd met HIV waren geïnfecteerd, de zogeheten long-term survivors. Vier groepen werden gedefinieerd, overeenkomstig het kalenderjaar van de HIV-diagnose: van 481 patiënten (6,3%) werd de diagnose gesteld voor 1987, 2278 (29,9%) tussen 1988 en 1995, 3128 (41,0%) tussen 1996 en 2000 en 1735 (22,8%) na 2000. Van de patiënten bij wie in of voor 1987 HIV werd vastgesteld had 37,0% AIDS doorgemaakt. Dit percentage nam af tot 20,2% in de groep van de meest recent gediagnosticeerde patiënten.

Bij patiënten die in leven waren op 1 januari 2003 werden na die datum 285 AIDS-diagnoses gesteld gedurende in totaal 14.784 persoonsjaren van follow-up. Er was geen verschil in de AIDS-incidentie tussen de verschillende diagnosegroepen. De mortaliteit na 1 januari 2003 nam af van 3,83 per 100 persoonsjaren in de groep van patiënten waarbij de HIV-diagnose voor 1987 was gesteld, tot 0,95 per 100 persoonsjaren in de groep van meest recent gediagnosticeerde patiënten ($p<0,0001$).

Na correctie voor leeftijd, wijze van transmissie, diagnose AIDS voor inclusie in de monitoring, CD4 cel aantal en HIV-RNA plasmaconcentratie, bleek er geen verschil tussen de vier diagnosegroepen ten aanzien van het krijgen van AIDS of overlijden. Van de sterfgevallen na 1 januari 2003 bleek 51% niet en 32% wel met HIV te zijn gerelateerd. Voor patiënten die voor 2000 werden gediagnosticeerd was dit 34%.

Effect van HAART

Tussen 1 juli 1996 en 31 december 2004 zijn 7986 HIV-1 patiënten gestart met HAART, van wie 1986 (25%) al eerder antiretrovirale therapie hadden gekregen. De kans om binnen 8 jaar na de start met HAART te overlijden was bij alle patiënten 13,0%, maar voorbehandelde patiënten hadden een hogere kans dan niet voorbehandelde (zogeheten therapie naïeve) patiënten, respectievelijk 19,0% en 9,3% ($p<0,0001$). Het risico op het krijgen van AIDS binnen 8 jaar na het begin van HAART was 16,4% en net als bij dood was het AIDS-risico significant hoger bij voorbehandelde patiënten (20,1%) in vergelijking tot therapie naïeve patiënten (14,2%; $p<0,0001$).

Sterfte

Van de therapie naiëve patiënten overleden 314 patiënten gedurende 24.074 persoonsjaren van follow-up. In multivariaat analyses naar het moment van overlijden binnen 3 jaar na het starten met HAART (14.271 persoonsjaren van follow-up, 208 sterfgevallen), hadden patiënten met een CD4 cel aantal tussen 50-200 cellen/mm^3 in vergelijking tot patiënten met 200-350 cellen/mm^3 een 2,12 maal hoger risico (HR) om te overlijden (p=0,005). Er waren geen significante verschillen tussen patiënten met CD4 cel aantallen bij start HAART tussen 200-350 cellen/mm^3, 350-500 cellen/mm^3, of >500 cellen/mm^3. Patiënten zonder een CD4 cel meting bij start HAART hadden een hoger risico (p=0,001), evenals patiënten zonder baseline HIV-RNA meting (p=0,003). Er waren geen significante verschillen onder de andere HIV-RNA strata. Hogere leeftijd, diagnose AIDS voorafgaand aan de start met HAART, intraveneus drugsgebruik als transmissieroute en begin met HAART in een later kalenderjaar, waren geassocieerd met sterfte. Van 1996 tot 2000 nam de sterftekans af, maar nam daarna weer toe en was het hoogst in 2003-2004. Verschillen in het sterfterisico bleken groter in het eerste jaar van behandeling met HAART, terwijl deze risico's hetzelfde waren tussen 1 en 3 jaar na de start met HAART.

AIDS

Na de start van de HAART-behandeling ontwikkelden 546 therapie naïeve patiënten tenminste één maal AIDS. Een laag CD4 cel aantal bij start van HAART, het doorgemaakt hebben van een AIDS-event voor de start met HAART, infectie via intraveneus drugsgebruik en geboren in een ander land dan Nederland bleken univariaat geassocieerd met de duur tot een nieuw AIDS-event na het starten van HAART. Alle univariaat geassocieerde variabelen bleken in een multivariaat analyse nog steeds significant. Het kalenderjaar waarin de HAART therapie werd gestart was gerelateerd aan de tijd tot AIDS.

Ziekteprogressie

Bij 5393 patiënten, waarbij CD4 cellen was gemeten op het moment dat HAART werd gestart, nam het aantal toe van mediaan 195 cellen/mm^3 tot 360 cellen/mm^3 na 48 weken behandeling. Vijf jaar na de start met HAART was het CD4 cel aantal toegenomen tot 500 cellen/mm^3. De grootste veranderingen werden waargenomen bij patiënten die met therapie begonnen met <50 CD4 cellen/mm^3. De toename vanaf baseline was bij deze patiënten mediaan 310 cellen/mm^3. De toename in het aantal CD4 cellen was na 240 weken het geringst (mediaan 160 cellen/mm^3) bij patiënten met ≥500 cellen/mm^3 bij start HAART. Dat aantal werd grotendeels bereikt 96 weken na start HAART en veranderde daarna niet significant. De toename van het aantal CD4 cellen sinds start HAART verschilde significant tussen de CD4 cel strata op het moment van de start van de HAART-behandeling, met uitzondering van de baselinestrata tussen 50 en200 en 200 en 350 cellen/mm^3.

Een significant lager aantal patiënten met baseline HIV-RNA concentraties van >100.000 kopieën/ml bereikten concentraties <50 kopieën/ml, in vergelijking met patiënten met concentraties van <10.000 kopieën/ml (66,0% vs. 81,5% in week 240, p<0,0001). Bij 59.9% van de 2558 patiënten die voor 30 juni 2000 begonnen met HAART en bij wie de HIV-RNA plasma concentratie daalde tot <500 kopieën/ml bleef dit zo gedurende de daaropvolgende vijf jaar. In 62,1% van de patiënten met >100.000 HIV-RNA kopieën/ml op baseline, 58,1% van de patiënten met een baseline concentratie tussen 10.000 en 100.000 kopieën/ml en bij 51,9% bij patiënten met <10.000 kopieën/ml bleef de HIV-RNA concentratie gedurende 5 jaar <500 kopieen/ml (respectievelijk p=0,003 en p=0,07).

Voorbijgaande viraemia (blips)

Therapiesucces, gedefinieerd als twee opeenvolgende

HIV-RNA plasma concentraties <50 kopieën/ml, werd behaald bij 4838 patiënten die met HAART begonnen. De follow-up na succes tot de laatste HIV-RNA meting was 11.856 persoonsjaren, met inbegrip van 2986 persoonsjaren voor de 956 voorbehandelde patiënten (19,8%) en 8870 persoonsjaren voor de 3882 therapie naïeve patiënten (80,2%).

Gedurende de follow-up werden 40.946 HIV-RNA metingen uitgevoerd, gemiddeld 3,45 metingen per persoonsjaar follow-up. In therapie naïeve patiënten bleek per persoonsjaar follow-up gemiddeld 0,22 keer HIV-RNA concentraties tussen 50 en 1000 kopieën/ml te worden gemeten en gemiddeld 0,076 maal HIV-RNA concentraties >1000 kopieën/ml. Bij voorbehandelde patiënten waren deze incidenties hoger ($p<0,0001$), respectievelijk 0,33 en 0,10 per persoonsjaar.

Van de 40.946 RNA-metingen was 9,5% hoger dan 50 kopieën/ml, 7,1% tussen de 50 en 1000 en 2,4% boven de 1000 kopieën/ml. Bij 3303 patiënten (68,3%) bleef de HIV-RNA plasma concentratie onder de 50 kopieën/ml, terwijl 1220 patiënten (25,2%) daar één of meer keren boven uitkwamen, maar nooit boven de 1000 kopieën/ml. 315 patiënten (6,5%) hadden minimaal één meting van meer dan 1000 HIV-RNA kopieën/ml plasma.

In de gehele populatie konden 8974 perioden van falen of succes worden onderscheiden: 6730 (75,0%) perioden van succes, 1896 (21,1%) met een HIV-RNA concentratie tussen 50 en 1000 kopieën/ml en 348 perioden (3,9%) met HIV-RNA concentraties boven 1000 kopieën/ml. Door het aantal HIV-RNA metingen in elke periode van falen of succes te gebruiken als marker voor de duur van een periode werd aangetoond dat het gemiddelde aantal CD4 cellen lager was gedurende perioden van drie achtereenvolgende HIV-RNA concentraties tussen 50 en 1000 kopieën/ml dan gedurende een succesperiode ($p=0,001$).

Mortaliteit en morbiditeit

De gemiddelde mortaliteit was 1,83 doden per 100 persoonsjaren. De mortaliteit nam af van 4,62 in 1996 tot een niveau van 1,55 per 100 persoonsjaren na 2000. Daarna veranderde de mortaliteit niet significant. Na 2000 was de mortaliteit in de therapie naïeve populatie 1,16 en in de voorbehandelde populatie 2,50 per 100 persoonsjaren.

Na de start met HAART werden gedurende 36.657 persoonsjaren follow-up 957 AIDS- diagnoses gesteld. Vanaf 1996 was er een continue afname van 15,4 tot 2,6 AIDS- diagnoses per 100 persoonsjaren in 2000 en 1,43 in 2004. Na 2000 veranderde de AIDS-incidentie niet significant meer. In de antiretrovirale therapie naïeve patiënten met in totaal 23.538 persoonsjaren van follow-up was de AIDS-incidentie na 2000 1,84 per 100 persoonsjaren, vergelijkbaar met de 1,69 per 100 persoonsjaren in de voorbehandelde populatie met in 13.119 persoonsjaren follow-up.

Transmissie van therapie-resistent virus

Uit plasmasamples van 251 patiënten afgenomen vlak na besmetting met HIV werd HIV-RNA geïsoleerd en werd het RT en protease gen gesequencet. In 8,4% werden aan resistentie gerelateerde mutaties gevonden. Dit resistentiepercentage daalde van 24% in 1994 tot 6% in 1996. Daarna fluctueerde, als gevolg van het beperkte aantal geregistreerde recente infecties, het percentage tussen de 0% en 15%. In de periode tot 1996 bleek 18% van het totale aantal recent geïnfecteerde patiënten besmet met resistent HIV en in de periode na 1996 6,0%.

Voor de eerste keer in het ATHENA cohort werd bij een recent geïnfecteerde patiënt HIV gevonden dat resistent bleek tegen zowel nucleoside HIV-RT remmers, niet-nucleoside RT-remmers en HIV-protease remmers.

Van 644 patiënten werden HIV-RT en protease sequenties verkregen uit viraal RNA geïsoleerd van plasma gesampled op het moment van de HIV-diagnose. In deze groep werd in 5,9% van de gevallen resistentie gevonden, in meerderheid in of na 2002. Het percentage nieuwe HIV-diagnoses waarbij resistent virus werd gevonden varieerde tussen 0% en 8% per jaar. In 2003 en 2004 werd bij 25 (6,8%) van 366 nieuwe diagnoses resistent virus aangetroffen. Van de nieuw gediagnosticeerde homoseksuele mannen bleek 8,4% besmet met resistent HIV tegen 3,3% van de heteroseksueel besmette patiënten (p=0,02). Bij één patiënt werd resistentie tegen drie klassen van antivirale middelen gedetecteerd.

Resistentie gedurende de behandeling

Virologisch falen tijdens behandeling met HAART nam af onder patiënten die al eerder met antivirale middelen waren behandeld van 39% in 1996 tot 18% in 2005. Gedurende dezelfde periode nam falen onder therapie naïeve patiënten toe van 7% in 1997 tot 10% in 2005. Van voorbehandelde patiënten waarbij therapie faalde, werd in 1996 in 11% en in 2003 in 28% een RT/protease sequentie verkregen. In meer dan 90% van deze sequenties werden een of meer resistentie gerelateerde mutaties gevonden. Onder therapie naïeve patiënten waarbij therapie faalde, nam het percentage van wie sequenties beschikbaar waren eveneens toe van een paar procent voor 1998 tot 24% in 2003. Na 2000 werd in 80% tot 85% van de sequenties resistentie geassocieerde mutaties gevonden.

Op 1 juli 2005 waren in totaal 9019 ATHENA patiënten nog steeds in de follow-up. In 1025 (11,4%) gevallen werd een HIV RT/protease sequentie verkregen waarin resistentie gerelateerde mutaties gevonden werden. 319 (35,4%) patiënten bleek besmet met HIV dat resistent was tegen één klasse antiretrovirale middelen. Resistentie tegen twee klassen werd gevonden bij 487 (54,0%) patiënten, terwijl bij 219 (24,3%) patiënten resistent HIV tegen drie klassen werd gedetecteerd.

Data c

quality

Continuing efforts to improve the quality of HIV monitoring data

Sima Zaheri

Introduction

Improving the quality of the data collected from HIV-infected patients participating in the ATHENA national observational cohort and stored in the HIV Monitoring Foundation (HMF) database is one of our main concerns. Quality control of data collection is a crucial element for all clinical research[1-5], including that of the HMF. With the steady increase of the number of included patients and, consequently, a steady increase in data, comparison of all collected data against the source documents is not possible. However, evaluation of data entry errors can provide further insight into the quality of collected data and the pitfalls of data entry procedures[4, 5]. Optimisation of data entry procedures is therefore of great importance in order to achieve and maintain high data quality[1, 4].

Data collection

Patient data (see Appendix 4.1) are collected for the HMF in 25 hospitals that are part of the 23 HIV Treatment Centres appointed by the Dutch Minister of Health. As of May 2003, the database is constructed in Oracle Clinical® (OC), a system designed for the data management of clinical trials and compliant with the guidelines of GCP and FDA. Its security is of outstanding quality, as it consolidates the management of all remote users and enhances the security of the network. OC provides highly sophisticated tracking and data cross-checking options and discrepancy checks for a quick resolution of queries, along with the capability of exporting data to analysis software packages such as SAS.

Data quality

To monitor quality, 'source data verification' of follow-up data is routinely conducted for a random 10% of the patients. In addition, efforts have been made to simplify the data abstraction methods in order to avoid data interpretation or assumption and thereby to upgrade accuracy. The ongoing efforts were described in our scientific report of 2004[9]. This year's developments include a programme of periodic and customised training for data collectors and an on-line-available protocol for HIV-defining events (per CDC) and other adverse events. The protocol includes a synonym list, guidelines to standardise documentation of diagnosis, tips for seeking related data/results, and tips for extraction of data from medical files.

The main development is an approach for uploading laboratory results directly from local laboratory data systems into the OC database, as an alternative to manual entry. This approach has been implemented at our largest participating centre (AMC), as summarised in the rest of this chapter.

Quality of laboratory data:

Comparison of the laboratory source database against manual data entry in OC at the largest participating centre (AMC)

Strategies were developed to replace the manual collection of laboratory results by 'direct uploading'[1] from hospital laboratory databases. In the Academic Medical Centre (AMC), one of the HIV treatment centres, manual data collection of laboratory results was recently replaced by an automated uploading procedure hereafter referred to as 'lablink'. Since lablink data overlap in part with data collected manually in OC, it was possible to evaluate the manual uptake, using lablink uptake as the "gold standard".

In this chapter we present results of a pilot study in which we compared OC data obtained through lablink and through manual data entry over a one-year period from 01/05/2003 to 01/05/2004. Five data items were chosen for comparison: plasma HIV viral load (VL), CD4 cell count (CD4), triglyceride (Tri), alanine transaminase (ALAT), and glucose (Glu) blood levels. Whereas data is collected on results of any measurement of viral load, CD4, and triglyceride, data on glucose and ALAT are collected only when results exceed a threshold of

5.6 mmol/L (Glu) and 135 mmol/L (ALAT). We were therefore able to evaluate whether the accuracy of data collection is influenced by the limitation of collecting data only above a threshold value.

Methods

Comparison of lablink data and the data manually entered in the OC database is shown in Figure 4.1. Records were selected on the basis of patient identification number (Pt), hospital code (Hosp), and a test date (Date) ranging from 01/05/03 to 01/05/04. A manually entered record was considered 'correct' if it had an identical lablink record for Pt, Date and Value. In the figure, the number of correct values is denoted as C.

Comparison as to Pt and Date in the lablink data versus the manually entered data within the given date window (DW) is represented in Figure 4.1 by the black stave. It contains records with correct dates and values (C) and records with correct dates but with incorrect values (I_V).

Lablink records within the date window (DW) that did not match as to Pt and Date with the manually entered records in the same date window (DW) ("lablink not in match") were assumed to be missing or to have an incorrect Date (Table 4.3). Furthermore, records manually entered in the database within DW that did not match for Pt and Date ("manual not in match") with lablink records were assumed to be 'extra' (e.g., results labelled with the wrong hospital code or patient identification number) or to have an incorrect Date. A comparison of "lablink not in match" (L_{nm}) against "manual not in match" (MA_{nm}) for Pt and Value yielded some records with incorrect dates (I_{d1}) (Table 4.3).

Manually entered records in the OC database with incorrect dates can be divided into three different groups:
I_{d1}: records within DW that match (Pt and value) the lablink records within DW.
I_{d2}: records within DW that match (Pt and value) lablink records outside DW.
I_{d3}: records outside DW that match lablink records within DW.
In addition, (I_{d1}+ I_{d2}) represents all records in the database within DW that were manually entered with an incorrect test date, and (I_{d1}+ I_{d3}) represents all lablink records within DW having an incorrect test date in the database.

To calculate I_{d2}, records in MA_{nm} were compared for Pt and value with records outside DW in lablink. I_{d3} was calculated by comparing L_{nm} with manually entered records outside DW.

For plasma viral load, comparison for Pt and Value was not performed for the 'undetectable' results, as they all share a value equal to 50. The total number of incorrect dates for the plasma viral load is therefore probably underestimated.

The number of missing records was calculated as $M = L_{nm} - (I_{d1}+ I_{d3})$. 'Extra' results that were manually entered in the database and did not appear in lablink were calculated as $E = MA_{nm}-(I_{d1}+ I_{d2})$. 'Extra' is included in the 'total' number of errors as given in Tables 4.1 and 4.2.

For glucose and ALAT, only values above the threshold were collected; thus values at or below threshold were not considered in the analysis. Only one value per day was collected (the maximum value), a factor taken into account in the analysis. Furthermore, to estimate the accuracy of the analysis, all comparisons were repeated for the half-year periods of 01/05/03–01/11/03 and 01/11/03–01/05/04. These estimates are indicated in Figure 4.2 as error bars.

Results

Table 4.1 represents the total number of correct, incorrect, and missing records for various lab results that were

manually entered in the OC database compared to the total number of records obtained by lablink within the period of May 2003 – May 2004. For glucose and ALAT, the total number of lablink records was based on above-threshold values and the maximum of one record per day. Incorrect records were divided into records with incorrect value and records with incorrect test date.

The number of incorrect values ranged from 0.6 to 1.1% for the five data collection items. The number of incorrect dates varied between 0.6 and 1.2%, with an average deviation of 32 days and a median deviation of 13 days. The number of missing records ranged between 10 and 29%.

In Table 4.2, the percentages of correct and incorrect records for the various laboratory results are shown relative to the total number of manually entered records in the OC database within the study period. Percentages in this table are corrected for the missing records and are considered to represent the quality of the collected data. The number of incorrect values and incorrect dates for the different data collection items ranged from 0.7 to 2.1% and from 0.6 to 1.2, respectively.

The number of incorrect values or dates did not vary widely for the different items, and most differences did not appear to be significant (Figure 4.2). However, the number of incorrect values for plasma viral load (VL) was significantly lower than the number of incorrect values for Tri and Glucose ($p<0.0001$). The number of missing items was substantially higher for glucose and ALAT than for the other items ($p<0.0001$).

Conclusions

Obviously, direct uploading from the hospital database instead of manual data entry of the laboratory results improved the quality of data. Nevertheless, the manually entered data contained inaccuracies to a maximum of 3%, which is a good result when compared to other collections of observational data related to HIV (The creation of a large UK-based multicentre cohort of HIV-infected individuals: The UK Collaborative HIV Cohort [UK CHIC] Study 115-24; Favalli et al. 1125-33; Warsi, White, and McCulloch 850-56). Our finding in 2005 is in accordance with the outcome of our 2004 analysis[9] and may indicate that the data entry checks programmed into the OC database have improved the quality of manual data entry.

The finding that missing records range from 10 to 29% was not unexpected. Although in some clinical trials the percentage of missing data is as low as 3.7%[3], more often the percentage is considerably higher[10]. Of particular interest is the impact of the percentage of missing data on the results of our data analyses. This effect was probably limited, as the overall frequency of missing items is normally distributed over many patients. The finding of more missing items for glucose and ALAT than for the other items suggests that the limitation of collecting data only above a certain threshold value may result in a larger number of missing records.

Finally, more detailed evaluation of missing and 'extra' records in the OC database can provide further insight into the optimisation of manual data entry procedures.

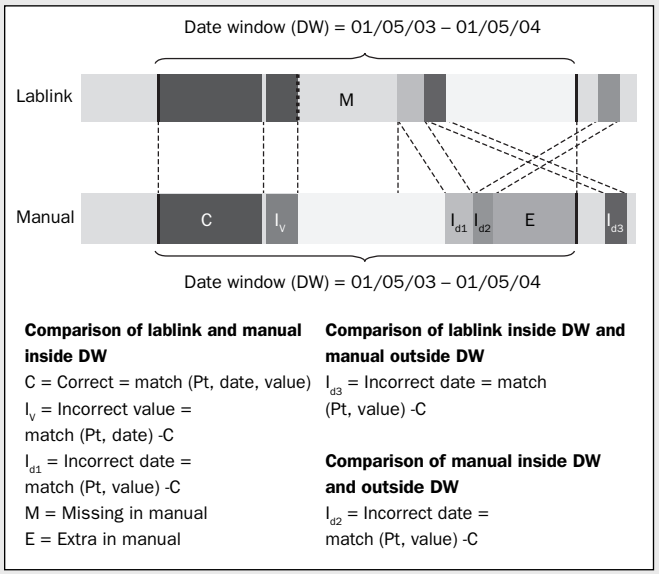

Figure 4.1: Schematic representation of the model used to determine incorrect and missing records. Details are explained in the Methods section.

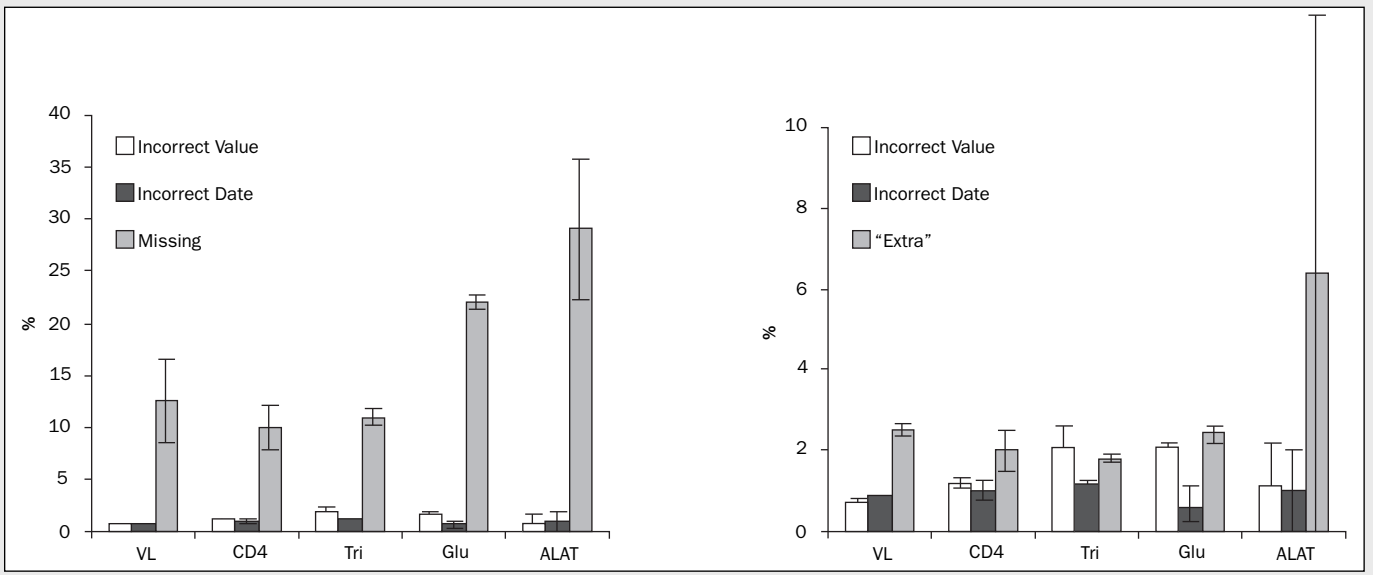

Figure 4.2: Left: Incorrect values, dates, and missing records (relative to lablink data). Right: Incorrect values, dates and 'extra' records (relative to manual entry).

	Viral Load		CD4		Triglyceride		Glucose		ALAT	
	N	%	N	%	N	%	N	%	N	%
Lablink	5316	100	5456	100	5370	100	1566	100	241	100
Correct (C)	4570	86	4791	88	4604	86	1181	75	169	70
Incorrect value (I_v)	34	0.6	62	1.1	105	1.9	26	1.7	2	1
Incorrect date (I_{d1}+ I_{d3})	43	0.8	49	0.9	62	1.2	10	0.6	2	1
Missing (M)	669	12.6	546	10	602	11	349	22	68	29
Total error	746	14	657	12	769	14	385	25	72	30

Table 4.1: Comparison between computerised and manual data collection.

	Viral Load		CD4		Triglyceride		Glucose		ALAT	
	N	%	N	%	N	%	N	%	N	%
Manual	4775	100	5002	100	4854	100	1245	100	185	100
Correct (C)	4570	96	4791	96	4604	95	1181	95	169	91
Incorrect value (I_v)	34	0.7	62	1.2	105	2.1	26	2.1	2	1
Incorrect date (I_{d1}+ I_{d2})	41	0.9	50	1	56	1.2	8	0.6	2	1
'Extra' records (E)	118	2.5	99	2	89	1.8	30	2.4	12	8
Total error	193	4.0	211	4.2	250	5.2	64	5.1	16	9

Table 4.2: Overview of correct and incorrect data in the manually entered part of the OC database.

	Viral Load	CD4	Triglyceride	Glucose	ALAT
	N	N	N	N	N
Match(Pt, Date)	4604	4853	4709	1207	171
Lablink not in Match (L_{nm})	712	595	664	359	70
Manual not in Match (MA_{nm})	159	149	145	38	14
Incorrect date within date window (I_{d1})	37	47	56	8	1

Table 4.3: Intermediate results used in the calculations of the data in Table 4.1.

Upon patient entry into the HMF database, the following information is collected:

Items collected upon initial enrolment for HIV-infected adults

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	
	Was the patient diagnosed with a primary HIV infection? (yes, no, most likely)	
HIV transmission	The most likely transmission route: homosexual heterosexual IDU blood and blood products during pregnancy/partum via breastfeeding other and unknown	For sexual transmission, the most likely transmission route is entered: either a steady sexual partner or multiple sexual contacts
	Country where the patient became infected	

Additional data for HIV-infected children

Demographic data	Nationality and country of birth of patient's parents
Family data	HIV status of patient's mother, father, brothers and sisters
Perinatal data	Pregnancy duration, way of birth, weight at birth, Apgar scores, cogenital defects, perinatal exposure to ARV therapy and co-medication, perinatal complications

Appendix 4.1(1)**:** data

After patient enrolment, clinical data are collected every time the patient is seen by his or her treating physician. These data contain the following information:

Items collected at every follow-up visit for HIV-infected adults

Clinical examination	Weight, blood pressure	
CDC events *Start and stop date and the status of event at current visit (ongoing: yes or no).*	HIV-related events as classified by CDC. Definition of diagnosis (possible, presumptive or definitive) are recorded using standard protocol	
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	Sexual dysfunction (loss of libido, erection failure)
	Myopathy	Alcohol or drug abuse
	Lactate acidosis	Non-CDC malignancies
	Hepatic cirrhosis	Diabetes mellitus
	Osteopenia / Osteoporosis	Myocardial infarction
	Hepatic steatosis	Hypertension
	Hepatic encephalopathy	Arrhythmia
	Pancreatitis	Stroke
	Nephrolithiasis	Coronary artery by-pass grafting
	Renal failure	Coronary angioplasty / stenting
	Lipodystrophy, fat loss in extremities	Carotid endarterectomy
	Lipodystrophy, central fat accumulation	Pregnancy
	Rash	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)*	Standard stop reasons are as follows:	
	Virological failure	Modification of the regimen
	Immunological failure	Plasma “ART” drug levels related
	Patient’s decision	Structured treatment interruption
	Toxicity	Newly available medication
	New CDC-B and or CDC-C events	Other
	Interaction with co-medication	Unknown
Co-medication *Start and stop date and the medication status at current visit (ongoing: yes or no)*	CDC events, prophylaxis	Anabolic steroids and appetite stimulants
	CDC events, treatment	Hepatitis B treatment
	Anti-epileptic agents	Hepatitis C treatment
	Anti-coagulant agents	Medication that interacts with antiretroviral therapy
	Platelet aggregation inhibitors	Miscellaneous: megestrol acetate, dranabinol and methadone
	Anti-hypertensive agents	
	Anti-arrhythmic agents	
	Lipid-lowering agents	
	Anti-diabetic agents	
	Insulin and its derivatives	

Appendix 4.1(2)**:** data

Lab results	HIV virology: RNA
	Value (copies/ml), laboratory, sample date, VL assay type, sample material, cut-off and undetectable yes or no
	Immunology T-cell count
	Value, units, laboratory and sample date for the following determinates: CD4 count, CD8 count, CD4 percentage, CD8 percentage, CD4/CD8 ratio
	Chemistry
	Value, units, laboratory and sample date for the following determinates
	Glucose >N*
	Amylase >250 mmol/l
	ALAT/SGPT >3 xN*
	ASAT/SGOT >3 xN*
	Alkalinephosphatase >3 xN*
	Gamma GT >3 xN*
	Lactate >N*
	Triglycerides always collected
	Cholesterol always collected
	Cholesterol HDL always collected
	* N is normal value; can vary for different laboratories.
	Haematology
	Value, units, laboratory and sample date for the following determinates:
	Haemoglobin <5.5 mmol/l
	Leukocytes <2.0 10e9/l
	Thrombocytes <75 10e9/l
	Other viral infections
	Value (positive or negative), laboratory, sample date for the following determinates:
	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV-DNA,
	HCV-Ab, HCV-RNA, CMV-IgG, CMV-IgM
	ART drug concentrations
	Plasma concentration, laboratory, sample data, time after drug intake, dosage and units of the medication
Patient's participation in clinical trials	Trial name, start and stop date

Appendix 4.1(3)**:** data

Additional data for HIV-infected children		
Clinical examination	Skull circumference, puberty stage	
Adverse events	Pathologic and traumatic fractures, abnormalities of psychological development, abnormalities of locomotion development, abnormalities of puberty development	
Additional treatment *Start and stop date, status at current visit*	Psychologist, pedagogue, psychiatrist, speech therapist, physiotherapist, rehabilitation worker, social worker	
Care and education	Care by:	Mother, father, parents, family, foster family, care institute, other and unknown
	Education:	Nursery school, playgroup, primary school, secondary school, other and unknown
Vaccinations date	DKTP1, DKTP2, DKTP3, DKTP4, HIB1, HIB2, HIB3, HIB4, BMR, BCG, PNCV, influenza, meningitis C, pneumovax, other	
Lab results	*HIV virology: DNA* Value (positive or negative), laboratory, sample date for the following determinates: HIV-1 DNA, HIV-2 DNA, HIV-1 antibodies, HIV-2 antibodies	
	Chemistry: The following determinates are always collected: Glucose, Amylase, ALAT/SGPT, ASAT/SGOT, Alkaline phosphatase, Gamma GT, Lactate, Triglycerides, Cholesterol, Cholesterol, HBA1c	
	Haematology: The following determinates are always collected: Haemoglobin, Leukocytes, Thrombocytes, MCV	

Appendix 4.1(4)**:** data

Base

lines

Characteristics of the population included in the ATHENA national observational cohort

Frank de Wolf

Introduction

The data used for the analyses presented in this year's scientific report was obtained from 10,854 patients, 1122 patients more than in 2004[9]. This population of HIV-infected persons has been the focus of the ATHENA project, which in 2001 was merged into HMF. In this chapter, we will present results as to the demographic changes of the population registered through the HMF monitoring system, including molecular epidemiological changes; the virological, immunological, and clinical effects of various long-term antiretroviral combination treatments; several important issues with regard to treatment strategies, including frequency of measurement of HIV-RNA and CD4 cell count; and the occurrence of drug resistance and changes in resistance patterns.

In the Netherlands, monitoring the course of the individual HIV infection is considered part of nationwide patient care. Entry of HIV-infected patients into the ATHENA national observational cohort is therefore unrestricted, and patients are registered and monitored by default. Individuals can opt out, preventing the inclusion of information about the course of their infection in the monitoring system. In such cases, their data will be omitted from the national ATHENA database with no consequences for their care and treatment. To safeguard the privacy of participating patients, data are stored anonymously and under a 6-digit code number in the secured national ATHENA database. The data collection procedure and the database are described more extensively in Chapter 4 of this report and the scientific report of 2003[11].

The prognosis of clinical outcome in both the untreated and treated infection is strongly correlated with baseline characteristics such as the patient's CD4 cell count and HIV-RNA plasma level, age, history of AIDS, and HIV transmission risk behaviour[12-20]. In this chapter, the characteristics at baseline of the patients registered are described to provide a comprehensive overview of the composition of the HIV-infected population monitored within the framework of ATHENA.

Patient numbers, median follow-up, and geographic distribution

Data obtained from 10,854 patients with 69,771 person-years of follow-up were available as of 1 June 2005. The study included 8326 men (76.7%) and 2432 women (22.4%) who were 13 years or older as of 1 June 2005; 96 (0.9%) patients were younger than 13 years.

The age distribution at the time of HIV diagnosis is depicted in Figure 5.1. Of the men, 70.2% were infected when 25-44 years of age; of women, 65.9% were infected when 18-34 years of age. Women were diagnosed with HIV at the median age of 30 (IQR 24.9-36.0) and therefore were significantly ($p<0.0001$) younger than men, whose median age at diagnosis was 35.9 (30.3-42.9).

The median follow-up of the study population was 5.4 years (IQR 2.2-9.6). Median was 5.8 (2.4-10.0) for men and 4.2 (1.9-8.2) for women. The median time between healthcare visits was 91 days (IQR 56-115); between plasma viral load measurements, the median was 92 days[63-119] and between CD4 measurements, it was likewise 92 days[63-120].

The West of the Netherlands – Amsterdam, Rotterdam, Utrecht, and The Hague – still harbour the majority of the known HIV-infected population in the Netherlands: currently 75.6 percent (Table 5.1).

HIV diagnosis

The prevalences of infections with HIV-1, HIV-2, and combined HIV-1/HIV-2 are summarised in Table 5.2. Of the total group, the large majority of 96.9% tested positive with HIV-1, with 0.5% testing positive for HIV-2. Antibody reactivity to both HIV-1 and HIV-2 was found in 1.1% of the patients. In 1.5% of the population registered, the data were inconclusive and need to be

reconfirmed. Infection with HIV is usually diagnosed using a HIV-1/HIV-2 antibody assay combined with a HIV-1 p24 antigen assay[21] followed by Western blot confirmation of an antibody response specific for HIV-1, HIV-2, or both.

Trends in baselines over time

The absolute number per year of HIV diagnoses from 1990-2005 is depicted in Figure 5.2. The date of HIV diagnosis was missing for 234 patients, and 973 patients were diagnosed before 1990. A steady increase of new HIV diagnoses was seen between 1990 and 2002, with 271 new diagnoses in 1990 and 945 in 2002, reflecting in part the improved intake procedure of the cohort but also the course of the HIV epidemic. Since 2002, the number of new HIV diagnoses seems to have stabilised; the number for 2005 is still incomplete, due to a backlog in the registration. The relative distribution of HIV-infected men and women per year of diagnosis changed from 85% men and 15% women in 1990 to 70% men and 30% women in 2000. Interestingly, gender distribution changed again after 2003: in 2004, 75% of the new HIV diagnoses were men, increasing to 77% in 2005.

HIV-RNA was measured at diagnosis in 5755 patients (53.0%). The median HIV-RNA plasma level was 4.8 log copies/ml (IQR 4.0-5.2). Per year of diagnosis, a steady decline was found, with 1996 levels being 4.8 log copies/ml and 2005 levels being 4.6. The levels measured in women, at median 4.4 log copies/ml (IQR 3.5-5.0), were significantly ($p<0.0001$) lower than levels in men, at median 4.9 (4.2-5.3).

The median CD4 cell number at diagnosis was 290 cells/mm^3 (IQR 110-500). For women, it was 300 (130-500) and for men, 288 (100-490). Median CD4 cell count at HIV diagnosis improved over time, from 260 cells/mm^3 in 1996 to 310 cells/mm^3 in 2005 ($p<0.001$).

HIV-infected children

The registration of children – patients below 13 years of age at diagnosis – began in 2004, and 96 such patients are now included. Their median age at HIV diagnosis was 0.8 year (IQR 0.3–2.4). The median current age is 6.5 years (4.4–9.6). Median HIV-RNA plasma levels at diagnosis are high compared to those seen in adults: 5.4 log copies/ml (4.8–5.9). Median CD4 cell counts at diagnosis are 1010 cells/mm^3 (310–1890).

Pregnant women

Amongst 661 of the women diagnosed with HIV, 847 pregnancies were registered. Of the pregnant women, 639 (97%) were diagnosed before their first pregnancy or a maximum of 3 months into that pregnancy. In the remaining 24 (4%), HIV was diagnosed more than 9 months after the date pregnancy was first registered. The pregnant women had a median age of 26 (IQR 23-31) at HIV diagnosis, a median HIV-RNA level of 4.0 log copies/ml (3.2-4.6), and a median CD4 cell count of 340 cells/mm^3 (200-525). HAART was initiated before the first registered pregnancy in 172 women (26%), during pregnancy in 290 (44%), and after the first pregnancy in 151 (23%). From the remaining 7%, data on HAART were not available. In 106 women (16%), at least one pregnancy was less than 26 weeks in duration. Amongst pregnant women, transmission of HIV was predominantly heterosexual (93%); the majority (61%) were from sub-Saharan Africa, and only 15% were of Dutch origin.

Antiretroviral treatment: HAART and pre-HAART

Antiretroviral treatment (ART) of HIV-infected patients began in 1987/1988, first in clinical trials and subsequently as a regular part of patient care[22, 23]. From the mid-1980s until 1996, a growing number of patients were treated with mono or dual antiretroviral combination therapy. With the introduction of highly active retroviral therapy (HAART), a large fraction of this so-called “therapy-

experienced" or pre-treated group changed from their ART regimen to HAART combinations in 1996-1999.

In the ATHENA observational cohort, 80.2% of the patients are currently registered as being treated with HAART: 21% with pre-HAART antiretroviral drug experience and 59.2% without. A small fraction of 1.3% is still using ART drug combinations that do not fit the HAART definition (i.e., at least three antiretroviral drugs from two different drug classes or a combination of three nucleoside reverse transcriptase inhibitors, recently including tenofovir and abacavir). The remaining 18.5% of the patients are not treated with any antiretroviral drug.

Between 1996 and 2004, the number of patients starting HAART without prior experience with ART rapidly increased (Figure 5.3). An apparent slowdown in 2005 most probably reflects only a backlog in the collection of therapy data. Since 1990, a relatively constant number of patients has started treatment with non-HAART regimens over time. Between 1996 and 1999, pre-treated patients frequently switched to HAART, as noted above.

Finally, as can been seen from Table 5.3, differences between the four treatment groups as to the characteristics at diagnosis, at start of ART, and at start of HAART indicate that those receiving no treatment or non-HAART treatment are clinically well. Compared to CD4 cell numbers and RNA levels found at diagnosis amongst the HAART- and ART-treated patients, the non-treated patients had high CD4 cell numbers at diagnosis and low HIV-RNA levels. This indicates that they were infected more recently and were thus ineligible for HAART according to current guidelines set by Fauci et al. (Panel on Clinical Practices of Treatment of HIV Infection).

Zidovudine in combination with lamivudine is still the most frequently used NRTI backbone. It was used in the first HAART combination in ART-naïve patients, of whom 52.4% received this combination as part of their initial treatment (Table 5.4). Lopinavir boosted with ritonavir and efavirenz have been most frequently added to this backbone. Compared to 2003-2004, the combination of tenofovir and lamivudine has slowly increased to 29.4% of the initially prescribed HAART regimens in 2004-2005. Emtricitabine together with tenofovir is emerging rapidly and now figures in 6.9% of the HAART regimens used.

Co-infections with HIV

Since the introduction of HAART, there has been a significant reduction in HIV-related mortality and morbidity in the Netherlands[24]. Consequently, morbidity and mortality from other infections may become more apparent. For example, infection with hepatitis C virus (HCV) is a major cause of death in HIV-infected patients[25, 26]. Although HCV co-infection is associated with increased HIV mortality, this association disappears in some studies after adjustment for other covariates[25, 27, 28]. No significant influence of HCV co-infection in virological or immunological responses to antiretroviral treatment were found[25, 29-32].

Co-infection with cytomegalovirus (CMV) is associated with a more rapid progression to AIDS[33-35]. After initiation of HAART, the rise in CD4 cells in CMV-negative patients is more rapid than in CMV-positive patients, but eventually the CD4 counts reach similar levels in the two groups[36].

In an HIV-infected population of 10,515, the patients positive and negative for CMV were distinguished by the presence or absence of anti-CMV IgG antibodies, just as those positive and negative for HCV were distinguished based on anti-HCV antibodies. For 6483 patients (61.2%), the CMV status could be determined; of these, 5868 (90.5%) were CMV-positive. Of the 243 male intravenous drug users, 174 (71.6%) were CMV-positive ($p<0.001$), but female intravenous drug users were no different from the average population ($p=0.5$).

The prevalence of CMV was lower in male patients infected with HIV through blood or blood contact than in the total HIV-infected population: 50 (73.5%) out of 68 patients.

The HCV status was known for 7951 patients (75.6%), of whom 839 (10.6%) were HCV-positive. HCV prevalence was highest amongst intravenous drug users – 413 (94.9%) out of 435 patients ($p<0.001$) – and did not differ between male and female drug users ($p=0.6$). In the population infected with HIV through heterosexual contact, the HCV prevalence was 5.1%, and was the same for men and women ($p=0.6$). Prevalence was higher ($p<0.001$) than amongst homosexual men, of whom only 130 (3.0%) of 4274 patients were HCV-positive. HCV was more prevalent amongst men infected with HIV through blood-blood contact, 35/82 (42.7%), and amongst men and women for whom the infection route was unknown: 78/485 (16.1%) for men and 50/82 (61.0%) for women, respectively.

Regarding HBV infection, HbsAg was measured at least once in 9088 patients, of whom 785 (8.6%) had at least one positive result. Prevalence of HbsAg positivity was higher in intravenous drug users (59/478, 12.3%) than in those sexually infected with HIV (648/7653, 8.5%).

Conclusions

Since 2004, the total number of HIV-infected patients registered and monitored through data collection in the HIV Treatment Centres increased by 1122 to a total of 10,854 patients. These patients have a follow-up of almost 70,000 person-years, with a median follow-up period of 5.4 years (IQR 2.2-9.6). Median time between healthcare visits was approximately 3 months.

In the 2004 scientific report[9], we discussed the slow-down in the increasing number of registered HIV-infected patients. The figures for 2005 so far confirm this trend. Interestingly, we find an absolute and relative increase in HIV-infected men, whereas the numbers for women remain stable. This finding might reflect the increase in high-risk sexual behaviour amongst homosexual men[37] in combination with a recent decrease in heterosexual immigrants coming from HIV-endemic areas, especially sub-Saharan Africa.

On average, women are still six years younger than men at HIV diagnosis. The number of pregnancies amongst HIV-infected women is still increasing, as is the number of pregnant women being treated with HAART before or during pregnancy. The majority of pregnant HIV-infected women originate from sub-Saharan Africa.

More than 80% of the patients registered with HMF are treated with HAART. Only very few are on an ART regimen that cannot be classified as HAART, whilst a relatively stable percentage of 18.5% of patients are not treated with antiretroviral agents at all. The majority of these untreated patients were diagnosed with HIV during or after 2000. This relatively recent diagnosis plus their relatively high CD4 cell numbers and low HIV-RNA plasma concentrations point to recent infection, which makes them HAART-ineligible by the current treatment guide.

	male		female		child		total group	
	N	%	N	%	N	%	N	%
Amsterdam	3821	45.9	813	33.4	44	45.8	4678	43.1
Northern provinces	470	5.6	189	7.8	6	6.3	665	6.1
Eastern provinces	652	7.8	203	8.3	1	1.0	856	7.9
Southern provinces	813	9.8	324	13.3	2	2.1	1139	10.5
Western provinces	2570	30.9	903	37.1	43	44.8	3516	32.4
total	**8326**	**100**	**2432**	**100**	**96**	**100**	**10854**	**100**

Table 5.1: Geographical distribution of HIV-infected patients registered in the Netherlands.

	male		female		child		total group	
	N	%	N	%	N	%	N	%
HIV-1	8115	97.5	2320	95.4	80	83.3	10515	96.9
HIV-2	30	0.4	26	1.1			56	0.5
HIV-1/2	73	0.9	47	1.9	1	1.0	121	1.1
unknown	108	1.3	39	1.6	15	15.6	162	1.5
total	**8326**	**100**	**2432**	**100**	**96**	**100**	**10854**	**100**

Table 5.2: Prevalence of HIV-1 and HIV-2.

Characteristic	HAART				NON-HAART		NON-TREATED	
	Naïve patients		Pre-treated patients					
N Total	6413		2274		137		2030	
Median (IQR) age:								
· at start HAART	37	(31-44)	39	(33-46)				
· at start non-HAART			36	(31-43)	36	(31-43)		
· at diagnosis	35	(29-42)	33	(28-40)	33	(27-39)	35	(28-41)
Gender:								
· Male (%)	4783	(75.3)	1866	(82.5)	106	(77.9)	1571	(74.5)
· Female (%)	1568	(24.7)	397	(17.5)	30	(22.1)	437	(25.5)
N (%) CDC-C event:								
· at start HAART	1598	(24.9)	477	(21.0)				
· at start non-HAART			539	(23.7)	22	(16.1)		
· at diagnosis	1138	(17.7)	347	(15.3)	14	(10.2)	62	(3.1)
Median (IQR) CD4 cells/mm^3								
· at diagnosis	N=4410		N=891		N=62		N=1381	
	220	(76-400)	230	(90-420)	335	(159-530)	522	(380-700)
· at start HAART	N=5488		N=1820					
	194	(80-320)	180	(70-320)				
· at start non-HAART			N=1292		N=86			
			190	(98-300)	252	(120-370)		
N (%) HIV-RNA <500 copies/ml								
· at start HAART	184	(2.9)	233	(10.2)				
· at start non-HAART			29	(1.3)	6	(4.4)		
· at diagnosis	278	(4.3)	40	(1.8)	3	(2.2)	145	(7.1)
Median (IQR) log HIV-RNA copies/ml								
· at start HAART	N=4997		N=1232					
	5.0	(4.5-5.4)	4.6	(3.9-5.1)				
· at start non-HAART			N=441		N=42			
			4.9	(4.3—5.3)	4.7	(4.1-4.9)		
· at diagnosis	N=3800		N=279		N=33		N=1176	
	5.0	(4.4-5.4)	5.0	(4.3-5.4)	4.8	(4.4-5.0)	4.4	(3.8-4.9)

Table 5.3: Baseline characteristics of patients receiving HAART, non-HAART, or no treatment

	Year of first HAART regimen					
	2003-2004		2004-2005		Total	
First HAART regimen	N	%	N	%	N	%
Total	759	100.0	598	100.0	1357	100.0
3TC+TDF+EFV	132	17.4	121	20.2	253	18.6
AZT+3TC+LOP/r	149	19.6	99	16.6	248	18.3
AZT+3TC+EFV	83	10.9	63	10.5	146	10.8
AZT+3TC+NVP	83	10.9	41	6.9	124	9.1
AZT+3TC+NFV	57	7.5	43	7.2	100	7.4
3TC+TDF+NVP	48	6.3	36	6.0	84	6.2
AZT+3TC+ABC+LOP/r	46	6.1	31	5.2	77	5.7
AZT+3TC+LOP/r+EFV	22	2.9	22	3.7	44	3.2
3TC+TDF+LOP/r	20	2.6	19	3.2	39	2.9
TDF+FTC+EFV			32	5.4	32	2.4
AZT+3TC+ABC+EFV	16	2.1	11	1.8	27	2.0
ddI+3TC+EFV	21	2.8	2	0.3	23	1.7
3TC+TDF+ATV/r			15	2.5	15	1.1
AZT+3TC+ABC	9	1.2	3	0.5	12	0.9
D4T+3TC+LOP/r	9	1.2	2	0.3	11	0.8
ABC+3TC+LOP/r	3	0.4	7	1.2	10	0.7
TDF+FTC+ATV/r	1	0.1	9	1.5	10	0.7

FTC=emtricitabine, TDF=tenofovir, AZT=zidovudine, 3TC=lamivudine, ddI=didanosine, ABC=abacavir, NVP=nevirapine, EFV=efavirenz, LOP/r=lopinavir/ritonavir, NFV=nelfinavir, ATV/r=atazanavir/ritonavir.
2003-2004: patients starting HAART from 1 July 2003 through 30 June 2004
2004-2005: patients starting HAART from 1 July 2004 through 30 June 2005.

Table 5.4: Overview of the most frequently used first-line HAART combinations 2003-2005 in previously ART-naïve patients.

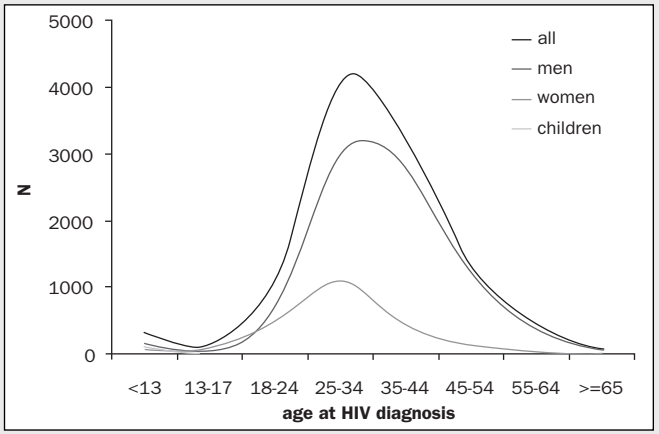

Figure 5.1: Age distribution at HIV diagnosis.

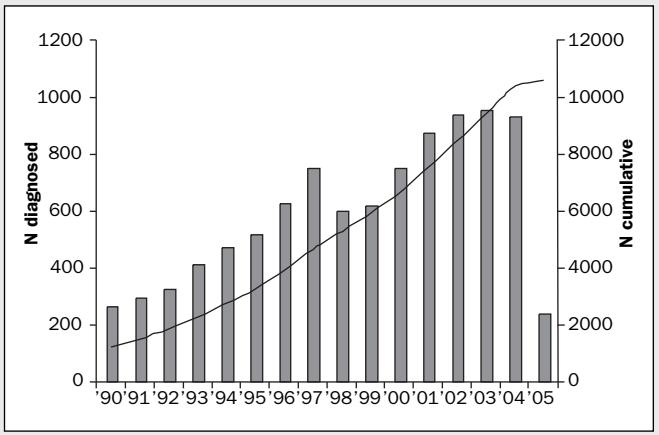

Figure 5.2: Number of new HIV diagnoses per year of diagnosis.

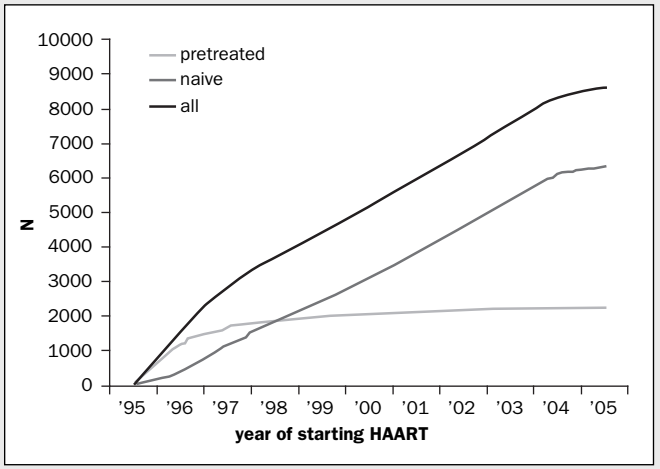

Figure 5.3: Annual numbers of patients previously ART-treated (pre-treated) or previously not ART-treated (naïve) starting HAART and the cumulative number of patients starting HAART


Follo

w-up

Declining frequency in later calendar years in the ATHENA national observational cohort

Luuk Gras

Introduction

The increased survival of HIV-infected patients in the HAART era[24] along with the annual number of newly infected patients results in a rising total of patients under active follow-up in the HIV Treatment Centres (see Chapter 5). As the number of HIV-treating physicians has not increased at the same rate as the number of patients in follow-up, scheduling routine clinical visits for all patients every three months has become difficult. To ease the time pressure, some physicians have introduced consults by telephone or refer patients to so-called 'HIV-clinical practice nurses.'

A less frequent follow-up schedule might not benefit the patient. Adverse responses to therapy or changes in adherence might be recognised too late, resulting in failure of therapy, development of drug resistance, and the exhaustion of treatment options. Moreover, less frequent follow-up might have an impact on disease progression. On the other hand, the impact does not have to be this dramatic. If problems do occur in a patient, they can be met with adjustment of care, although possibly at a somewhat later stage of disease. Less frequent follow-up does not necessarily have to have serious consequences for the patient.

Randomised clinical trials are the "gold standard" when comparing treatment strategies. However, a study with clearly defined and suitable endpoints that ideally randomises patients into low- and high frequency arms, even if possible, would take a long time to have enough power to detect differences amongst patients followed. Alternatively, the use of observational data to address the question of frequency would have the advantage that a lot of data are already available. The disadvantage of observational data is that to establish a causal relationship between follow-up frequency and clinical endpoints is difficult. A high follow-up frequency may result in a better clinical outcome, but this effect might be hard to detect because patients with an advanced state of disease would likewise have a higher follow-up frequency.

In this chapter we describe frequencies of clinical visits and measurements of HIV-RNA concentration and CD4 cells within the ATHENA HIV/AIDS observational cohort in the Netherlands. We also quantify the effect of patient characteristics on follow-up frequency.

Methods

Study observations

Entry of clinical visit dates in the HMF database was required from cohort registration onwards (registration started in 1998), whilst for CD4 and HIV-RNA, all measurements from the start of HAART onwards were entered. For each patient aged 18 years or more at the date of HIV diagnosis, we selected clinical visits with the treating physician that fell in the period starting one year after his/her cohort registration and ending 31 December 2003. In addition, we selected measurements of HIV-RNA and CD4 cells that were taken between one year after the patient started HAART and 31 December 2003. For all visits/measurements, the number of days since the previous visit/measurement was determined. Of clinical visits, only those with the treating physician were analysed in this report.

Patient-specific characteristics were extracted, including date of birth, HIV diagnosis, and registration into the cohort; gender, region of origin, calendar year of starting HAART and transmission risk group. For every visit/measurement, the level of CD4 and HIV-RNA at the prior visit/measurement was determined. Furthermore, we determined whether the patient had experienced a CDC C-event and whether the patient was participating in a clinical trial or was pregnant at the time of the visit/measurement. In addition, we considered the calendar year of the visit/measurement, the hospital at which the patient was under observation, whether the

patient was taking antiretroviral therapy or was untreated, and whether there had been a change in the drug combination (the cessation or addition of a drug).

Statistical analysis

Parametric accelerated lifetime models were used to find factors independently predictive of the time between consecutive clinical visits and, separately, the time between HIV-RNA and CD4 measurements. Models included a gamma frailty for each patient, reflecting the re-visit schedules and unmeasured confounders amongst individual patients. The Weibull distribution was initially used to model the number of days between visits, but the log-logistic distribution was found to better fit the peak in hazard for visits about 90 days apart. The results from the accelerated lifetime models are presented as acceleration factors (AF). When the AF is greater than 1, follow-up frequency is lower compared to the reference group; when AF is less than 1, follow-up frequency is higher. For example, an AF of 1.2 represents a 20% increase in the time to the next visit/measurement, compared to the reference group. Patients were censored at 31 December 2003 or 365 days after their last clinical visit/measurement, whichever came first. Patients who died or moved from the Netherlands were censored at their last clinical visit/measurement. Reported confidence intervals are based on type I error rate of 0.05.

Results

In total, 46,760 clinical visits (from 4893 patients), 79,519 HIV-RNA measurements (from 5920 patients), and 75,197 CD4 measurements (from 5918 patients) were selected. The median time (IQR range) between visits/measurements according to demographic, clinical, and other characteristics of the patients at the time of visit or measurement is shown in Table 6.1. Overall, the median time between clinical visits/measurements of CD4 and HIV-RNA was approximately 3 months (91, 92, and 92 days, respectively).

Clinical visit frequency

Clinical visit frequency was higher in earlier calendar years. The median number of days between visits in 1999 was 84 days in 1999 but 98 days in 2003. The time between visits was shorter when there was a lower CD4 count and/or a higher HIV-RNA concentration at the previous visit. Median time between visits was 29 days when the last CD4 count was <25 cells/mm^3 and 42 days when the last HIV-RNA was $>100{,}000$ copies/ml. When CD4 count at the last visit was ≥ 500 cells/mm^3, the median time to the next visit was 124 days; when HIV-RNA at last visit was <500 copies/ml, median time to next visit was 98 days. Median time between visits was 57 days when a change in therapy was made, compared to 92 days when no change was made. Median gap-time was also shorter during clinical trial participation (49 days) or during a pregnancy (54 days).

HIV-RNA measurement frequency

The median time between HIV-RNA measurements was shorter for homosexually infected patients and those infected through blood-to-blood contact (both 91 days) than for heterosexually infected patients (96 days) or patients infected through intravenous drug use (98 days). Median time between HIV-RNA measurements increased with later calendar years, from 75 days in 1997 to 103 days in 2003. HIV-RNA measurement frequency increased with higher HIV-RNA and lower CD4 count at the prior HIV-RNA measurement.

CD4 measurement frequency

CD4 count measurement frequency was slightly lower in IDUs (median gap-time between CD4 measurements was 98 days) and heterosexually infected patients (median gap-time 96 days) compared to patients infected through blood-to-blood contact (91 days) or homosexual contact (92 days). As with HIV-RNA measurement and clinical visit frequency, CD4 measurement frequency declined with later calendar years. Median gap-time in 1997 was 62 days, and in 2003 had increased to 100 days.

If CD4 count was lower than 50 cells/mm^3, the median time to the next CD4 measurement was 56 days, increasing to 98 days if CD4 cell numbers were ≥500 cells/mm^3. Median time to the next CD4 measurement likewise increased if there was a lower HIV-RNA at the time of the last CD4 measurement. Median time between CD4 measurements was slightly shorter after a first CDC-C event (97 days) than before such an event (91 days).

Multivariate analyses

Table 6.2 shows the acceleration factors (AF) and 95% confidence intervals obtained through multivariate analysis of time between clinical visits/measurements of CD4 and HIV-RNA.

Clinical visits

Time between visits, adjusted for other factors, was 1.23 times longer (95% CI 1.14-1.35) in patients infected through intravenous drug use than in homosexually infected patients. For heterosexually infected patients, time between visits was also slightly longer – AF 1.08 (1.02-1.14) – compared to homosexually infected patients. Time between visits was 27% longer in calendar year 2003 compared to 2000. Independent of the calendar year of the visit, the calendar year when HAART was started also had a significant effect. For patients starting HAART in 1996, time between visits was 8% shorter (95% CI 2-15%) than for those starting in 2000. For patients starting in 2002, the interval was 10% longer (1-19%) than for patients starting in 2000.

Time between visits was 35% shorter if the CD4 count at the last visit was <25 cells/mm^3 compared to ≥500 cells/mm^3. It was 38% shorter if HIV-RNA at the last visit was ≥100,000 copies/ml compared to <500 copies/ml. Time between visits was 24% shorter (95% CI 22- 25%) when there was a change in therapy compared to no change. Finally, time between clinical visits was 11% shorter after a first CDC-C event than before such an event.

HIV-RNA measurements

Time between HIV-RNA measurements in later calendar years was significantly longer than in earlier calendar years. Time between HIV-RNA measurements in 2003 was 22% longer than in 2000. The time between HIV-RNA measurements was 21% shorter when the last HIV-RNA measurement was ≥50,000 compared to <500 copies/ml. Time between HIV-RNA measurements performed during a therapy interruption was 14% longer (95% CI 11-15%) than between measurements performed during uninterrupted therapy.

CD4 measurements

Time between CD4 measurements was 19% longer for patients infected through intravenous drug use than for homosexually infected patients. As with time between clinical visits and HIV-RNA measurements, time between CD4 measurements increased with later calendar years. In 2003, it was 23% longer (22-25%) than in 2000. The year of starting HAART had no independent, significant effect on time between CD4 measurements. Frequency of measurement was higher when the last measured CD4 count was low. Time to the next visit was 29% shorter when the last CD4 measurement was <50 cells/mm^3 than when it was ≥500 cells/mm^3. On the other hand, the interval between CD4 measurements was not apparently affected by the level of the HIV-RNA concentration ratio. Time to the next CD4 measurement was not significantly different whether HIV-RNA <500 or ≥100,000 copies/ml was found at the last CD4 measurement. During therapy interruptions, whereas time between HIV-RNA measurements was longer, the time between CD4 measurements was shorter: AF 0.91 (0.88, 0.93).

There was no significant effect of age or region of origin on time between clinical visits/measurements of CD4 or HIV-RNA (data not shown). Once models were adjusted for visits/measurements during a pregnancy there were no significant differences in visit/measurement frequency between men and women.

Finally, there were differences in follow-up frequency amongst hospitals (Table 6.3) when age and region were included and adjustments were made for the patient- and visit-specific characteristics listed in Table 2. Compared to reference hospital 23, HIV-RNA was measured 1.96 (95% CI 1.75-2.17) and 1.85 (1.69-2.00) times less frequently in hospitals 1 and 2, respectively. However, in time between CD4 measurements, they did not differ significantly from the reference hospital. Time between CD4 measurements in hospitals 3 and 4 was twice the time in hospital 23. Differences in frequency of CD4 and HIV-RNA measurement between hospitals 5-22 and hospital 23 were smaller than between hospitals 1-4 and 23 (see Figure 6.1).

Discussion

Although the median time between clinical visits, as between measurements of CD4 and HIV RNA, is approximately three months in the ATHENA national observational cohort, there are substantial differences in frequency amongst individuals and subgroups. Patients with more advanced HIV disease have higher frequencies for visits to the outpatient clinic as well as measurements of CD4 and HIV-RNA. The present analysis only establishes an association between higher follow-up frequency and more advanced state of HIV disease, not a causal relationship. However, it is safe to assume that the advanced state of HIV disease causes more frequent visits and measurements of HIV-RNA concentration and CD4 cell numbers. Likewise, it is probable that visits/measurements were more frequent in earlier calendar years than in later years largely because of the ever-increasing number of patients per physician.

When analysing data from observational cohorts, it is important to consider the variation amongst groups of patients in frequency of follow-up. Widely reported estimates based on analyses – such as hazard ratios based on analysis of time to undetectable viral load, time to rebound of viral load above a certain threshold, or time to an increase of more than 100 CD4 cells/mm^3 from baseline – indeed depend on frequency of measurements. When HIV-RNA is found to be undetectable for the first time, the actual time-point of undetectability lies between the last positive and the first negative viral load measurement. However, most often an analysis looks at the time to the first negative measurement[16, 38, 39]. Comparing certain groups of patients, such as those starting HAART in different calendar years, without taking into account their differences in measurement frequency might result in biased estimates. Hazard ratios will most likely be biased upward in groups with higher follow-up frequency. Also, imputation of the midpoint between the measurement taken when HIV-RNA was last detectable and the measurement taken when it was first undetectable can lead to biased estimates. Analyses using methods applicable to interval-censored data reduce the bias[40].

The substantial differences found in follow-up frequency amongst hospitals indicate a lack of consensus on the best follow-up frequency. The fact that higher follow-up frequency is an effect of more advanced disease tends to obscure the effect of low versus high frequency on clinical outcome in a given patient. However, methods dealing with causality problems are increasingly being developed and may be helpful in evaluating the effect of follow-up frequency on clinical outcome.

Conclusion

Follow-up frequency in the ATHENA national observational clinical cohort depends on the clinical stage in the patient and has declined in more recent calendar years.

		Clinical visits			HIV-RNA measurements			CD4 measurements		
		N	Median	IQR	N	Median	IQR	N	Median	IQR
Total		46760	91	56-115	79519	92	63-119	75197	92	63-120
Gender	Male	39356	91	56-118	65824	92	63-119	62688	92	63-119
	Female	7404	91	55-112	13695	93	63-121	12509	95	63-126
Transmission risk group	Homosexual	30063	91	56-116	49868	91	63-117	47270	92	63-119
	Heterosexual	10664	91	56-115	18847	96	66-124	17710	96	64-126
	IDU	2264	91	43-119	3861	98	67-133	3692	98	68-136
	Blood-to-blood contact	808	87	40-105	1484	91	54-120	1356	91	51-126
	Other	2472	91	56-119	4576	96	64-126	4419	95	64-126
Year visit/measurement	1997				2191	75	42-98	2400	62	35-91
	1998				8644	77	49-98	8280	77	49-98
	1999	1980	84	42-98	10942	86	56-105	10467	89	59-105
	2000	9001	91	49-99	12577	91	63-112	12026	92	66-112
	2001	10883	91	49-105	14166	95	66-118	13026	98	70-124
	2002	11169	95	56-122	15314	98	75-126	13591	99	78-133
	2003	13727	98	62-126	15685	103	78-133	15407	100	77-132
CD4 count (cells/mm^3	0-25	621	29	16-56	1094	56	34-91	1067	56	32-89
at last visit/measurement)	25-50	538	35	21-63	1092	60	35-97	1067	56	34-96
	50-100	1253	56	28-91	2582	70	42-102	2459	68	39-103
	100-200	4696	70	35-98	9225	84	51-108	8988	84	49-106
	200-350	9165	91	49-106	17221	91	63-114	16516	91	62-116
	350-500	10968	91	58-119	18496	94	70-119	17477	97	70-124
	≥500	19456	124	98-70	29379	98	77-126	27500	98	80-126
HIV-RNA (copies/ml at last	<500	35410	98	65-119	58150	98	77-124	54464	98	76-125
visit/measurement)	500-1,000	1121	77	42-98	2410	82	49-105	2127	83	49-110
	1,000-10,000	3748	77	36-98	7534	82	49-105	6947	84	50-109
	10,000-50,000	2786	70	36-98	5331	77	47-105	5228	84	50-111
	50,000-100,000	1823	43	22-84	2477	66	41-98	2605	72	42-106
	≥100,000	1865	42	22-80	3617	58	35-92	3672	64	36-101
Therapy	Change in therapy	5625	57	34-98	11776	75	43-112	11301	84	49-132
	Same therapy	38484	92	63-119	63765	96	70-119	59665	96	70-119
	No therapy	2971	82	42-113	5887	85	48-125	6064	84	44-120
Visit/measurement	During trial participation	1175	49	23-84	3444	56	28-84	3236	56	29-84
specific characteristics	During pregnancy	244	54	28-98	544	49	28-92	421	59	35-100
	Prior to any CDC-C event	28835	93	63-119	48834	96	69-121	45891	97	70-125
	After any CDC-C event	17925	90	42-105	30685	91	58-113	29306	91	57-114

Table 6.1: Median number of days (IQR) between clinical visits/measurements of CD4 and HIV-RNA by demographic patient characteristics and visit-specific characteristics.

		Clinical visits		HIV-RNA		CD4	
		AF*	95%CI**	AF*	95%CI**	AF*	95%CI**
Gender	Male vs female	0.99	0.93-1.05	0.97	0.94-1.01	0.98	0.94-1.01
Transmission risk group	Homosexual	1.00		1.00		1.00	
	Heterosexual	1.08	1.02-1.14	1.05	1.02-1.09	1.04	1.00-1.06
	IDU	1.23	1.14-1.35	1.25	1.20-1.32	1.19	1.14-1.25
	Blood-to-blood contact	1.08	0.93-1.27	1.03	0.96-1.12	0.97	0.90-1.06
	Other	1.18	1.09-1.28	1.05	1.01-1.10	1.02	0.98-1.06
Year visit / measurement	1997			0.93	0.90-0.94	0.81	0.80-0.83
	1998			0.89	0.88-0.91	0.88	0.87-0.89
	1999	0.96	0.93-0.99	0.94	0.93-0.95	0.94	0.93-0.96
	2000	1.00		1.00		1.00	
	2001	1.02	1.00-1.03	1.02	1.01-1.03	1.05	1.04-1.06
	2002	1.11	1.10-1.14	1.08	1.06-1.10	1.14	1.11-1.15
	2003	1.27	1.25-1.28	1.22	1.20-1.23	1.23	1.22-1.25
Year HAART first started	1996	0.92	0.85-0.98	1.01	0.97-1.04	0.96	0.92-1.00
	1997	0.97	0.91-1.04	1.02	0.98-1.05	1.00	0.96-1.04
	1998	0.98	0.92-1.06	1.05	1.01-1.10	1.02	0.98-1.06
	1999	1.05	0.97-1.14	1.05	1.01-1.09	1.02	0.98-1.06
	2000	1.00		1.00		1.00	
	2001	1.05	0.98-1.15	0.98	0.93-1.02	1.00	0.95-1.04
	2002	1.10	1.01-1.19	1.05	1.01-1.11	1.03	0.98-1.09
CD4 count (cells/mm^3) at previous visit/measurement	<25	0.65	0.60-0.69	0.89	0.85-0.93	0.71	0.68-0.74
	25-50	0.67	0.63-0.72	0.85	0.71-0.88	0.71	0.68-0.74
	50-100	0.78	0.74-0.81	0.88	0.86-0.90	0.75	0.72-0.77
	100-200	0.84	0.81-0.86	0.92	0.91-0.94	0.82	0.81-0.84
	200-350	0.93	0.90-0.94	0.96	0.95-0.97	0.89	0.88-0.91
	350-500	0.98	0.96-0.99	0.99	0.98-1.00	0.96	0.95-0.98
	≥500	1.00		1.00		1.00	
HIV-RNA (copies/ml) at previous visit/measurement	<500	1.00		1.00		1.00	
	500-1000	0.87	0.84-0.90	0.84	0.82-0.86	0.93	0.90-0.94
	1000-10000	0.83	0.81-0.85	0.83	0.81-0.83	0.94	0.93-0.96
	10000-50000	0.81	0.79-0.83	0.82	0.81-0.84	0.98	0.96-1.00
	50000-100000	0.70	0.68-0.72	0.79	0.78-0.81	0.98	0.96-1.01
	≥100000	0.72	0.70-0.75	0.79	0.77-0.81	1.00	0.97-1.02
Therapy	Change in therapy vs no change	0.76	0.75-0.78	0.87	0.86-0.88	0.96	0.95-0.97
	Therapy interruption vs no interruption	1.19	1.16-1.23	1.14	1.11-1.15	0.91	0.88-0.93
Visit / measurement specific	After any CDC-C event vs before	0.89	0.86-0.93	0.97	0.95-0.99	0.93	0.92-0.95
characteristics	During pregnancy vs not	0.70	0.64-0.76	0.59	0.56-0.62	0.64	0.60-0.68
	During trial participation vs not	0.67	0.64-0.69	0.67	0.66-0.68	0.69	0.68-0.70

* AF: Acceleration factor. ** 95% CI: 95% confidence interval

Table 6.2: Variables independently associated with time between clinical visits/measurements of CD4 /HIV-RNA.

Hospital	Clinical visits		HIV-RNA		CD4	
	AF*	95% CI**	AF*	95% CI**	AF*	95% CI**
1	0.83	0.70-0.97	1.96	1.75-2.17	1.05	0.95-1.18
2	1.04	0.93-1.18	1.85	1.69-2.00	1.03	0.96-1.10
3	1.22	1.14-1.30	1.72	1.67-1.79	2.04	1.96-2.13
4	1.16	0.97-1.41	1.47	1.33-1.61	2.00	1.79-2.22
5	1.37	1.27-1.49	1.32	1.25-1.37	1.18	1.12-1.23
6	1.09	0.99-1.19	1.28	1.22-1.35	1.09	1.03-1.15
7	1.27	1.18-1.35	1.27	1.22-1.32	1.19	1.14-1.23
8	1.18	1.09-1.27	1.23	1.18-1.28	1.15	1.10-1.20
9	1.06	0.98-1.15	1.23	1.18-1.28	1.11	1.06-1.18
10	1.02	0.92-1.12	1.23	1.16-1.30	1.18	1.11-1.25
11	1.25	1.12-1.37	1.20	1.14-1.27	0.99	0.93-1.05
12	0.56	0.43-0.73	1.19	1.05-1.33	1.10	0.97-1.25
13	0.79	0.67-0.92	1.18	1.05-1.32	1.01	0.90-1.12
14	0.97	0.88-1.06	1.18	1.11-1.23	1.09	1.03-1.15
15	0.98	0.85-1.12	1.18	1.08-1.30	1.06	0.97-1.18
16	1.32	1.22-1.43	1.15	1.10-1.19	1.09	1.04-1.12
17	1.00	0.91-1.10	1.12	1.05-1.19	0.91	0.85-0.96
18	0.85	0.78-0.93	1.12	1.06-1.19	1.02	0.96-1.08
19	0.99	0.90-1.09	1.10	1.04-1.16	1.20	1.14-1.27
20	0.91	0.83-1.00	1.10	1.05-1.16	1.05	1.00-1.11
21	0.75	0.65-0.86	1.09	1.00-1.19	1.37	1.25-1.52
22	1.20	1.10-1.33	1.03	0.98-1.09	0.94	0.89-1.00
23	1.00		1.00		1.00	
24	0.76	0.68-0.85	0.88	0.82-0.93	0.79	0.74-0.84

* AF: Acceleration factor, ** 95% CI: 95% confidence interval

Table 6.3: Differences in frequency of clinical visits and CD4 and HIV-RNA measurements between hospitals (after adjustment for factors listed in Table 2). Hospitals are ordered according to the size of the AF for times between HIV-RNA measurements. Hospital 23 is the reference hospital. Its median time between clinical visits was 89 days; the interval was 84 days for both CD4 measurements and HIV-RNA measurements.

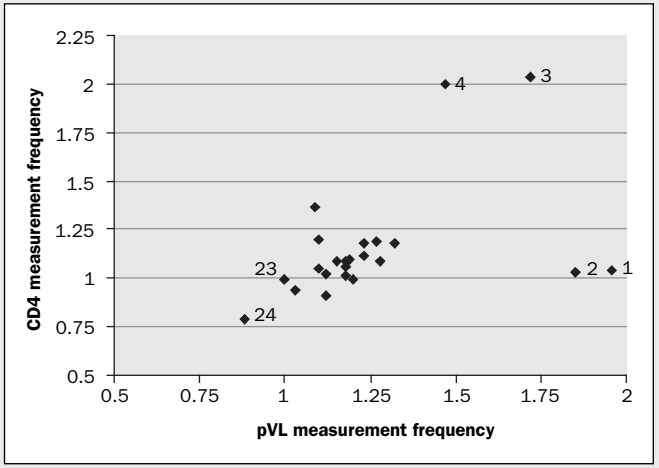

Figure 6.1: Adjusted acceleration factors of CD4 and HIV-RNA measurement frequency of all hospitals relative to reference hospital 23.

Trends o

over time

The changing face of the HIV epidemic in the Netherlands

Ard van Sighem

Introduction

We have previously shown that the HIV-infected population in the Netherlands has evolved from a population dominated by individuals with male homosexual contacts or a history of intravenous drug use to a population in which heterosexual transmission has become a substantial risk[9, 11]. This shift is also reflected in an increasing proportion of infections amongst women. In addition, the increase of infections with non-B HIV-1 subtypes suggests that some HIV infections in the Netherlands are imported from HIV-endemic areas.

This chapter will present the most recent data on changes over time in the three main risk groups, the geographical origin of HIV-1-infected patients, and the differences amongst these groups at diagnosis. Particular attention will be paid to four large immigrant populations in the Netherlands, namely those from the Netherlands Antilles (including Aruba), Suriname, Ghana, and Cape Verde.

Study population and methods

The study population consisted of 10,445 HIV-1 infected patients with a known year of diagnosis. Of those, 10,337 (99.0%) were diagnosed at age 13 years or older. Countries of origin or infection were considered as 12 regions: the Netherlands, Western Europe excluding the Netherlands, Central Europe, Eastern Europe, South and Southeast Asia, North Africa and the Middle East, sub-Saharan Africa, North America, Latin America, the Caribbean, Australia, and the Pacific islands[41]. Kaplan-Meier curves were used to assess the time to loss of follow-up. Patients were censored if they died or if they had a date of last contact after 1 January 2004. Drop-out rates for patients from the various regions were compared using a Cox proportional hazards model.

HIV-1 subtypes were determined using the nucleotide sequences of protease and reverse transcriptase (RT). Sequences were available from five virology laboratories: AMC-UvA in Amsterdam (Suzanne Jurriaans, Nicole Back, Lia van der Hoek, and Ben Berkhout), Erasmus MC in Rotterdam (Martin Schutten and Ab Osterhaus), UMCU in Utrecht (Rob Schuurman and Charles Boucher), LUMC in Leiden (Eric Claas and Louis Kroes), and VUMC in Amsterdam (Annika Petterson and Paul Savelkoul). Subtypes were determined separately for every genotypic sequence available for each patient. Sequences were compared pair-wise using the Kimura 2-parameter model for distances[42]. A representative set of reference sequences was obtained from the Los Alamos sequence database – http://www.hiv-web.lanl.gov – and was included in the distance calculations. Sequences were clustered using the neighbour-joining method; they were assigned a specific subtype when the bootstrap value of the cluster containing the sequences and a reference sequence exceeded 85%[43]. Sequences that could not be classified as a specific non-B subtype or a circulating recombinant form (CRF) were labelled 'non-B'. The CRFs designated as CRF01_AE and CRF02_AG will be referred to, more briefly, as AE and AG.

Changes over time were assessed by studying changes in the patient's characteristics at diagnosis. Proportions were compared by an χ^2-test or, if sample sizes were small, by Fisher's exact test. Differences in age, CD4 count, and RNA levels were tested using Wilcoxon Mann-Whitney and χ^2 non-parametric tests. The significance of proportional changes over time was assessed with the Cochran-Armitage test for trends or with logistic regression modelling. For continuous variables, changes over time were studied using analysis of variance; medians are reported together with the interquartile range (IQR).

Results

Homosexual men

For 5507 men (53.3%), of whom 3480 (63.2%) were diagnosed in or after 1996, the reported mode of HIV transmission was homosexual contact. Between 2000 and 2004, such diagnoses increased from 326 per year

to 455 per year ($p<0.0001$). The majority of these homosexually-infected men, 4080 (74.1%), were of Dutch origin. Other frequently reported regions of origin were the other Western European countries (423 patients, 7.7%), Latin America (326, 5.9%), the Caribbean (146, 2.7%), and South/Southeast Asia (150, 2.7%). These proportions did not significantly change across the years of diagnosis. Of the 326 patients from Latin America, 140 (42.9%) were from Suriname; of the Caribbean population, 117 of 146 (80.7%) originated from the Netherlands Antilles. The sub-Saharan African population consisted of 68 (1.2% of the homosexually-infected total), of whom two originated from Cape Verde and three from Ghana.

Five years after HIV diagnosis, 96.5% (95% CI 95.7–97.2) of homosexual patients originating in the Netherlands were still in follow-up or had died. This proportion was similar in the Caribbean patients, 96.8% (93.3–100), but was lower in those from non-Dutch countries of Western Europe, 93.2% (90.3–96.1), and those from Latin America, 92.1% (88.5–95.7). The Cox proportional hazards model showed a significant difference in drop-out rates between patients from the Netherlands and those from other Western European countries ($p<0.0001$) or from Latin America ($p=0.0006$). A preliminary analysis of reasons why patients in general discontinue follow-up showed that about 30% moved away from the Netherlands whilst about 60% were truly lost to follow-up. That is, they probably remained in the country but simply dropped out for undocumented reasons.

Median HIV-1 RNA plasma levels and CD4 cell counts at diagnosis were 4.9 $\log_{10}$ copies/ml (IQR 4.3–5.3) and 320 x 10^6 cells/l (IQR 120–510), respectively. For patients originating from the Netherlands, RNA levels were higher than for other patients ($p=0.0007$), being 4.9 (4.3–5.3) and 4.8 (4.1–5.2), respectively; CD4 counts did not differ amongst patients from different regions ($p=0.03$). Median CD4 cell counts increased from 250 (IQR 90–410) to 370 (IQR 226–580) in 2005 ($p<0.0001$), whilst RNA levels slightly decreased ($p=0.007$) from 4.8 (4.1–5.4) in 1996 to 4.7 (4.0–5.0) in 2005.

The median age at diagnosis of patients of Dutch origin, 38.7 years (IQR 33.1–46.0), was higher than in patients from other regions, 33.8 years (29.2–39.5) ($p<0.0001$). It increased over time from 36.3 years (IQR 31.5–44.1) in 1996 to 38.8 years (IQR 32.7–45.2) in 2005 ($p=0.002$). Of the patients diagnosed in or after 1996, 286 (8.2%) had a CDC-B event at diagnosis, and 550 (15.8%) had a CDC-C event[44].

For 1322 men (24.0%) in the study population, the HIV subtype could be determined. Of these, 1287 were infected with subtype B (97.4%). The annual proportion of homosexuals diagnosed with a subtype B virus did not change between 1996 and 2005 ($p=0.1$). Other subtypes found amongst homosexuals were AE (13 patients), C (9), AG (6), A (3), G (2), and other non-B subtypes (2) (Table 7.1).

For 3823 men (69.4%), the most likely country of infection was known (Table 7.2). A majority of 3395 (88.8%) were infected in the Netherlands. Of the 3029 patients born in the Netherlands, 2928 (96.7%) were infected in the Netherlands, whilst the remaining 101 patients were infected largely in other Western European countries, in South/Southeast Asia, or in North America. Of the 794 patients born outside the Netherlands, 467 (58.8%) were infected in the Netherlands and 285 (35.9%) in the region from which they originated. The proportion of patients born and/or infected in the Netherlands or elsewhere did not change with time ($p=1.0$). For 69 (59.0%) of the patients originating from the Netherlands Antilles and 87 (62.1%) of those from Suriname, the country of infection was known. Of the 69 from the Antilles, 12 (17.4%) were infected there and 51 (73.9%) infected in the Netherlands, whilst of the 87 patients from Suriname, 13 (14.9%) got their HIV-infection in Suriname and 74 (85.1%) in the Netherlands.

Intravenous drug users (IDUs)

The group of patients infected by intravenous drug use consisted of 409 men and 152 women. Of the total (561), the majority (363 patients, 64.7%), was diagnosed in or before 1995; only 70 IDUs were diagnosed between 2000 and 2004. Most of the IDU population originated from the Netherlands (374 patients, 66.7%), other Western European countries (99 patients, 17.6%), Latin America (22 patients, 3.9%), and the Caribbean (5 patients, 0.9%). The five patients from the Caribbean all originated from the Antilles, whilst 19 (86%) of the 22 patients from Latin America were of Surinamese origin. No patients from Cape Verde or Ghana were registered in the HMF as being infected through drug use.

For 408 (72.7%) of the IDUs, the country of infection was known. The majority were infected in the Netherlands (356 patients, 87.3%) or in other Western European countries (31 patients, 7.6%). Of the 118 patients born outside the Netherlands and having a known country of infection, 40 (34%) were infected in their region of origin. However, whilst all three Antilleans with known country of infection were infected in the Antilles, 12 of the 13 Surinamese patients were infected in the Netherlands.

For IDUs diagnosed in or after 1996, the median age at diagnosis was 37.4 years (IQR 32.9–42.7). The median CD4 cell count and HIV-1 RNA plasma level at diagnosis were 279 x 10^6 cells/l (87–470) and 4.9 $\log_{10}$ copies/ml (4.3–5.3), respectively. Between women and men, the only difference observed was that women tended to have higher viral loads: median 5.2 versus 4.8 $\log_{10}$ copies/ml (p=0.04). Between IDUs from inside and outside the Netherlands, those from outside were observed to be younger than those of Dutch origin: 34.2 versus 38.4 years at diagnosis (p=0.01).

Of the IDU population, 18 (3.2%) were born in Central and Eastern Europe, of whom 7 were diagnosed before 1996. The other 11 patients were diagnosed in or after 2000. Ten patients originated from the former Soviet Union (Russia, Ukraine, Azerbaijan, and Georgia), four patients from former Yugoslavia (Yugoslavia and Bosnia), two from Poland, one from the Czech republic, and one from Turkey. The number of non-B subtypes in the IDU population remained very limited. Of the 98 patients with a known subtype, 94 (96%) had a subtype B virus. The four non-B subtypes were A (1 patient), AE (2 patients), and G (1 patient).

Heterosexuals

Of 3361 patients infected by heterosexual contact, 1373 were men (13.2% of the total infected population, 40.9% of the heterosexual subgroup), and 1988 were women (19.2% of the total and 59.1% of heterosexuals). Most patients were diagnosed in or after 1996: 1134 men (82.6%) and 1620 women (81.5%). Between 2000 and 2004, the mean number of diagnoses was 146 for men and 226 for women, without a significant change over time (p=0.8).

The majority of the male population originated from the Netherlands (508 patients, 37.0%) and sub-Saharan Africa (493 patients, 35.9%), whilst 138 patients (10.1%) originated from Latin America and 75 (5.5%) from the Caribbean. In the female population, the most frequent region of origin was sub-Saharan Africa (975 patients, 49.0%). Only 494 women (24.8%) originated from the Netherlands. The proportions of female patients from Latin America and the Caribbean were similar to those of male patients: 9.5% (188 patients) and 5.8% (116 patients), respectively.

The distribution over region of origin for the entire heterosexual population is shown in Figure 7.1. Of the 326 patients from Latin America, 256 (78.5%) originated from Suriname, whilst 147 (77.0%) of the 191 patients from the Caribbean originated from the Netherlands Antilles. Amongst the patients from sub-Saharan Africa, 139 (9.5%) originated from Ghana and 26 (1.8%) from Cape Verde.

Five years after diagnosis, 97.3% (95% CI 96.1–98.5) of the population originating from the Netherlands was still in follow-up. The proportion in follow-up was lower in the populations from sub-Saharan Africa (87.3%, 85.1–89.4), from the Caribbean (93.3%, 88.9–97.6), and from Latin America (92.4%, 88.9–95.8). The Cox proportional hazards model showed a significant difference in the drop-out rates between patients originating from the Netherlands and those from sub-Saharan Africa ($p<0.0001$) or Latin America ($p<0.0001$). The reasons for drop-out were the same as for the homosexual population, regardless of regional origin, as was the proportion of patients who moved away or were otherwise lost to follow-up.

Between 1996 and 2002, the proportion of annually diagnosed heterosexual patients originating from sub-Saharan Africa increased from 34.2% to 59.2% ($p<0.0001$). Thereafter, this proportion declined to 40.2% in 2005 ($p<0.0001$). In contrast, the proportion of patients originating from the Netherlands decreased from 39.2% in 1996 to 19.7% in 2002 ($p<0.0001$) and rebounded to 27.2% in 2005 ($p=0.03$).

Table 7.3 shows the age, CD4 counts, and RNA plasma levels at HIV diagnosis for heterosexual men and women. In general, regardless of the region of origin, men were older at diagnosis than women and had lower CD4 counts and higher viral loads. When comparing characteristics between men and women from different regions of origin, there was no difference between Dutch patients and patients from other Western European countries. On the other hand, men and women from sub-Saharan Africa were generally younger and had lower CD4 counts compared to Dutch patients. Patients from Latin America ($p<0.0001$) and the Caribbean ($p=0.003$) likewise had lower CD4 counts than Dutch patients. Between male and female patients from South/Southeast Asia, CD4 and RNA levels showed no significant difference, perhaps because of the small sample size. In general, no significant changes occurred in patient age, CD4 counts, or RNA levels between 1996 and 2005.

Of the 2754 heterosexual patients diagnosed in or after 1996, 481 (17.5%) had an AIDS-defining (CDC-C) event at diagnosis, whilst 156 (5.7%) had a CDC-B event. The proportion of patients presenting with AIDS declined from 22.8% in 1996 to 14.1% in 2005 ($p=0.003$), whilst the proportion of CDC-B diagnoses declined from 9.5% to 5.4% during the same period ($p=0.006$).

The majority of the heterosexual patients (60.0%; men 57.7%, women 61.5%) was infected outside the Netherlands (Table 7.2). Only 42.3% of the men and 38.5% of the women were infected within the Netherlands. Of those born elsewhere, 402 of the 574 men (70.0%) and 838 of the 1110 women (75.5%) were infected in the region from which they originated. Of the combined male and female patients from the Netherlands Antilles and Aruba, 61 of 110 (55.5%) were infected in the home country, as were 50 of 156 patients (32.1%) from Suriname, 55 of 69 (79.7%) from Ghana, and 2 of 12 (16.7%) from Cape Verde. Of patients from these regions infected in the Netherlands, there were 43 (39.1%) from the Antilles/Aruba, 101 (64.7%) from Suriname, 14 (20.3%) from Ghana, and 10 (83.3%) from Cape Verde.

In the male population originating from the Netherlands (371 patients), 252 (67.9%) were infected in the Netherlands, 42 (11.3%) in sub-Saharan Africa, and 50 (13.5%) in South/Southeast Asia. Of the 400 women originating from the Netherlands, 343 (85.8%) were infected in the Netherlands, whilst 27 (6.8%) were infected in sub-Saharan Africa.

Of the 654 patients with a known HIV-1 subtype, 288 (44.0%) harboured a subtype B virus. Subtype B virus strains were more prevalent amongst women than amongst men: 132 (45.8%) of 261 men and 156 (54.2%) of 393 women ($p=0.006$). In 1996, 53.3% of the diagnosed

infections were with a subtype B virus. Thereafter, this proportion declined to 20.3% in 2002, then rebounded to 49.3% in 2004.

Figure 7.2 shows the distribution of subtypes in the infected heterosexual population. Although subtype B is the most prevalent countrywide, it was found in only 4% of the infections amongst the 281 heterosexuals from sub-Saharan Africa living in the Netherlands. It was harboured by 75% of the 373 patients originating in other 11 regions, but in heterosexuals from sub-Saharan Africa, the most prevalent subtypes were C (28%), AG (30%) and A (12%).

Discussion

As already observed in our previous annual reports, this study shows that from 1996 onwards, an increasing proportion of the newly diagnosed patients was infected by heterosexual contact and originated from sub-Saharan Africa[9, 11, 45]. However, since the year 2000, the annual number of diagnoses amongst heterosexuals has been stable, whilst the annual number amongst homosexuals has continued to rise.

Homosexual men still form the largest HIV-infected group in the Netherlands[9, 11]. This group is mainly of Dutch origin and was infected in the Netherlands with a subtype B strain. Age and CD4 counts at diagnosis increase with calendar time, suggesting that homosexual men are diagnosed sooner after infection and are infected at older ages than patients in other risk groups.

In contrast to the homosexual population, infections in heterosexuals are mainly imported from sub-Saharan Africa and, to a lesser extent, from Latin America and the Caribbean. The majority of heterosexual patients of Dutch origin are infected in the Netherlands and in sub-Saharan Africa, although a considerable number of heterosexual men are infected in South/Southeast Asia, mainly in Thailand. Men are generally diagnosed at older age and in a later stage of infection than women. Our data from 2004 showed that viral loads in women are lower than in men when CD4 cell counts are high, but higher when CD4 counts are low, typically below 200 x 10^6 cells/l[46]. This finding is consistent with our current observation that women with high median CD4 counts have lower median viral loads than men. The similar viral loads observed in men and women from South/Southeast Asia are explained by the low CD4 counts (i.e., below 200 x 10^6 cells/l) found for both men and women in that region.

Recently it was reported that in Eastern Europe, the rate of new HIV infections, occurring mainly in IDUs, is amongst the highest in the world[47]. Although several countries in Eastern Europe are now part of the European Union and migration to Western Europe is easier, import to the Netherlands of infections by Eastern Europe IDUs is still very limited.

After 2002, there was a decline in the proportion of heterosexual patients originating from sub-Saharan Africa and hence, given the constant annual number of diagnoses, a decline in the absolute number of diagnoses. This is consistent with the decreasing number of people immigrating from Africa into the Netherlands since 2002. The number of immigrants from Africa reportedly declined from 21,410 in 2002 to 10,759 in 2004 (Statistics Netherlands, available via https://statline.cbs.nl).

Within the three risk groups considered in this chapter, we focussed on four large immigrant populations in the Netherlands. In the homosexual and IDU group, there were few if any patients from Ghana and Cape Verde; however, patients originating from Suriname and the Netherlands Antilles are well represented in all three risk groups.

Most of the Surinamese and Antillean homosexuals and drug users were infected in the Netherlands. In the

heterosexual group, importation of infections from the country of origin was largest for patients from Ghana, and next (in descending amount) for Antilleans, Surinamese, and Cape Verdians. The Cape Verdians consisted mainly of women and were infected mainly in the Netherlands.

The ranking of the three regions after Ghana is consistent with the travelling behaviour to those regions (e.g., most frequent for Antilleans) and the related sexual behaviour. More men than women have sexual contacts during travel; they acquire infections abroad and subsequently infect their wives[48]. A study now being conducted in patients originating from Suriname and the Netherlands Antilles seeks, amongst other things, to discover the extent to which infections are imported by these individuals who live in the Netherlands and regularly visit their country of origin (HMF research project I04031).

The proportion of patients originating from the Netherlands and still in follow-up (or already dead) five years after HIV diagnosis is similar for homosexuals and heterosexuals. The proportion in follow-up is slightly lower for patients from Latin America. Drop-out rates for the largely heterosexual patients from sub-Saharan Africa and the largely homosexual patients from Latin America and non-Dutch Western Europe are higher than for their counterparts from the Netherlands.

As the number of drop-outs is fairly small in general, its influence on the composition of the HIV-infected population is limited. Results do not change significantly when the population still in follow-up is considered instead of the entire of the HIV-diagnosed population.

There are no indications that reasons for discontinuing follow-up differ between patients from the Netherlands and those from other parts of the world. Patients lost to follow-up might be a potential source of new infections if they are also lost to proper treatment. Such patients include, for example, HIV-infected asylum seekers who illegally stay in the Netherlands despite being refused a residence permit. At this time, however, we can only speculate on these matters, as questions concerning HIV-infected illegal immigrants in the Netherlands are difficult to address within the framework of HMF.

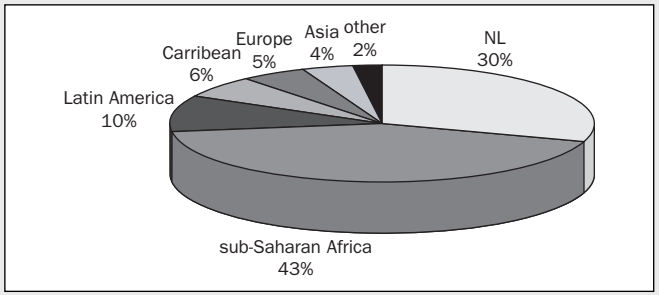

Figure 7.1: Distribution of regions of origin for the heterosexual HIV-infected population. NL: the Netherlands; Europe: combined Western Europe (excluding the Netherlands), Central Europe and Eastern Europe.

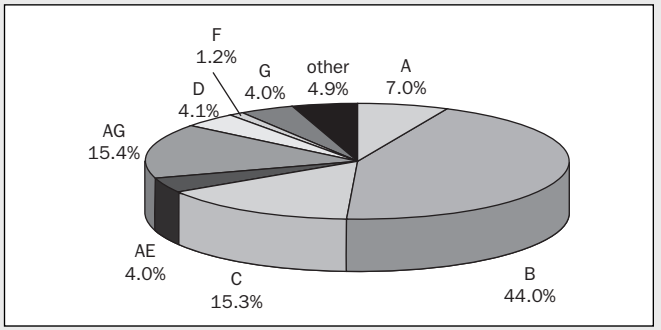

Figure 7.2: Distribution of the 654 known subtypes in the HIV-infected heterosexual population of the Netherlands.

	male										female							
	homosexual		heterosexual		IVD		blood		unknown		heterosexual		IVD		blood		unknown	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
A	3	0.2	17	6.5	1	1.4	1	4.3	5	4.0	29	7.4						
AE	13	1.0	15	5.7	2	2.8	1	4.3	1	0.8	11	2.8			1	10.0		
AG	6	0.5	36	13.8			1	4.3	13	10.3	65	16.5			1	10.0		
B	1287	97.4	132	50.6	68	94.4	19	82.6	91	72.2	156	39.7	26	100	3	30.0	13	92.9
C	9	0.7	35	13.4			1	4.3	4	3.2	65	16.5			3	30.0	1	7.1
D			3	1.1					5	4.0	24	6.1			1	10.0		
F			3	1.1					1	0.8	5	1.3						
G	2	0.2	9	3.4	1	1.4			2	1.6	17	4.3			1	10.0		
non-B	2	0.2	11	4.2					4	3.2	21	5.3						
	1322		**261**		**72**		**23**		**126**		**393**		**26**		**10**		**14**	

IVD: intravenous drug users.

Table 7.1: HIV-1 subtypes by gender and mode of transmission.

	total population	country of infection known		born in NL infected in NL		born in NL infected outside NL		not born in NL infected in NL		not born in NL not infected in NL	
		N	%	N	%	N	%	N	%	N	%
men											
homosexual	5507	3823	69.4	2928	76.6	101	2.6	467	12.2	327	8.6
heterosexual	1373	945	68.8	252	26.7	119	12.6	148	15.7	426	45.1
IVD	409	299	73.1	222	74.3	5	1.7	40	13.4	32	10.7
blood	105	94	89.5	47	50.0	12	12.7	8	8.5	27	28.7
unknown	658	324	49.2	155	47.8	6	1.9	44	13.6	119	36.7
women											
heterosexual	1988	1510	76.0	343	22.7	57	3.8	239	15.8	871	57.7
IVD	152	109	71.7	62	56.9	1	0.9	32	29.4	14	12.8
blood	41	39	95.1	9	23.1	2	5.0	4	10.3	24	61.5
unknown	103	72	69.9	45	62.5	4	5.6	14	19.4	9	12.5

IVD: intravenous drug use.

Table 7.2: Number of patients infected in the Netherlands (NL) or elsewhere, stratified by gender and mode of transmission.

	men			women		
	age (years)	CD4 ($\times 10^6$ cells/l)	RNA ($\log_{10}$ copies/ml)	age (years)	CD4 ($\times 10^6$ cells/l)	RNA ($\log_{10}$ copies/ml)
the Netherlands	40.9	280	4.9	34.5	423	4.4
	33.7-50.3	60-482	4.3-5.4	28.3-45.1	160-656	3.6-5.0
Europe	38.8	260	4.9*	30.8	395	4.6*
	33.0-49.3	80-410	4.0-5.4	28.2-35.6	268-615	3.2-5.1
sub-Saharan Africa	33.7	161	4.9	28.4	270	4.3
	28.2-38.6	71-322	4.2-5.2	23.6-33.9	130-430	3.5-5.0
Latin America	38.8	130	4.9	31.8	281	4.4
	33.8-46.7	30-330	4.1-5.3	27.2-39.0	105-432	3.6-5.0
the Caribbean	37.8	100	4.7*	31.2	325	4.4*
	32.2-43.9	25-258	4.3-5.3	23.7-38.1	100-550	3.8-5.0
South/Southeast Asia	47.7	150*	4.5*	31.6	135*	4.8*
	41.3-52.5	60-316	3.8-5.0	28.2-36.3	28-310	3.8-5.1
total	36.7	190	4.9	30.3	290	4.4
	31.3-44.6	60-380	4.3-5.3	25.1-36.5	126-490	3.6-5.0

*p>0.01 men vs. women; all other men-women comparisons have p<0.01.

Table 7.3: Median age, CD4 count, and RNA plasma level at diagnosis for heterosexual men and women from the most prevalent regions of origin.

Long-term

n survivors

Characterisation of a population infected with HIV for more than 15 years

Ard van Sighem

Introduction

The course of untreated HIV-1 infection varies greatly amongst patients. Some patients progress rapidly to a CD4 level at which therapy should be initiated, whilst a small proportion of the patients shows no apparent progression in the absence of therapy[49-53]. It is still unclear if progression will eventually occur in this latter group, or if CD4 counts will remain high indefinitely.

Of the patient population included in the ATHENA national observational cohort, a small number of patients has been infected for more than 20 years. The primary aim of this chapter is to explore and describe these patients. In addition, disease progression in this group is compared to progression in more recently diagnosed patients.

Study population and methods

The study population consisted of HIV-1 infected patients who were diagnosed before 1 January 2003 (baseline) and were still alive and in follow-up on that date. The patients were divided into four groups according to their year of diagnosis: in or before 1987, between 1988 and 1995, between 1996 and 2000 (early HAART era), and after 2000 (late HAART era). The first two groups were chosen such that both contain only patients diagnosed in the pre-HAART era. Moreover, patients in the first group had been HIV-positive for at least 15 years at baseline.

The demography, immunology, and virology of patients in each group were assessed at diagnosis and at baseline. In addition, CDC-B and CDC-C events and other adverse events occurring before 1 January 2003 were also considered. Resistance to antiretroviral drugs was determined as described in Chapter 15. All resistance-associated mutations ever detected in a patient before baseline were used to determine his/her resistance level at baseline.

In the subpopulation of those patients whose measurements of CD4 T cell count and RNA plasma level were available within the period starting three months before baseline and ending three months after baseline, progression to death and AIDS after baseline was analysed using Cox proportional hazards models. Patients included in the model were censored at their last follow-up visit or, for progression to AIDS, at the time of death. Wald 95% confidence intervals (CI) were determined for the hazard ratios (HR).

Results

The total study population consisted of 7622 patients divided into four groups according to calendar year of diagnosis: 481 (6.3%) before 1987, 2278 (29.9%) between 1988 and 1995, 3128 (41.0%) between 1996 and 2000, and 1735 (22.8%) after 2000. Characteristics of the population alive at 1 January 2003 are shown in Table 8.1. The proportions of men, patients originating from the Netherlands, patients infected through homosexual contact, and patients infected by intravenous drug use have decreased over time since the early 1980s.

Of patients diagnosed in or before 1987, 178 (37.0%) had experienced an AIDS- defining event. This proportion decreased to 20.2% in the group of most recently diagnosed patients. The most common CDC-C events seen in the oldest population were oesophageal candidiasis (57 patients, 11.9%), Kaposi sarcoma (50 patients, 10.4%), P. carinii pneumonia (PCP) (26 patients, 5.4%), other pneumonia (21 patients, 4.4%), pulmonary tuberculosis (12 patients, 2.5%), and AIDS dementia (13 patients, 2.7%). In patients diagnosed after 2000, these proportions were 2.8% for oesophageal candidiasis, 2.4% for Kaposi sarcoma, 6.7% for PCP, 0.6% for other pneumonia, 3.1% for pulmonary tuberculosis, and 0.5% for AIDS dementia.

Since the introduction of HAART in 1996, the most frequently reported adverse event in the population of patients diagnosed in or before 1987 was lipodystrophy (both fat accumulation and fat loss), which was

reported for 216 (44.9%) patients. Fat accumulation was found in 93 (19.3%) patients and fat loss in 174 (36.2%) patients. In patients diagnosed between 1988 and 1995, fat accumulation and fat loss were reported for 442 (19.4%) and 712 (31.3%), respectively; lipodystrophy of both types was reported for 908 (39.9%). In patients diagnosed between 1995 and 2000, lipodystrophy was reported for 706 (22.6%), and in patients diagnosed after 2000, it was reported for 40 (2.3%).
Other frequently reported adverse events in the population diagnosed in or before 1987 were neuropathy (111 patients, 23.1%), diarrhoea (104 patients, 21.6%), and nausea (77 patients, 16.0%). Likewise in the population diagnosed between 1988 and 1995, these events were recorded for similar or slightly smaller proportions of the population.

In the group of patients diagnosed in or before 1987, 16.2% harboured one or more mutations associated with resistance to nucleoside reverse transcriptase (RT) inhibitors; 5.6% had mutations associated with resistance to non-nucleoside RT inhibitors, and 7.9% had mutations giving resistance to protease inhibitors. These percentages were similar in the group of patients diagnosed between 1988 and 1995. Genotyping was performed in about 20% of the patients in the two groups.

Amongst the 7622 patients still alive on 1 January 2003, 285 AIDS-defining events were recorded after 1 January 2003 during 14,784 person-years of follow-up, corresponding with an incidence of 1.93 events (1.71–2.17) per 100 person-years. The incidence did not differ amongst the four diagnosis groups ($p=0.07$). Mortality after 1 January 2003 declined from 3.83 (2.69–5.31) per 100 person-years in the group of patients diagnosed in or before 1987, to 0.95 (0.65–1.78) per 100 person-years in the group of most recently diagnosed patients ($p<0.0001$).

For 6293 (82.6%) of the patients, both a baseline CD4 count and HIV-RNA level measurement were available. The proportional hazards model showed – when corrected for age, mode of transmission, having experienced a CDC-C event before baseline, CD4 count, and RNA level – that progression to AIDS did not differ amongst the four diagnosis groups ($p=0.8$). Analogously, after correction for the same set of covariates, the model showed that progression to death did differ amongst the four groups. Compared to the group of most recently diagnosed patients, the hazard ratio was 2.8 (95% CI 1.6–4.8) for the group of patients diagnosed in or before 1987; it was 1.9 (95% CI 1.2–3.0) for the group diagnosed between 1988 and 1995, and 1.2 (95% CI 0.8–2.0) for the group diagnosed between 1996 and 2000. Drug resistance and hepatitis C co-infection were not associated with disease progression.

Of the 194 cases of death after baseline, 98 (51%) were scored as non-HIV-related and 63 (32%) as HIV-related; for 33 deaths (17%), the cause could not be scored[24]. For patients diagnosed before 2000, 34% of deaths were HIV-related in cases occurring after 1 January 2003 that could be scored. There was no difference in this proportion amongst the three groups of patients diagnosed before 2000 ($p=0.4$). In the group of most recently diagnosed patients, 16 (70%) out of 23 deaths were HIV-related, a proportion significantly different from the other diagnosis groups ($p=0.001$). When considering progression to HIV-related death (i.e., by censoring deaths due to unknown or non-HIV-related causes), no difference in progression was found amongst the four diagnosis groups.

Discussion

The population of patients in the Netherlands who were HIV-positive for at least 15 years on 1 January 2003 constituted 6% of the country's total HIV-infected population at that time. Of these so-called long-term survivors, 10% had never been treated with antiretroviral therapy. Such untreated patients are usually called long-term non-progressors[50]. In contrast, although the

long-term survivors were alive after more than 15 years of HIV-infection, they suffered from a broad range of CDC-C and other adverse events.

Previous cohort studies show no correlation between mode of transmission and HIV disease progression[54]. However, most cohorts with a long-term follow-up have consisted of male homosexuals and IDUs. Even in our cohort, patients infected through heterosexual contact have become a substantial group only since the end of the 1980s, and no long-term follow-up is yet available on such patients. Short-term disease progression reportedly does not differ between homosexuals and heterosexuals[15, 24], nor is there correlation between ethnicity and progression[50].

The set-up of the HMF database does not enable comparison of long-term survivors with more rapid progressors who died before 1998 and did not use HAART. Such patients are not included in the database. Hence, long-term survivors cannot be compared with patients who were HIV-infected in the pre-HAART area. Compared with the most recently diagnosed patients, HMF data show – not surprisingly – that long-term survivors had higher CD4 counts at diagnosis, as well as lower RNA levels. This observation merely illustrates the absence from our database of rapid progressors who were diagnosed in the 1980s.

Despite such limitations, it was possible to compare disease progression after 1 January 2003 amongst the four groups stratified according to year of diagnosis. No difference in rates of progression to AIDS was found. In contrast, patients diagnosed in the early eighties progressed more rapidly to death after 1 January 2003 than the most recently diagnosed patients, even with correction for age. This difference was due to non-HIV-related causes of death that apparently are not fully explained by the older age of the group diagnosed in or before 1987. Probably, the life-style of the group differs from that of more recently diagnosed patients. Indeed, more use of drugs and alcohol was reported by patients diagnosed in or before 1987, compared to the other groups. Also the older patients had a higher prevalence of hepatitis C infection, a cause of liver-related deaths. However, there was no direct association of hepatitis C status and AIDS progression.

The underlying cause of non-progression cannot be determined from the data collected by the HMF. It has been shown that non-progressors are the extreme cases in a continuous distribution of progression rates[51], although immunological and host genetic factors surely play a role. Significant correlations of human lymphocyte antigen (HLA) genes with progression rates[55, 56] and varying susceptibility to HIV-infection[57] have been found. In particular, allele B27 is associated with non-progression[58, 59].

Host genetic information is not routinely available for patients registered in the HMF. Several cohorts, in particular the Multicenter AIDS Cohort (MACS) in the United States and the Western Australian HIV Cohort Study, have some information available on known AIDS-restriction genes. Preliminary analyses showed that some of those genes significantly influence the efficacy of HAART. It might be interesting to set up a similar (prospective) study within HMF, which has a more diverse and complete cohort than the two mentioned.

	diagnosis ≤ 1987 (N=481)		diagnosis 1988-1995 (N=2278)		diagnosis 1996-2000 (N=3128)		diagnosis >2000 (N=1735)	
	N (%) /	median (IQR)	N (%) /	median (IQR)	N (%) /	median (IQR)	N (%) /	median (IQR)
male gender	401	(87.7%)	1759	(81.8%)	2307	(77.9%)	1172	(71.5%)
Dutch origin	328	(68.2%)	1519	(66.7%)	1764	(56.4%)	842	(48.5%)
transmission category								
MSM	327	(68.0%)	1378	(60.5%)	1623	(51.9%)	789	(45.5%)
heterosexual	34	(7.1%)	491	(21.6%)	1113	(35.6%)	747	(43.1%)
IDU	64	(13.3%)	206	(9.0%)	116	(3.7%)	29	(1.7%)
AIDS before baseline	178	(37.0%)	721	(31.7%)	905	(28.9%)	351	(20.2%)
total follow-up (years)	939		4526		6219		3380	
progression to death	36	(7.5%)	99	(4.3%)	69	(2.2%)	32	(1.8%)
progression to AIDS	18	(3.7%)	94	(4.1%)	97	(3.1%)	76	(4.4%)
HCV status*								
negative	276	(75.8%)	1436	(84.2%)	2260	(91.9%)	1220	(94.3%)
positive	88	(24.2%)	270	(15.8%)	198	(8.1%)	74	(5.7%)
therapy at baseline								
none	49	(10.2%)	176	(7.7%)	451	(14.4%)	754	(43.5%)
HAART pre-treated	263	(54.7%)	1209	(56.4%)	302	(9.7%)	32	(1.8%)
HAART naïve	159	(33.1%)	831	(36.5%)	2345	(75.0%)	943	(54.4%)
ART	10	(2.1%)	62	(2.7%)	30	(1.0%)	6	(0.3%)
status at baseline								
age (years)	46.0	(41.3–51.8)	42.6	(37.9–49.2)	39.8	(34.2–46.7)	36.7	(29.7–43.9)
CD4 ($\times 10^6$ cells/l)	440	(287–620)	480	(300–680)	470	(324–670)	400	(240–580)
CD8 ($\times 10^6$ cells/l)	1070	(750–1490)	1003	(710–1390)	950	(681–1316)	951	(661–1350)
RNA < 50 copies/ml	255	(61.0%)	1262	(63.4%)	1904	(69.3%)	648	(43.9%)
RNA ($\log_{10}$ copies/ml)	3.6	(2.4–4.7)	3.8	(2.7–4.6)	3.9	(2.9–4.6)	4.1	(3.1–4.9)
resistance at baseline								
never genotyped	388	(80.7%)	1858	(81.6%)	2731	(87.3%)	1586	(91.4%)
NRTI	78	(16.2%)	312	(13.7%)	148	(4.7%)	27	(1.6%)
nNRTI	27	(5.6%)	140	(6.1%)	62	(2.0%)	11	(0.6%)
PI	38	(7.9%)	154	(6.8%)	65	(2.1%)	7	(0.4%)
status at diagnosis								
age (years)	29.4	(24.6–34.6)	32.2	(27.4–38.9)	35.2	(29.7–42.0)	35.7	(28.8–42.9)
CD4 ($\times 10^6$ cells/l)	760	(570–920)	360	(177–581)	260	(80–460)	300	(110–510)
CD8 ($\times 10^6$ cells/l)	785	(610–1200)	900	(650–1350)	860	(550–1255)	870	(580–1250)
RNA < 50 copies/ml	9	(35%)	20	(20%)	95	(4.5%)	51	(3.5%)
RNA ($\log_{10}$ copies/ml)	4.6	(4.3–5.4)	4.6	(4.0–5.1)	4.9	(4.3–5.4)	4.9	(4.2–5.2)

MSM: men having sex with men; IDU: intravenous drug use; HCV: hepatitis C virus; NRTI: nucleoside reverse transcriptase (RT) inhibitor; nNRTI: non-nucleoside RT inhibitor; PI: protease inhibitor; *percentages given are percentages of the population in whom the variable has been measured. Log-transformed RNA values at baseline and at diagnosis are given for those patients with RNA > 500 copies/ml.

Table 8.1: Characteristics of patients diagnosed in four time periods.


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dren

HIV-infected children and adolescents in the ATHENA national observational cohort

Ard van Sighem

Introduction

Although the pathogenesis and treatment of HIV infection in children and adolescents are the same as for adults, there are some major issues that complicate extrapolation of results obtained in studies in adults to children[60-62]. HIV-infection in children and adolescents takes place in an immature and still developing immune system. Therefore, clinical symptoms and virological and immunological characteristics differ from those observed in adults. Besides, the dosage of antiretroviral drugs requires adaptation as children get older. Also, compliance to therapy has problems specific to children[63-66].

The HMF registration of HIV-infected children – patients in follow-up in one of the four children's hospitals that treat HIV-infection – started in 2003, although the entry of data started only at the end 2004. Data on children are contained in a separate database, with more information available than for adult patients. This chapter presents the first survey of the children in the ATHENA cohort.

Study population and methods

The study population consisted of HIV-1-infected children and adolescents for whom the year of diagnosis was known. Children were defined as those patients who were below 13 years of age at 1 June 2005; were infected by mother-to-child transmission or breast- feeding; or were diagnosed below 13 years of age.

CD4 cell counts and HIV-RNA plasma levels were assessed at diagnosis, at start of HAART (T_0), and at 24 weeks after start of HAART (T_1). If the first HIV-positive test was performed later than the first RNA measurement, the date of the RNA measurement was used as date of diagnosis. In addition to the routinely collected demographic data, information was collected on the parents' country of origin. HIV-1 subtypes were obtained as described in Chapter 7 of this report. Genotypic sequences were scanned for major mutations associated with drug resistance, as listed in the IAS-USA table[67] and discussed in Chapter 15.

Confidence intervals (CI) on the proportions of diagnosed children amongst the total number of diagnoses were obtained using a binomial distribution. The significance of changes in the proportions over time was assessed using a χ^2-test. Differences in CD4 counts and RNA levels were tested using Wilcoxon Mann-Whitney and χ^2 non-parametric tests. For continuous variables, medians are reported together with the interquartile range (IQR).

Results

The total study population consisted of 112 children, of whom 57 (51%) were boys and 55 (49%) were girls. Characteristics of the population are summarised in Table 9.1. The proportion of children born in the Netherlands was larger for boys than for girls, but this difference was not statistically significant (p=0.2). For 88 children (79%), at least one of the parents originated from outside the Netherlands. The majority of the children, 63 (56%), had at least one parent from sub-Saharan Africa.

The majority of the children were infected by mother-to-child transmission (76%). Six girls were infected by sexual contact and were diagnosed between 14 and 17 years of age. Three of these girls originated from sub-Saharan Africa and also had been infected there; one girl was born and infected in Suriname; one was born and infected in the Netherlands; one was born in the Antilles but infected in the Netherlands. Of the eight boys infected by contact with blood or blood products, seven suffered from haemophilia.

The percentage of children diagnosed with HIV amongst the total annual number of persons diagnosed with HIV increased (p=0.002) from 0.2% (95% CI 0.0–0.9) to 2.4% (1.5–3.7) in 2001 (Figure 9.1). Thereafter, this percentage declined (p=0.02) to 0.7% (0.2–1.4) in 2004. Between 1996

and 2004, the overall percentage of diagnosed children was 1.2% (0.9–1.5).

The total follow-up during childhood (i.e., until the age of 18) was 591 person-years, including 270 person-years for boys and 321 person-years for girls. By 1 June 2005, only one of the children had died, a haemophilia patient born in 1972, diagnosed in 1985, and deceased in 1999. A total of 45 patients (40%), including 23 boys and 22 girls, were diagnosed with AIDS during follow-up. For 37 (82%), this AIDS diagnosis took place within half a year after diagnosis.

The median CD4 count and $\log_{10}$ RNA levels at diagnosis were 780 x 10^6 cells/l (IQR 380–1790) and 5.2 $\log_{10}$ copies/ml (4.5–5.8), respectively. The difference in RNA levels between boys and girls was not statistically significant (p=0.09). Within the first six months after birth, CD4 counts were 1580 (620–1970) in children not yet treated (Figure 9.2). Thereafter, CD4 counts declined with increasing age in both those treated and untreated to levels comparable to levels observed in adult HIV-infected patients. Especially in the first years after birth, CD4 counts were lower in HIV-infected than in uninfected children[68]. In untreated patients, RNA plasma levels were 5.7 $\log_{10}$ copies/ml (5.3–6.0) in the first year after birth. Thereafter, HIV-RNA levels decreased to 5.2 (4.6–5.8) in untreated children aged between 1 and 2.5 years and to 4.6 (4.1–5.1) in children between 2.5 and 6 years.

Of the 112 children, 98 (88%) initiated HAART during follow-up with a median time between diagnosis and start of HAART of 0.2 years (0.1–3.3), or about two and a half months. The most frequently used nucleoside reverse transcriptase (RT) inhibitor combinations were d4T+3TC (45 patients), AZT+3TC (40 patients), and ddI+3TC (10 patients). The most frequent additions to these combinations were nelfinavir (44 patients), indinavir (18 patients), lopinavir (17 patients), efavirenz (13 patients), and abacavir (11 patients). The last three additions have been used only since 2000.

At start of HAART, HIV-RNA plasma levels were 5.1 $\log_{10}$ copies/ml (4.4–5.8), with a somewhat lower viral load in girls than in boys (p=0.1). CD4 cell counts at start of HAART were 490 x 10^6 cells/l (145–1040). After 24 weeks of HAART, 67% of the HIV-infected children reached RNA plasma levels below 500 copies/ml, whilst CD4 counts increased to a median of 975 (507–1640). The median increase in CD4 cells from start of HAART was 330 (90–590). In 33 patients (29%), resistance-associated mutations were found after the start of therapy. Most of these children (31) had one or more major mutation associated with resistance to nucleoside RT inhibitors, whilst 16 patients had mutations conferring resistance to non-nucleoside RT inhibitors, and 17 had mutations associated with protease inhibitor resistance.

Discussion

As of 1 June 2005, data on 112 HIV-infected children are available in the ATHENA national observational cohort. The total number of HIV-infected children in the Netherlands for whom data will be entered by the end of 2005 is estimated to be around 200; thus approximately half of the children were available for the current analysis. Accordingly, the significance of the decline in the relative contribution of newly diagnosed children to the total annual number of diagnoses in children and/or adults is not yet established.

Although the majority of the HIV-infected children now registered in the HMF were born in the Netherlands, most had at least one parent born outside the Netherlands. The most important route of transmission was vertical transmission from mother to child, suggesting that HIV-prevention activities in the Netherlands are not fully reaching immigrant populations with a high prevalence of HIV. Few infections by contact with infected blood/blood products have occurred in the Netherlands since the 1980s, when adequate screening was installed; however, they continue to occur in HIV-endemic areas with less advanced healthcare systems.

Infections by sexual contact were limited to girls age 14-17 who almost all belonged to immigrant populations and were largely infected in their region of origin.

In the period of 2003 to June 2005, a total of 221 pregnant women were tested HIV-positive during routine prenatal screening. All these women gave birth to children not infected with HIV [Mariëlle Laakman, personal communication]. This finding suggests that the HIV-infected children registered in these years in the ATHENA national observational cohort were born of mothers who were not HIV-tested or not adequately treated during pregnancy. It is also possible that the children were infected only after birth, through breast-feeding.

Our data show that HIV-infection in children has different dynamics compared to adults. Plasma HIV-RNA levels in untreated children decrease by at least a factor of ten from shortly after birth to the age of about 6 years. Over a comparable period, CD4 counts decrease, in both HIV-infected and non-infected children. Hence, a steady-state comparable to that seen in adult patients is not reached in children[61]. Increases in absolute CD4 counts during HAART are larger than in adult patients. This increase is reportedly dependent on age, although CD4 cell restoration in terms of percentages of normal values is not age-dependent[69, 70].

After 24 weeks of treatment with HAART, virological success had been reached in 67% of the treated children. This proportion is similar to that observed in adults[11]. The number of children harbouring virus strains with one or more resistance- associated mutations was quite high, almost three times as high as what was observed in the total HIV-infected population (see Chapter 15). This higher prevalence of resistance might be explained, at least in part, by the larger number of children in whom genotypic sequences were obtained, compared to adults in the HMF database. On the other hand, it might reflect inadequate treatment of HIV-infected mothers during pregnancy and subsequent transmission of resistant HIV-strains to their children. Moreover, rapid selection for drug-resistant virus strains could stem from the treatment difficulties and suboptimal adherence in very young children, in combination with their high viral load.

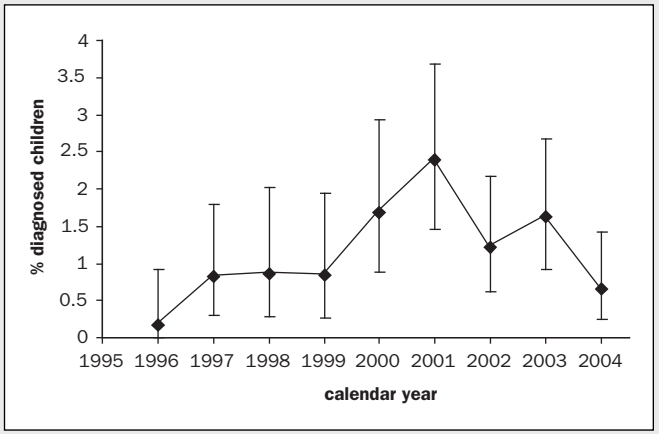


Figure 9.1: Percentage of diagnosed children amongst the annual number of diagnoses. The error bars show the 95% confidence intervals on the percentages.

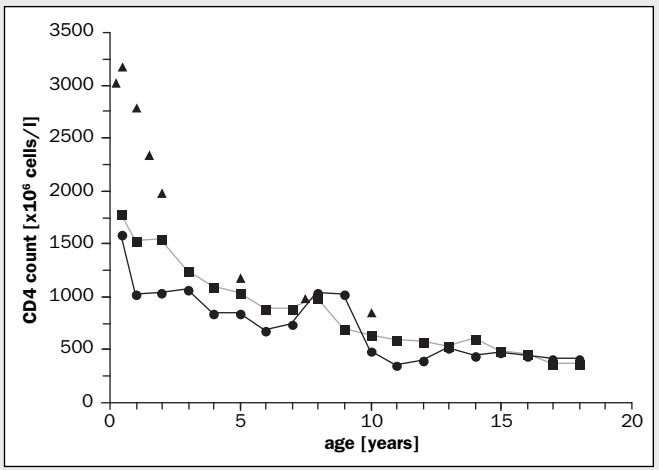


Figure 9.2: Median CD4 count in HIV-infected children as a function of age. The black line represents the CD4 count in untreated children, whilst the grey line represents CD4 counts in the total population of children, including those already on treatment. The triangles are median CD4 counts in uninfected children.

	males, N=57 N (%) / median (IQR)		females, N=55 N (%) / median (IQR)		all, N=112 N (%) / median (IQR)	
region of birth						
the Netherlands	40	(70%)	30	(55%)	70	(63%)
sub-Saharan Africa	13	(23%)	17	(31%)	30	(27%)
region of origin, parents						
both the Netherlands	4	(7%)	5	(9%)	9	(8%)
one or both sub-Saharan Africa	33	(58%)	30	(55%)	63	(56%)
one or both other region	11	(19%)	14	(25%)	25	(22%)
region of infection						
the Netherlands	32	(56%)	26	(47%)	58	(52%)
sub-Saharan Africa	13	(23%)	14	(26%)	27	(24%)
HIV-1 subtype						
unknown	29	(51%)	25	(45%)	54	(48%)
B	11	(19%)	9	(16%)	20	(18%)
transmission group						
mother-to-child	43	(75%)	42	(76%)	85	(76%)
blood	8	(14%)	3	(6%)	11	(10%)
sexual contact			6	(11%)	6	(5%)
other/unknown	6	(11%)	4	(7%)	10	(9%)
tested HIV-positive in first year	23	(40%)	23	(42%)	46	(41%)
year of HIV diagnosis						
≤ 1995	14	(25%)	17	(31%)	31	(28%)
1996-2000	15	(26%)	14	(25%)	25	(22%)
2000-2005	28	(49%)	24	(44%)	52	(46%)
started HAART	52	(91%)	46	(84%)	98	(88%)
age at diagnosis (years)	1.1	(0.6–5.7)	2.1	(0.3–7.0)	2.1	(0.4–5.9)
follow-up (years)	3.9	(2.1–6.8)	4.4	(2.1–9.3)	4.3	(2.1–7.5)
RNA (log_{10} copies/ml) at diagnosis	5.4	(4.8–5.9)	4.8	(4.3–5.5)	5.2	(4.5–5.8)
CD4 ($\times 10^6$ cells/l) at diagnosis	930	(320–1890)	680	(380–1760)	780	(380–1790)
time diagnosis to start of HAART	0.2	(0.1–3.3)	0.3	(0.1–3.5)	0.2	(0.1–3.3)
RNA < 500 copies/ml at T_0			1		1	
RNA (log_{10} copies/ml) at T_0	5.2	(4.6¬–5.8)	4.9	(4.1–5.7)	5.1	(4.4–5.8)
CD4 ($\times 10^6$ cells/l) at T_0	560	(170–1058)	475	(120–850)	490	(145–1040)
RNA < 500 copies/ml at T_1	29/47	(62%)	30/41	(73%)	59/88	(67%)
RNA (log_{10} copies/ml) at T_1	3.1	(2.9–5.0)	3.5	(2.9–4.3)	3.4	(2.9–4.7)
CD4 ($\times 10^6$ cells/l) at T_1	970	(450–1620)	1030	(600–1660)	975	(507–1640)

T_0: start of HAART; T_1: 24 weeks after start of HAART; IQR: interquartile range. Median log-transformed RNA values at T_0 and T_1 are given for those patients with RNA > 500 copies/ml.

Table 9.1: Characteristics of HIV-infected children.

Effect of

f HAART

Mortality, morbidity and markers of disease progression

Luuk Gras

Introduction

Progression to AIDS and death have been pushed back amongst HIV-infected patients since the introduction of highly active antiretroviral therapy (HAART)[24, 71, 72]. However, there is a cost. Lifelong HAART is needed because the combination of drugs from different classes that are currently in use do not eradicate HIV from the body[73]. As a consequence of lifelong treatment, patients do suffer from adverse events and clinical manifestations due to the toxic effect of antiviral drugs on cells and all cell metabolisms[74, 75]. In addition, these adverse events and toxic responses reduce quality of life[76, 77], especially in patients treated at an early stage when the infection is asymptomatic and not itself reducing quality of life.

The decision as to when to start HAART is based on a balance between the risk of developing HIV-related disease and that of serious toxic responses to the drugs used[78, 79]. These toxic responses are addressed in recent guidelines advising clinicians in the Netherlands against starting HAART too early in infection[80]. The CD4 cell count at the start of HAART has been shown to be strong predictor for occurrence of AIDS-defining events and/or death. Several observational cohort studies have shown the importance of commencing treatment of an asymptomatic HIV infection before the CD4 cell number has declined to below 200 per mm^3 [15, 18, 81], and the recent guidelines[80] recommend starting HAART accordingly.

In this chapter we report a study in antiretroviral therapy-naïve HIV-infected ATHENA participants that evaluates the effect of HAART on mortality and morbidity and on CD4 cell count and HIV-RNA levels in plasma, according to different baseline characteristics.

Methods

Study population and endpoints

HIV-1 infected patients who commenced HAART between 1 July 1996 and 31 December 2004 were selected. Patients were 16 years or older at the start of HAART, which was defined as a combination of at least 3 antiretroviral drugs from at least 2 drug classes or a combination of $\geq$3 nucleoside reverse transcriptase inhibitors (NRTi) including tenofovir or abacavir. Death and new AIDS-defining events occurring after HAART initiation were the two primary end-points. In univariate analyses, we evaluated the probability of death and probability of AIDS within 8 years after HAART initiation. We restricted multivariate analyses to endpoints occurring within three years after the start of HAART, because calendar year was included as a confounder and because the follow-up period was short in those initiating HAART in later calendar years. Time to death and time to AIDS was compared between therapy-naïve and pre-treated patients and, separately, amongst various subgroups in the naïve group. Patients without a CD4 cell or HIV-RNA measurement when commencing HAART were included as a separate category. Sensitivity analyses were performed that excluded patients with missing baseline measurements.

Longitudinal CD4 cell counts and HIV-RNA levels measured within the first five years after starting HAART were analyzed according to different baseline strata for CD4 count ($<$50, 50-200, 200-350, 350-500 and $\geq$500 cells/mm^3) and HIV-RNA level ($<$10,000, 10,000-100,000, $\geq$100,000 copies/ml).

Statistical analysis

Linear regression was used to model the effect of the calendar year of starting HAART on baseline CD4 cell count using cubic polynomials. Kaplan-Meier estimates of the probability of patients reaching an endpoint were used to present the results of univariate analyses. The log-rank test was used to assess differences between baseline strata. Cox proportional hazard models were used to model the effect of baseline characteristics on time to death and time to the first new CDC-C event within 3 years after starting HAART.

The CD4 cell and HIV-RNA measurement taken closest to 48, 96, 144, 192, and 240 weeks after the start of HAART, with a margin of 24 weeks on either side, were selected. Median values and interquartile ranges (IQR) were calculated. In case a patient had died, the last measured CD4 count and HIV-RNA concentration were carried forward to avoid an over-optimistic trend over time. The Wilcoxon test was used to compare CD4 cell count and changes in CD4 cell count over time, amongst different groups, and Fisher's exact test was used to compare the proportion of patients with HIV-RNA <50 copies/ml. All comparisons used a 2-sided α level of 0.05.

Results

Between 1 July 1996 and 31 December 2004, 7986 HIV-1-infected patients started HAART, of whom 1986 (25%) had received prior antiretroviral therapy. The probability of progression to death and progression to AIDS is shown in Figure 10.1, sub-divided according to whether patients were treated previously with antiretroviral drugs or were therapy naive at the start of HAART. In all patients, the cumulative probability of death 8 years after the start of HAART was 13.0% (95% CI 11.9-14.1%), but this differed between pre-treated patients and therapy naive patients, being 19.0% (17.2-21.0) and 9.3% (8.1-10.7; log-rank-p<0.0001), respectively. The risk of an AIDS-defining event occurring within 8 years after the start of HAART was 16.4% (15.3-17.6) and, like mortality, was significantly higher in pre-treated patients, being 20.1% (18.2-22.2) as compared to the 14.2% (12.8-15.7) in therapy-naïve patients (p<0.0001).

In the remainder of this chapter, we report on the 6000 patients who were therapy-naïve when commencing HAART. Baseline characteristics are summarised in Table 10.1. Of the 6000 patients, 274 (4.6%) had no baseline CD4 measurement available; 784 (13.1%) had no baseline pVL measurement available, and 573 patients (9.6%) had both missing. These patients are nevertheless included in the analyses. The distribution of the calendar years of starting HAART is shown in Figure 10.2. Mean CD4 cell count at the start of HAART gradually decreased from 259 cells/mm^3 in 1996 to 200 cells/mm^3 in 2004, a mean decrease of 7 CD4 cells/mm^3 per year (p<0.0001).

Death

During 24,074 person-years of follow-up, 314 patients died. Male gender, lower baseline CD4 cell count, a CDC-C event prior to starting HAART, HIV infection through intravenous drug use, older age, and Dutch origin were significantly associated with a shorter time to death in univariate analyses (see Figures 10.3a-g). In multivariate analyses of time to death within 3 years after HAART initiation (14,271 person-years of follow-up, 208 deaths), gender and Dutch origin were no longer significantly associated with an increased risk of death (Table 10.2). Patients initiating HAART with a CD4 cell count between 50-200 cells/mm^3 had a hazard ratio (HR) of 2.12 (95% CI 1.26-3.56; p=0.005) as compared to patients with 200-350 cells/mm^3. There were no significant differences amongst patients with a baseline CD4 cell count of 200-350 cells/mm^3, 350-500 cells/mm^3, or >500 cells/mm^3. Patients without baseline CD4 cell count measurement were at an increased risk of death (p=0.01), as were patients without baseline HIV-RNA measurement (p=0.03). There were no significant differences amongst the other strata of baseline HIV-RNA plasma levels. Older age, a CDC-C event prior to starting HAART, intravenous drug use as the HIV transmission route, and initiation of HAART in later calendar years were all associated with death. From 1996 to 2000, hazard ratios for death decreased but thereafter increased and were highest in 2003-2004. Inspection of the hazard of death over time per calendar year of starting HAART revealed that the differences in hazards were greatest in the first year after commencing HAART, whereas hazards were similar between 1 and 3 years after starting HAART.

CDC-C events

During follow-up, 546 patients developed at least one new AIDS-defining event after starting HAART. The 8 most frequent events were oesophageal candidiasis in 94, Kaposi sarcoma in 81, tuberculosis in 70, recurrent pneumonia (more than one episode in a 1-year period) in 51, *Pneumocystis carinii* pneumonia in 50, Burkitt's or immunoblastic lymphoma in 48, toxoplasmosis of the brain in 39, and cytomegalovirus retinitis in 31 patients. Baseline characteristics which were univariately associated with a shorter time to a new AIDS-defining event after starting HAART were a low baseline CD4 count, having experienced a CDC-C event before HAART initiation, infection through drug use, and originating from countries other than the Netherlands (see Figures 10.3h-n). All the variables univariately associated with the risk of AIDS remained significant in multivariate analyses of time to a new AIDS-defining event within 3 years after the start of HAART (see Table 10.2). The calendar year of HAART initiation was not significantly associated with time to a new AIDS-defining event.

Markers of disease progression over time

In 5393 patients for whom the CD4 cell count was measured when HAART was started, the median CD4 cell count at the start of HAART increased from 195 cells/mm^3 (IQR 80-320) to 360 cells/mm^3 (220-530) at 48 weeks after the start of HAART. Five years after starting HAART, the median CD4 cell count had increased to 500 cells/mm^3 (IQR 330-710). Figure 10.4a shows the median CD4 cell count over time, according to baseline strata. After 240 weeks of HAART, median CD4 cell count had increased to 810 cells/mm^3 (IQR 630-1050) in patients with a baseline CD4 cell count of $\geq$500 cells/mm^3; to 672 (486-890) in those with 350-500; to 570 (400-730) in those with 200-350; to 420 (285-570) in those with 50-200, and to 340 (192-480) in patients with <50 cells/mm^3 at baseline. These CD4 cell counts at week 240 differed significantly from each other (all p<0.0001). The largest changes from baseline CD4 cell count were seen in those patients with a baseline value of <50 cells/mm^3 (Figure 10.4b). The median increase from baseline in these patients was 310 cells/mm^3 (IQR 170-460). The changes in CD4 cell count from baseline at week 240 were smallest in those patients initiating HAART with $\geq$500 cells/mm^3, and the median change was 160 cells (-80 to 410), which was not significantly different from the CD4 levels reached at week 96. Apart from the patients with baseline CD4 cell counts of 50-200 or 200-350 cells/mm^3, increases in CD4 cell count at week 240 differed significantly amongst the CD4 strata.

Figure 10.5 shows the percentage of patients with HIV-RNA plasma levels <50 copies/ml over time (i.e., in those patients tested with a sufficiently sensitive assay), according to baseline HIV-RNA levels. A significantly lower percentage of patients having baseline HIV-RNA concentrations of <10,000 copies/ml reached levels <50 copies/ml when compared to patients with concentrations of >100,000 copies/ml (66.0% versus 81.5% at week 240, p<0.0001). Amongst the 2558 patients who started with HAART before 30 June 2000 and achieved suppression of HIV-RNA levels to <500 copies/ml, 1533 (59.9%) maintained HIV-RNA levels of <500 copies/ml during the first five years of follow-up. Again, this percentage was higher in those patients having higher baseline HIV-RNA plasma levels, being 58.1% in patients with 10,000-100,000 copies/ml at baseline and 62.1% in patients with >100,000 copies/ml compared to 51.9% in patients with <10,000 copies/ml (p=0.07 and p=0.003, respectively).

Discussion

This study confirms that it is important to start HAART before CD4 cell count has reached a level <200 cells/mm^3. Patients starting HAART below this threshold are at an increased risk of death or developing AIDS-defining events. Patients without a CD4 cell count or a HIV-RNA

measurement when starting HAART are likewise at an increased risk of death or AIDS. This indicates that most of these patients must have had low CD4 levels and/or some other unrecorded confounding factor. No significant differences in the risk of progression to AIDS or death are seen between patients starting HAART with 200-350 CD4 cells/mm^3 and patients starting with a higher CD4 cell number. These results support the guidelines that recommend starting HAART as soon as CD4 cell counts have reached levels between 200 and 350 cells/mm^3.

Interestingly, the increase in CD4 cell count to levels that are normal for non-HIV-infected individuals seems possible, irrespective of the cell count at baseline, although it may take more time when HAART is deferred until CD4 cell count has declined to <350 cells/mm^3. Our study shows the highest increases in CD4 cell count from baseline in patients who commence HAART whilst having a CD4 cell count of <50 cells/mm^3. However, the absolute number of CD4 cells after 5 years in these patients remains significantly lower than in patients commencing HAART with a higher number of CD4 cells. Restoration of CD4 cells in the patient group with >500 CD4 cells/mm^3 at HAART initiation seemed not to increase further than a median of about 800 cells/mm^3. Within this subgroup, it might be of interest to evaluate the characteristics of patients whose CD4 cell count continues to increase to >800 cells/mm^3 and compare them to patients who do not experience further increases.

One study found an ongoing increase in median CD4 cell count in patients who had a baseline CD4 cell count ≥500cells/mm^3 and who were continuously treated with HAART for 4 years[82]. However, this discrepant finding might be partly explained by the increasing number of ATHENA patients who interrupt HAART after reaching a certain CD4 cell count (data not shown) and by our handling of patients who died (see Statistical Analysis). Both of these factors would cause median CD4 cell counts to level off more than in Kaufmann's study. Another study found CD4 increases were strongly associated with the ability to maintain HIV-RNA <400 copies/ml. Levels ≥400 copies/ml are associated with complete interruption of antiretrovirals[83]. In accord with our own finding, they found increases in CD4 cell count were slightly higher in patients with lower baseline CD4 cell count.

HIV-RNA levels were <500 copies/ml in nearly 60% of the patients at all measurements taken within the first 5 years after the start of HAART. Of this group, 75-80% of the patients at 1, 2, 3, 4 and 5 years had HIV-RNA levels <50 copies/ml. These high percentages are of importance, as higher HIV-RNA levels during therapy are strongly associated with progression of disease[84, 85].

We found that the risk of death within 3 years of starting HAART increased from the year 2000 onwards. The hazard of dying was significantly higher in patients starting HAART in 2003-2004 compared to patients starting HAART between 1997 and 2001. However, we found no significant effect of the calendar year of HAART initiation on progression to AIDS. The increased hazard of death in later calendar years persisted in sensitivity analyses that excluded patients who started HAART without baseline CD4 or HIV-RNA measurements.

The most likely cause for this calendar year effect is an incomplete registration of HIV-related deaths in the Netherlands before the HIV Monitoring Foundation started in 2002. The resulting lack of information probably relates especially to patients who died shortly after commencing HAART, since differences in hazards of death were most pronounced in the first year of treatment. The comparison of different calendar years of start of HAART in this chapter is much more sensitive to incomplete registration of deaths than the analysis of mortality per calendar year in pre-treated and therapy naive patients presented in Chapter 14.

Conclusion

This study confirms the importance of starting HAART once CD4 cell count has reached levels of 200-350 cells/mm^3. Median CD4 cell count continued to increase during the first 5 years after the start of HAART for patients with baseline CD4 cell count <500 cells/mm^3.

		N	%
Total		6000	100.0
Gender	Male	4519	75.3
	Female	1481	24.7
Transmission risk group	Homosexual	2942	49.1
	Heterosexual	2248	37.5
	IDU	246	4.1
	Other	564	9.3
Region of origin	Netherlands	3247	54.1
	Other	2753	45.9
Clinical stage prior to starting HAART	CDC-A, B	4346	72.4
	CDC-C	1654	27.6
		Median	**IQR**
Age at starting HAART		37.1	31.3-44.3
CD4 cell count at starting HAART (cells/mm^3)		195	80-320
HIV-RNA at starting HAART (log_{10} copies/ml)		5.0	4.4-5.4

Table 10.1: Baseline characteristics of therapy-naïve patients starting HAART between 1 July 1996 and 31 December 2004.

		Death			AIDS		
		HR (95% CI)		p-value	HR (95% CI)		p-value
Year of starting HAART	1996	0.60	(0.34-1.06)	0.08	1.07	(0.69-1.65)	0.76
	1997	0.59	(0.37-0.95)	0.03	1.01	(0.71-1.44)	0.95
	1998	0.45	(0.27-0.75)	0.002	0.84	(0.58-1.22)	0.36
	1999	0.38	(0.22-0.65)	0.0004	0.84	(0.58-1.22)	0.35
	2000	0.34	(0.19-0.60)	0.0003	1.09	(0.77-1.54)	0.62
	2001	0.47	(0.29-0.78)	0.003	0.97	(0.68-1.37)	0.85
	2002	0.65	(0.41-1.03)	0.07	0.81	(0.56-1.17)	0.26
	2003-2004	1.00			1.00		
CD4 cell count at starting HAART (cells/mm^3)	<50	3.12	(1.83-5.32)	<0.0001	2.78	(2.07-3.74)	<0.0001
	50 - 200	2.12	(1.26-3.56)	0.005	1.54	(1.15-2.05)	0.004
	200 – 350	1.00			1.00		
	350 - 500	1.57	(0.78-3.13)	0.20	1.00	(0.68-1.48)	0.99
	>500	0.85	(0.29-2.50)	0.76	1.41	(0.92-2.15)	0.12
	Missing	2.19	(1.17-4.10)	0.01	1.80	(1.24-2.60)	0.002
HIV-RNA at starting HAART (copies/ml)	<10000	1.00			1.00		
	10000 - 100000	1.22	(0.65-2.28)	0.53	1.04	(0.75-1.43)	0.82
	>100000	1.27	(0.68-2.36)	0.45	0.93	(0.68-1.29)	0.68
	Missing	2.06	(1.06-4.02)	0.03	1.22	(0.84-1.78)	0.29
Transmission risk group	Homosexual	1.00			1.00		
	Heterosexual	1.21	(0.82-1.80)	0.34	0.88	(0.69-1.13)	0.31
	IDU	4.41	(2.77-7.03)	<.0001	2.02	(1.43-2.85)	<.0001
	Other	1.96	(1.31-2.92)	0.001	1.24	(0.94-1.63)	0.13
Gender	Male	1.00			1.00		
	Female	0.76	(0.50-1.15)	0.20	1.01	(0.79-1.30)	
Age at starting HAART (per year increase)		1.03	(1.01, 1.05)	<.0001	1.00	(0.99, 1.01)	0.43
Clinical stage prior to starting HAART	CDC-A, B	0.35	(0.26-0.48)	<.0001	0.53	(0.44-0.64)	<.0001
	CDC-C	1.00			1.00		
Region of origin	Netherlands	1.10	(0.80-1.51)	0.54	0.72	(0.59-0.87)	0.0007
	Other	1.00			1.00		

Table 10.2: Hazard ratios (95% CI) of time to death or AIDS within 3 years after HAART initiation, Cox proportional hazard models.

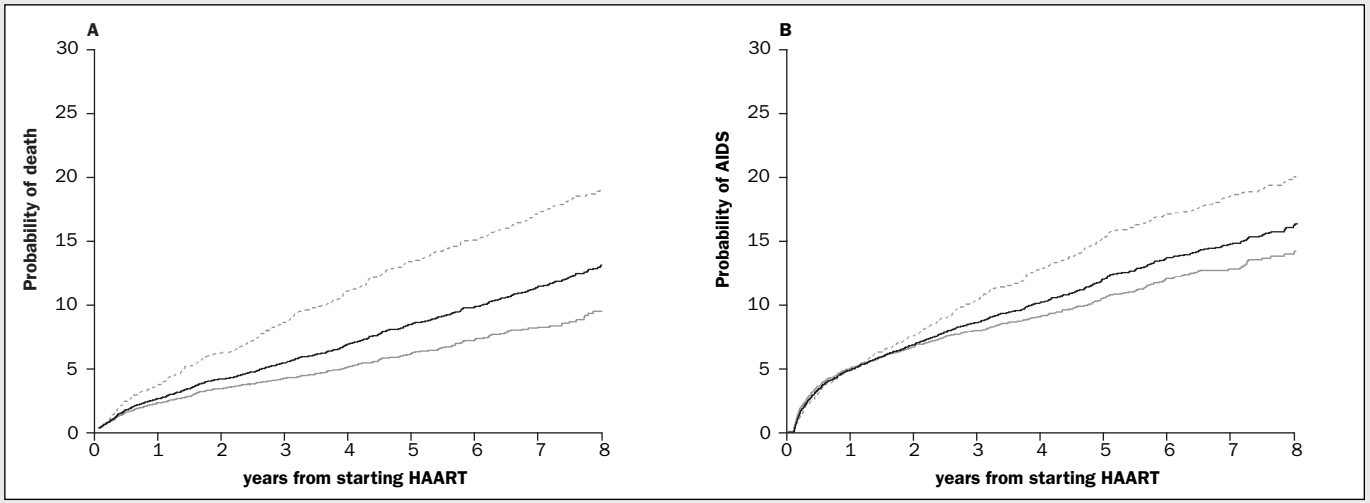


Figure 10.1: Kaplan-Meier estimates of the probability of death (a) and AIDS (b) for all patients (black line), for patients therapy-naïve at the start of HAART (solid grey line), and for patients who were pre-treated at the start of HAART (grey dashed line).

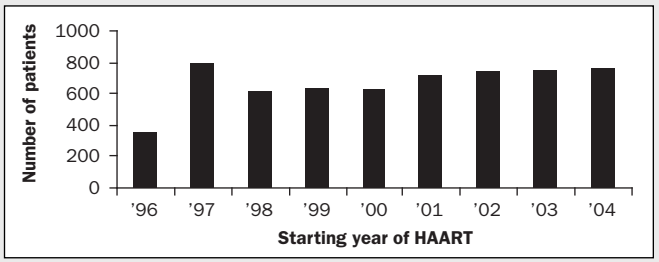


Figure 10.2: Year of HAART initiation in 6000 antiretroviral therapy-naïve patients. Only those patients starting HAART after 1 July 1996 were included.

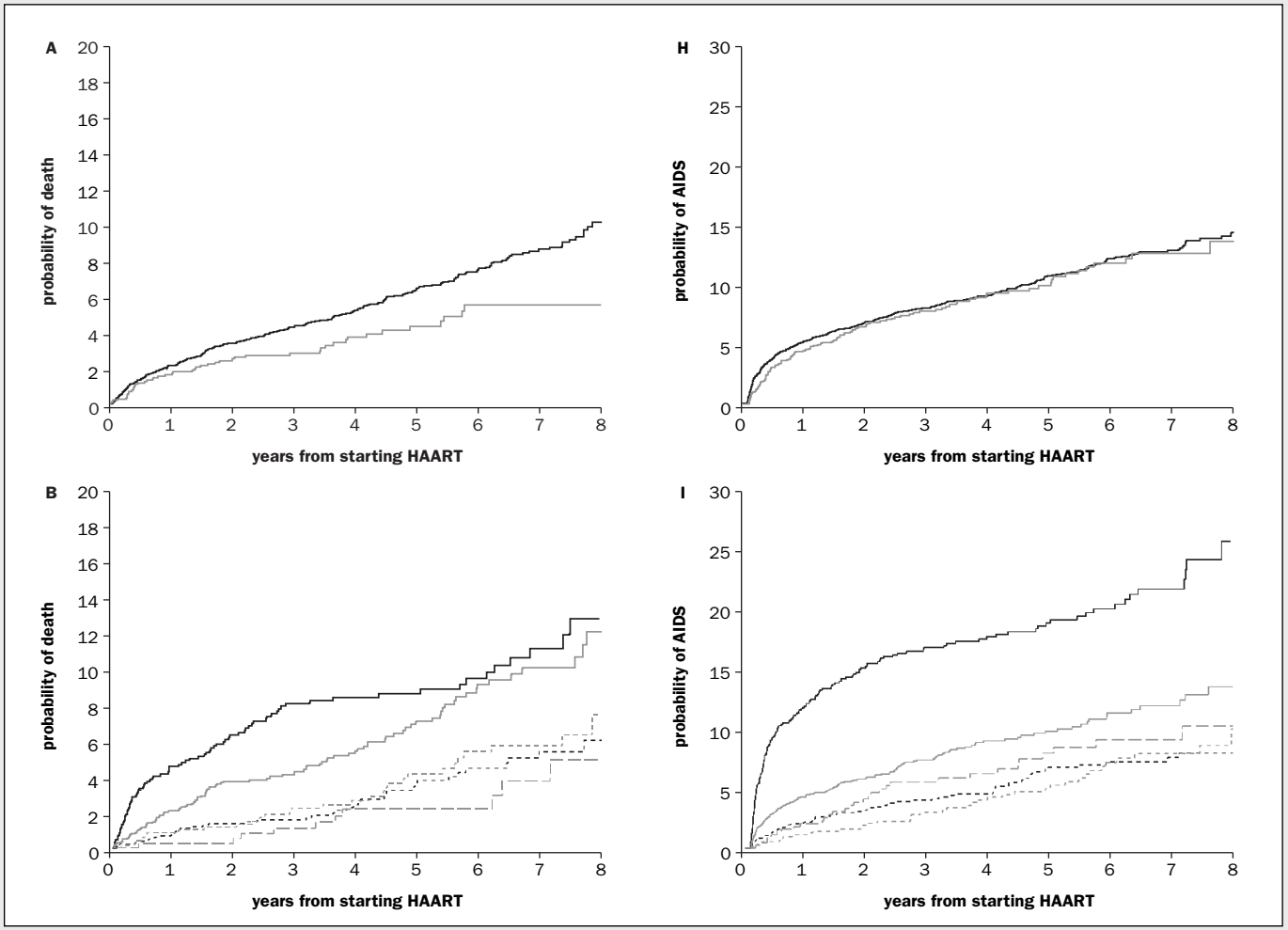
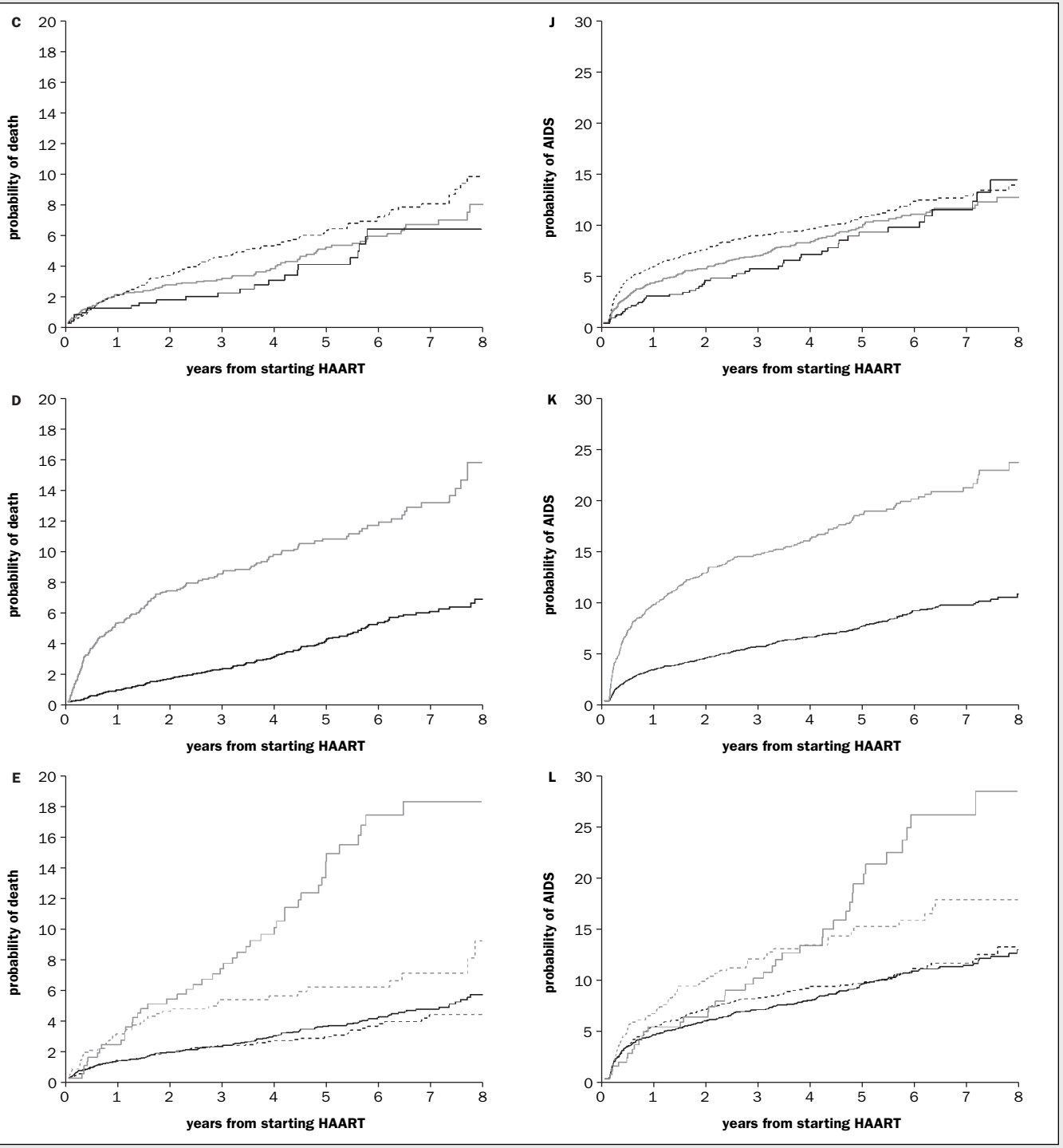


Figure 10.3a-n: Kaplan-Meier estimates of probability of death (left column) and AIDS (right column) according to gender (male = black, female = grey); CD4 cell count at the start of HAART (<50 cell/mm^3 = solid black, 50-200 = solid grey, 200 – 350 = dashed black, 350-500 = dashed grey, and ≥500 cells/mm^3= long dashed black); HIV-RNA at the start of HAART (<10,000 copies/ml = solid black, 10,000-100,000 = solid grey, and ≥100,000= dashed black); clinical stage prior to starting HAART (CDC-A/B = solid black and CDC-C = solid grey); transmission risk group (homosexual = solid black, intravenous drug use = solid grey, heterosexual = dashed black, and other = dashed grey); age at the start of HAART (<30 years = solid black, 30-40 = solid grey, 40-50 = dashed black, and ≥50 = dashed grey), and region of origin (Netherlands = solid black and other = solid grey).


C
probability of death
years from starting HAART
J
probability of AIDS
years from starting HAART
D
probability of death
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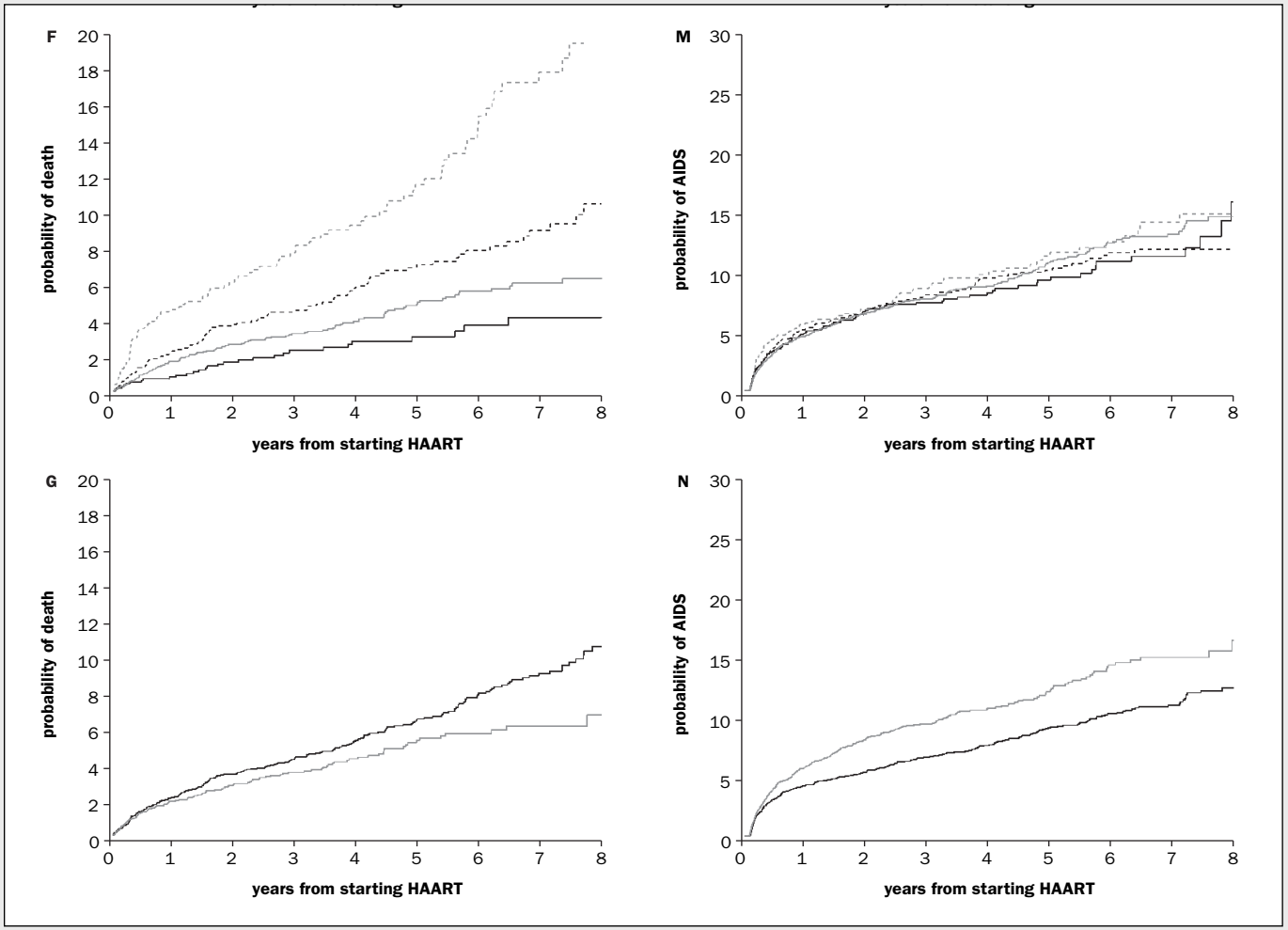

Figure 10.3a-n: continued

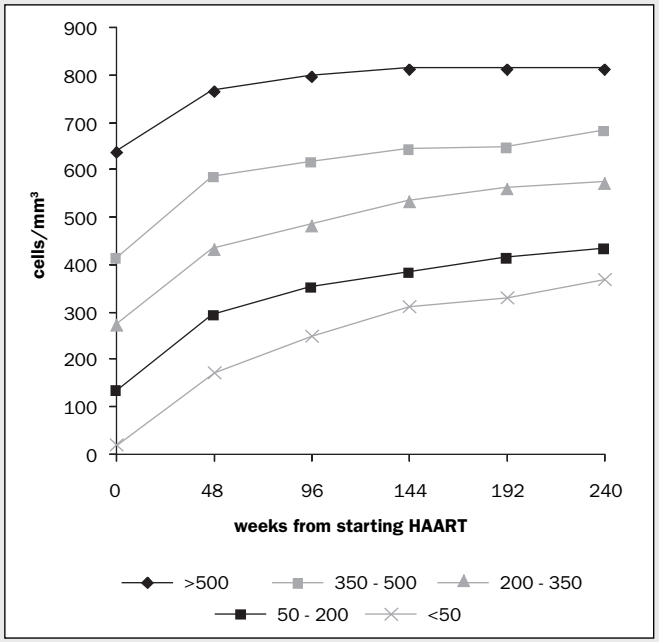

Figure 10.4a: Median CD4 cell count over time, stratified by baseline CD4 cell count.

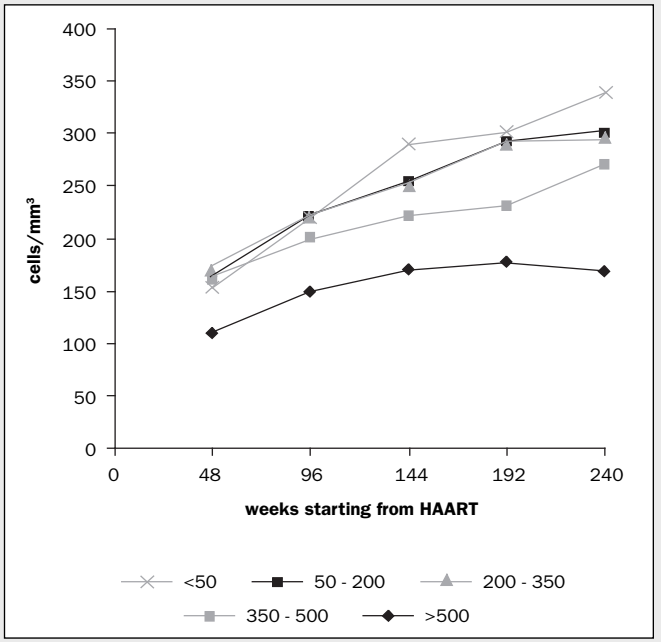

Figure 10.4b: Median changes in CD4 cell count from baseline over time, stratified by baseline CD4 cell count.

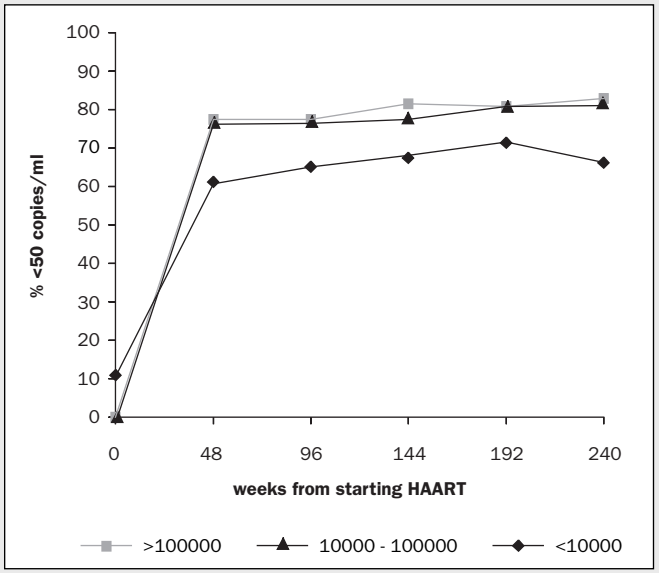

Figure 10.5: Percentage of patients with HIV-RNA below 50 copies/ml in patients tested with a sensitive assay according to baseline HIV-RNA (copies/ml).

Side e

ffects

Lower total cholesterol and triglyceride levels at 24 weeks after switch to atazanavir

Luuk Gras, Marit van Vonderen, Ferdinand Wit, Peter Reiss

Introduction

Protease inhibitor-encompassing highly active antiretroviral therapy (HAART) is associated with elevated cholesterol and triglyceride levels[86-88]. Since HAART has been shown to improve the prognosis for HIV-infected patients[15], concern is rising as to the side effects of lifelong antiretroviral treatment and, equally, the effect of elevated lipid levels on the risk of cardiovascular complications[89-91]. Atazanavir is a new protease inhibitor (PI) given in a once-daily dose in combination with two nucleoside reverse transcriptase inhibitors (NRTI). In patients naïve to antiretroviral therapy, it has been shown to have no significant effect on plasma levels of total cholesterol, LDL cholesterol, and triglycerides measured after fasting[92-94]. Patients switching from nelfinavir to atazanavir have experienced significant improvement of lipid parameters[95]. Even patients with hyperlipidemia who switch to ritonavir-boosted atazanavir have had improvement of lipid levels in plasma[96-98].

Because of the favorable dosing schedule and the limited effect on plasma lipid levels, a switch to HAART combinations including atazanavir is anticipated in a substantial number of patients in the ATHENA national observational cohort. Therefore, a study was designed to evaluate the effect of a switch to atazanavir on plasma viral load levels (pVL) and on lipid parameters. HAART patients who switched to atazanavir were compared with HAART patients who did not. In this chapter, we report an interim analysis of 51 patients at 24 weeks after switching to atazanavir.

Methods

Study population

Atazanavir has become widely available for standard HIV treatment in the Netherlands since June 2004. Prior to that time, 198 ATHENA patients started HAART with atazanavir as part of a compassionate use program. For the current study, we selected those patients in the ATHENA national observational cohort who were already using HAART before 1 June 2004 and switched to a regimen including atazanavir after that date. This 'atazanavir-switch' group included only those patients who had maintained a plasma viral load (pVL) $\leq$50 copies/ml for more than 6 months before starting atazanavir. In addition, we included patients who had experienced a viral blip (defined as one pVL measurement >50 copies/ml preceded and succeeded by a pVL $\leq$50 copies/ml) in the 6 months before starting atazanavir.

As a comparison group, we selected HAART-treated patients who had a pVL $\leq$50 copies/ml for more than 6 months at 1 June 2004 and did not switch to atazanavir during the follow-up period. For this 'non-switch group', 1 June 2004 was regarded as baseline, whilst the date of starting atazanavir was regarded as baseline for the atazanavir-switch group. All selected patients were $\geq$16 years old at HAART initiation. This chapter reports the results for those whose total cholesterol or triglyceride measurements were available 24 weeks after baseline.

Study measurements

The proportion of patients with virological failure within 24 weeks after baseline in the atazanavir-switch group was compared with the proportion in the non-switch group. Virological failure was defined as 2 consecutive HIV-RNA measurements >50 copies/ml. Total cholesterol and triglyceride levels at 24 weeks and differences from the baseline were also compared. Information on whether fasting preceded the testing was not recorded. HAART was defined as at least three drugs from two drug classes or at least three drugs from the NRTI class, including abacavir or tenofovir.

Statistical analysis

Baseline characteristics were compared for continuous variables using the Wilcoxon test and chi- square tests for categorical variables. The proportion of patients in the two groups with pVL>50 copies/ml at 24 weeks

were compared using Fisher's exact test. The two groups were compared as to the difference between the baseline and 24-week total cholesterol and triglyceride levels by means of paired t-tests. All comparisons used a two-sided α level of 0.05.

Results

Baseline characteristics

From 1 June 2004 to 7 July 2005, 412 patients started atazanavir. For 51 patients in the atazanavir-switch group and 945 in the non-switch group, 24 weeks of follow-up data were available. In the atazanavir group, 42 patients (82%) had been treated with a PI-based HAART combination before switching, and 14 patients (27%) had been using a non-nucleoside reverse transcriptase inhibitor (nNRTI)-based HAART before the switch. Baseline characteristics for the patients with 24 weeks of follow-up data are shown in Table 11.1. The patients in the atazanavir-switch group had a longer history of antiretroviral therapy than did patients not switching to atazanavir. In the atazanavir group, the HAART regimen more often included ritonavir than in the non-switch group (87% versus 18%), whilst the HAART combination in the non-switch group more often included an nNRTI than in the switching group (66% versus 18%). Median CD4 cell count at baseline was higher in the patients switching to atazanavir (p=0.04), and baseline lipid values were significantly higher in these patients. The median total cholesterol was 5.5 mmol/L in the atazanavir-switch group and 5.3 mmol/L in the non-switch group (p=0.02). The proportion of patients with total cholesterol values of more than 6.2 mmol/L at baseline was also higher in the patients switching to atazanavir: 39% (20 patients) versus 23% (216 patients) in the non-switch group. Patients with total cholesterol levels higher than 6.2 mmol/L are generally regarded as being at high risk for coronary heart disease, as outlined in the US National Cholesterol Education Programme guidelines[99].

Lipid profiles during follow-up

Of the 51 patients in the atazanavir-switch group, total cholesterol levels at 24 weeks were available for 50. As shown in Table 11.2, there was a mean total cholesterol decrease of 0.72 mmol/L. The levels fell from 5.96 mmol/L at baseline to 5.23 mmol/L at week 24, which was a decrease of 12%. Mean triglyceride levels decreased 0.90 mmol/L, the levels falling from 3.44 at baseline to 2.54 mmol/L at week 24, for a decrease of 26%. In the non-switch group, there was likewise a mean decrease of total cholesterol and triglyceride, but it was less pronounced. The absolute decrease in both total cholesterol and triglycerides between baseline and week 24 was significantly higher in the atazanavir group than in the non-switch group ($p<0.0001$ and $p=0.0004$, respectively).

Virological failure

Of the 51 patients switching to atazanavir, six (11.8%) experienced virological failure within 24 weeks after the switch. In the non-switch group, failure occurred in 37 of the 905 patients (3.9%). The difference between the groups was 7.8% (95% CI 16.8 -1.0). In three of the six who experienced failure, pVL levels at failure did not exceed 150 copies/ml and these three continued the atazanavir regimen, although one boosted it with ritonavir. Two of the three subsequently achieved pVL<50 copies/ml following failure; results for the third patient were unavailable. The NRTI backbones in the HAART regimen for these three patients were AZT+3TC, TDF+3TC+ddI, and TDF+3TC, respectively. Of the remaining three, one used ABC+3TC in combination with atazanavir. The other two had completely stopped HAART with atazanavir even before the failure event, due to toxicity.

In addition to the two last mentioned, there were five patients with no virological failure who had stopped atazanavir by 24 weeks. In three of these, the reason given for stopping was "patient's decision." In the fourth, there was a structured therapy interruption. In the fifth, lamivudine and ritonavir had been used with the combi-

nation of atazanavir, tenofovir and didanosine. Because of the high risk for virological failure, atazanavir, tenofovir and didanosine were replaced by stavudine and saquinavir. The patient continued with lamivudine and ritonavir.

Discussion

Patients who switched to atazanavir-containing HAART experienced a significant reduction in lipid levels at 24 weeks after the switch. The absolute decrease between levels at baseline and at week 24 was significantly higher in patients who had switched to atazanavir, but this was partly because the baseline total cholesterol and triglyceride levels were higher in patients who switched. Lipid levels measured in patients 24 weeks after the switch to HAART with atazanavir did not differ significantly from lipid levels in non-switching patients. Further monitoring is needed to study the long-term effect of HAART regimens with atazanavir on plasma lipid levels.

Of the patients in the atazanavir-switch group, a higher proportion (7.8% more) showed virological failure, compared to the non-switch group. However, a higher proportion of patients in the atazanavir group were pre-treated with antiretroviral drugs prior to start HAART than in the non-switch group. Also, they had used HAART for a longer time and had maintained suppressed pVL levels below 50 copies/ml for a shorter period of time than patients in the other group. More patients and longer follow-up are needed to allow adjustment for these and other confounders and to report on additional lipid parameters.

Conclusion

Patients who switched to a HAART regimen with atazanavir whilst their pVL was below 50 copies/ml had improvement in total cholesterol and triglyceride plasma levels at 24 weeks after the switch. No firm conclusion can be drawn from this preliminary analysis as to the ability of such a strategy to maintain pVL below 50 copies/ml.

	ATAZANAVIR-SWITCH		NON-SWITCH		
	N	%	N	%	p-value
Total	51	100.0	945	100.0	
Male	43	84.3	775	82.0	0.85
Transmission risk group					0.45
Homosexual	35	68.6	568	60.1	
IDU	2	3.9	23	2.4	
Heterosexual	10	19.6	279	29.5	
Other	4	7.8	75	7.9	
CDC-C event prior to baseline	19	37.2	334	35.3	0.77
nNRTI included	9	17.6	628	66.5	<0.0001
Ritonavir included	40	78.4	174	18.4	<0.0001
Prior failure on PI-based regimen	12	23.5	137	14.5	0.08
Naive at start of HAART	28	54.9	736	77.9	0.0005
Prior lipodystrophy	31	60.8	340	36.0	0.0001
Cholesterol >6.2 mmol/L at baseline	20	39.2	216	22.9	0.01
		Median (IQR)		Median (IQR)	
Age (years)		44.2 (38.8-48.7)		43.6 (38.6-51.3)	0.72
Years since starting HAART		7.1 (3.8-7.9)		4.9 (2.7-7.0)	<0.0001
Months pVL <50 copies/ml		16.4 (11.1-39.0)		26.4 (14.5-40.6)	0.08
CD4 cell count/mm^3	51	630 (350-830)	939	530 (360-700)	0.04
Total cholesterol (mmol/L)	50	5.5 (4.8-7.1)	941	5.3 (4.5-6.1)	0.02
Triglycerides (mmol/L)	50	3.1 (1.7-5.4)	920	1.9 (1.2-3.0)	<0.0001

Table 11.1: Baseline characteristics of patients with 24 weeks of follow-up.

		ATAZANAVIR-SWITCH	NON-SWITCH	p-value*
Mean (SD) total cholesterol in mmol/L	N	50	938	
	At baseline	5.96 (1.72)	5.37 (1.25)	0.02
	Week 24	5.23 (1.03)	5.29 (1.24)	0.85
	Difference	0.72 (0.95)	0.08 (0.87)	<0.0001
Mean (SD) triglycerides in mmol/L	N	47	906	
	At baseline	3.44 (2.45)	2.37(2.47)	0.001
	Week 24	2.54 (1.77)	2.32 (2.06)	0.47
	Difference	0.90 (1.74)	0.05 (1.60)	0.0004

* p-value using paired t-test

Table 11.2: Total cholesterol and triglyceride levels between baseline and week 24.

Simplifi

ied ART

Switching to triple-NRTI combinations in patients on successful HAART

Luuk Gras, Guido van den Berk, Kees Brinkman

Introduction

Given the various toxicities associated with protease inhibitors (PI) and non-nucleoside reverse transcriptase inhibitors (nNRTI), there is increased interest in reducing exposure to these drug classes[100]. In patients with viral suppression, change from PI-based or nNRTI-based highly active antiretroviral therapy (HAART) to combinations consisting of triple nucleoside reverse transcriptase inhibitors (NRTI) has the advantages of simple administration, a beneficial effect on lipid levels, and fewer drug-drug interactions.

Several randomised trials have explored the strategy of changing to triple-NRTI HAART. In patients who had maintained viral loads below detectable levels for at least 6 months, a switch to triple NRTI, most often AZT+3TC+ABC, had an equal[101-103] or superior[104] virological effect, as compared with patients who were randomised to continue their PI-based or nNRTI-based regimen. However, in a meta-analysis that included some of these studies[101, 103, 104], it was concluded that a switch to triple NRTI was virologically inferior to continuation with PI-based HAART, although this conclusion might have been based on the result of a suboptimal NRTI combination given prior to the switch[105].

Another study found a higher rate of failure in patients who switched from PI-based HAART to triple NRTI than in patients who switched from PI-based to nNRTI-based HAART[106]. Equivalent virological efficacy was reported in a trial that compared patients who switched to AZT+3TC+ABC after an induction phase with AZT+3TC+ABC+EFV to patients who continued on that induction regimen[107]. Finally, patients who had switched from virologically successful HAART to TDF+3TC+ABC[108] or to other triple-NRTI combinations including TDF[109] were found to be at an increased risk of virological failure. Studies including data for patients with no history of a suboptimal response to NRTI that evaluate a switch to triple NRTI are fairly limited. In this chapter, we report on the ATHENA patients switching to triple-NRTI therapy and evaluate its virological effect, its effect on lipid parameters, and the factors associated with an increased risk of virological failure.

Methods

Study population

Patients infected with HIV-1 who switched to triple NRTI were eligible for the study when the last plasma viral load (pVL) measured within six months before commencing triple-NRTI therapy was below 50 copies/ml. Their prior HAART combination must have included a PI or an nNRTI. Female patients using a triple-NRTI combination during a pregnancy were excluded, as were patients participating in clinical trial. Patients who were treated with antiretroviral drugs before commencing HAART were excluded. Eligible patients were $\geq$16 years of age at their initiation of HAART.

Measurements

Virological failure was defined as two consecutive pVL measurements >50 copies/ml. The primary analysis looked at the time to virological failure whilst the patient was receiving a triple-NRTI combination. The time was censored when triple-NRTI treatment was stopped or when a PI or nNRTI was added. Changing to alternative combinations of triple NRTI was allowed. As a secondary analysis, the time to virological failure was analysed using an intention-to-continue-therapy approach. The time to virological failure was analysed regardless of whether the patient was still using a triple NRTI. Predictors of the time to the complete stop of triple-NRTI combinations or the addition of a PI or nNRTI were also evaluated.

Median total cholesterol and triglyceride levels at week 24, 48, 96, and 144 were calculated and compared with levels at the start of triple NRTI. Whether or not fasting preceded the testing was not recorded.

Any sequences of reverse transcriptase (RT) obtained at virological failure were evaluated for the following mutations: K65R, L74V, Y115F, M184V/I, E44D, V118I, M41L, D67N, K70R, L210W, T215Y/F and K219O/E.

Statistical analysis

The Cox proportional hazard model was used to evaluate the effect of potential predictors on the time to the defined endpoints. These variables included patient gender, age, region of origin (Netherlands or other), and transmission risk group (homosexual, heterosexual, or other); CD4 cell count at start of triple NRTI; viral blip in the 6 months prior to start of triple NRTI (blip = a pVL measurement > 50 copies/ml preceded and followed by a pVL <50 copies/ml); CDC-C event prior to start of triple NRTI; plasma virus load always <500 copies/ml between the initial suppression after the start of HAART and the change to triple NRTI; the time since the last pVL measurement of >500 copies/ml; use of nNRTI in the regimen prior to the start of triple NRTI; reason for switching from prior regimen (toxicity, simplification, or other). Variables with a p-value of 0.20 or less univariately were included in multivariate models. Variables were retained when p-values remained below 0.20 in multivariate analyses. To evaluate the influence on estimates of the differences in follow-up frequency amongst groups of patients, final Cox models were checked with parametric survival models, taking into account the interval-censored endpoints[40]. The percentage of patients reaching the endpoint was estimated using the Kaplan-Meier product-limit method. Changes in lipid levels from the start of triple-NRTI therapy were assessed using the Wilcoxon test. Reported two-tailed p-values are based on a type I error rate of 0.05.

Results

Sufficient data were available from 424 patients to include in the current analyses. The median time from the start of triple-NRTI treatment to the end of the follow-up was 27.3 months (IQR 17.7-36.5).

The drugs included in the triple-NRTI combination are shown in Table 12.1. AZT+3TC+ABC was administered to most of the patients (87%). In 27 patients (6%), tenofovir was included in the regimen. To assess virological efficacy, patients using 3TC+ddI+TDF, 3TC+ABC+TDF or 3TC+ddI+ABC were placed together in the non-thymidine analogues group (last three in table). Patients using AZT+3TC+ABC were compared to this group, to patients using AZT+3TC+TDF, and to patients using the remaining regimens.

In 333 patients (79%), a PI was included in the regimen used prior to the start of triple-NRTI treatment. An nNRTI was part of the prior regimen in the remaining 91 (21%).

The most frequent reasons for switching to triple-NRTI combinations were treatment simplification in 133 patients (31%) and toxicity of the previous regimen in 127 patients (30%).

Baseline characteristics of the 424 patients are shown in Table 12. 2. Most patients were male (82%), and the median age at the time of the switch to a triple-NRTI combination was 42 years. A total of 13 patients used a combination of non-thymidine analogues: 9 patients used 3TC+ddI+TDF, 3 used 3TC+ABC+TDF, and 1 used 3TC+ddI+ABC. The median CD4 cell count at the start of triple-NRTI combination therapy was 450 cells/mm^3 (IQR 290-640).

Virological efficacy

A total of 53 patients experienced virological failure during triple NRTI. The Kaplan-Meier estimates for virological failure at one, two, and three years were 12.2% (95% CI 9.1-16.2), 15.9% (12.2-20.5), and 17.70% (13.5-23.0), respectively (Figure 12.1).

The strongest predictor for virological failure during NRTI therapy was the use of a combination of non-thymidine analogues, with a hazard ratio (HR) of

15.96 (95% CI, 6.37-39.98), compared to AZT+3TC+ABC (Table 12.2). Of 13 patients using a combination of non-thymidine analogues, 8 experienced virological failure whilst still using a triple-NRTI combination: 5 patients used 3TC+ddI+TDF, 2 used 3TC+ABC+TDF, and 1 used 3TC+ddI+ABC. For 7 of these 8 patients, virological failure occurred within 6 months. Amongst patients using AZT+3TC+TDF (HR 3.96, 95% CI 0.85-18.41, p=0.08) or other triple-NRTI combinations (HR 2.12, 95% CI 0.86-5.22, p=0.10), there was no significant difference in the time to virological failure compared to patients initiating triple NRTI with AZT+3TC+ABC.

A lower baseline CD4 cell count was predictive for failure during triple-NRTI usage. For baseline CD4 count $\geq$500 cells/mm^3 compared with <200 cells/mm^3, the HR was 0.28 (95% CI 0.11-0.72, p=0.008). Non-Dutch patients were also at increased risk for virological failure (HR 2.64, 95% CI 1.47-4.76), compared to patients of Dutch origin. Of patients for whom one-year follow-up data were available, only 4 out of 73 (5%) from the Netherlands who were not using a non-thymidine analogue combination and who had a baseline CD4 count of $\geq$500 cells/mm^3 experienced virological failure within a year whilst they were still using a triple NRTI. By contrast, 10 of 88 (12%) Dutch patients with a baseline CD4 cell count of 200-500 cells/mm^3 had virological failure within a year, and 4 of 16 (25%) Dutch patients with a baseline CD4 cell count of <200 cells/mm^3 had failure within a year.

In addition to the 53 who experienced failure whilst using triple NRTI, 29 experienced failure after discontinuing the regimen, making a total of 82 patients experiencing virological failure during follow-up. Of the 29, 23 (79%) had completely stopped antiretroviral therapy, whilst 6 patients had virological failure whilst using another drug combination. As shown in Figure 12.2 the Kaplan-Meier estimate of the percentage of patients who experienced virological failure one year after the start of triple NRTI was 15.3% (95% CI 11.9-19.1); after two years, the estimate was 20.5% (16.7-25.1), and after three years, 24.7% (20.1-30.3). Predictors of the time to virological failure after discontinuing triple NRTI were largely similar to those predictive of failure whilst using NRTI, except that a higher CD4 cell count at the start of the triple-NRTI regimen was no longer significantly associated with the time to failure (Table 12.2).

In all 424 patients, the median baseline CD4 cell count was 450 cells/mm^3 (IQR 290-640). The median CD4 count was 500 (320-710) at 48 weeks, 530 (350-750) at 96 weeks, and 560 (390-800) at 144 weeks.

Discontinuation of triple-NRTI therapy

After the switch to triple-NRTI therapy, 171 of the 424 patients (40%) stopped their initial triple-NRTI combination during follow-up. Of those 171 patients, 29 continued treatment with another triple-NRTI combination. Of those 29, 11 discontinued the second triple-NRTI combination as well. Thus a total of 153 patients discontinued triple-NRTI usage. Kaplan-Meier estimates of time to discontinuation were 22.3% (95% CI 18.5-26.7) at one year, 33.0% (28.5-38.1) at two years, and 44.5% (38.7-50.7) at three years (Figure 12.3). Factors significantly associated with early discontinuation of triple-NRTI treatment were using a combination of non-thymidine analogues and switching from an nNRTI-based HAART regimen. A plasma viral load >500 copies/ml in the 6 months prior to the start of triple-NRTI treatment was borderline significant.

The most frequent reason for stopping at least one drug of the triple-NRTI regimen was toxicity, reported in 50 of 153 patients (33%). Of the 42 patients for whom there was sufficient data, liver-related toxicity (9 patients) and systemic toxicity (9 patients) were the most frequent reasons given for NRTI discontinuation. Five patients reported lipodistrophy as the reason for stopping, and three reported abacavir hypersensitivity.

Resistance

In 26 of the 82 patients (32%) with virological failure, RT sequences were available. Ten patients had one NRTI-associated mutation, 5 had 2, and 11 had 3 or more NRTI-associated mutations. The most frequently reported mutation was 184V, which occurred in 22 patients (85%); 65R was reported in 5 patients (19%) and 215Y in 2 patients (7%).

Lipid measurements

The median total cholesterol and triglyceride levels were calculated regardless of changes in the regimen. Of the 368 patients for whom a total cholesterol measurement was available at start of the triple-NRTI therapy, 91 (25%) had a level >6.2 mmol/L[99]. Median total cholesterol levels were 5.30 mmol/L (IQR 4.50-6.20), and median triglyceride levels were 2.15 mmol/L (1.40-3.20). After triple-NRTI initiation, the median total cholesterol levels decreased by 11% to 4.0 mmol/L (IQR 4.00-5.30, $p<0.0001$) by week 24, and triglyceride levels decreased by 29% to 1.53 mmol/L (IQR 1.02-2.30, $p<0.0001$). After week 24, median total cholesterol and triglyceride levels slowly increased; at week 144 they were 4.90 mmol/L (IQR 4.20-5.70) and 1.92 (1.28-2.80), respectively (Figure 12.4). These levels were still significantly lower than the levels at the start of triple-NRTI treatment ($p<0.0001$ for cholesterol and $p=0.03$ for triglycerides). The percentage of patients with total cholesterol levels >6.2 mmol/L decreased to 6% at week 24 and then slowly increased to 8% at week 96 and 10% by week 144.

Discussion

Patients who switched to a triple-NRTI HAART combination consisting of non-thymidine analogues experienced a high virological failure rate, as reported previously[108]. Although patients using AZT+3TC+ABC were at lower risk of virological failure, we did not find significant differences when the non-thymidine analogues were compared with AZT+3TC+TDF and the other non-AZT+3TC+ABC regimens. However, this might be due to small sample size: only 14 patients initiated triple NRTI with AZT+3TC+TDF, and 24 used other combinations.

Patients from countries other than the Netherlands were also at an increased risk of virological failure. One study found that viral efficacy (defined as pVL <50 copies/ml at week 48 after the start of HAART) was lower in non-Dutch patients than in Dutch patients[110]. The rate of virological failure was lower in patients with higher CD4 counts at the start of the triple-NRTI combination. Overall, 75% of the patients who switched to triple NRTI were still virologically successful after three years of its continued use.

There was an increased risk for discontinuation of triple-NRTI in patients who had used an nNRTI-based regimen before starting the triple-NRTI regimen. This might be due to the fact that 52% of patients had stopped the nNRTI-based regimen due to toxicity, whereas only 24% stopped a PI-based regimen for that reason ($p<0.0001$).

Conclusion

The risk of virological failure in switching to a triple-NRTI regimen is low for patients who come from the Netherlands and who have a high CD4 cell count after successful PI-based or nNRTI-based HAART. Switching to a triple-NRTI regimen has a beneficial effect on total cholesterol and triglyceride levels.

Acknowledgements

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NRT combination	N	%
AZT+3TC+ABC	368	86.8
d4T+3TC+ABC	24	5.7
d4T+3TC+TDF	1	0.2
d4T+ddI+ABC	1	0.2
AZT+ddI+3TC	1	0.2
AZT+ddI+ABC	2	0.5
AZT+3TC+TDF	14	3.3
3TC+ddI+TDF	9	2.1
3TC+ABC+TDF	3	0.7
3TC+ddI+ABC	1	0.2

Table 12.1: Composition of 424 selected triple-NRTI regimens used after a switch from PI-based or nNRTI-based regimens.

Total	N (%)	424 (100.0)
Male	N (%)	349 (82.3)
Age at start of triple NRTI	median (IQR)	42 (35-48)
Born in the Netherlands	N (%)	265 (62.5)
Transmission risk group	N (%)	
Homosexual		251 (59.2)
IDU		10 (2.4)
Heterosexual		124 (29.2)
Other		39 (9.2)
Year/month triple NRTI initiated		Oct 2002 (Jan 2002-Mar 2003)
CD4 cell count (cells/mm^3) n=415	median (IQR)	450 (290-641)
Prior CDC-C event	N (%)	136 (32.1)
Years since start of HAART	median (IQR)	2.0 (0.9-4.0)
Months since last pVL>50 copies/ml	median (IQR)	12.1 (6.1-27.6)
Viral load always below 500 since start of HAART	N (%)	365 (86.1)
Viral blip in the 6 months prior to 3 NRTI	N (%)	17 (4.0)
Highest pVL (copies/ml) in the 6 months prior to triple NRTI initiation	N (%)	
	<500	373 (88.0)
	500-50000	24 (5.7)
	50000	27 (6.4)

Table 12.2: Baseline characteristics.

	Virological failure on triple NRTI		Virological failure intention-to-continue triple NRTI analysis	
	HR (95% CI)	**p-value**	**HR (95% CI)**	**p-value**
Female vs male	0.45 (0.18-1.11)	0.08	0.58 (0.31-1.08)	0.08
Born outside the Netherlands vs born in the Netherlands	2.64 (1.47-4.76)	0.001	2.31 (1.45-3.66)	0.0004
Intravenous drug use vs sexual transmission and other transmission			0.47(0.19-1.17)	0.11
CD4 cell count (cells/mm^3)		0.05		
<200	1.00			
200-500	0.64 (0.32-1.29)	0.19		
>500	0.28 (0.11-0.72)	0.008		
missing	0.85 (0.19-3.73)	0.83		
Months since last pVL>50 copies/ml (per month increase)	0.97 (0.95-1.00)	0.08	0.98 (0.96-0.995)	0.01
Triple-NRTI combination				
AZT+3TC+ABC	1.00		1.00	
3TC+ddI+TDF, 3TC+ABC+TDF or 3TC+ddI+ABC	15.96 (6.37-39.98)	<0.0001	8.61 (4.16-17.80)	<0.0001
AZT+3TC+TDF	3.96 (0.85-18.41)	0.08	2.69 (0.96-7.55)	0.06
Other	2.12 (0.86-5.22)	0.10	2.07 (1.03-4.14)	0.04

Table 12.3: Hazard ratios (HR) and 95% confidence intervals (CI) of variables predicting the time to two consecutive pVL measurements <50 copies/ml.

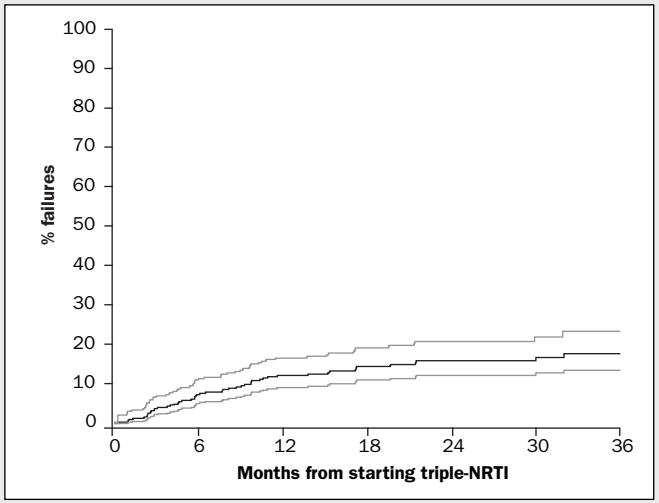

Figure 12.1: Kaplan-Meier estimates (95% CI) of the percentage of patients with virological failure (two consecutive pVL measurements >50 copies/ml after the start of the triple-NRTI regimen).

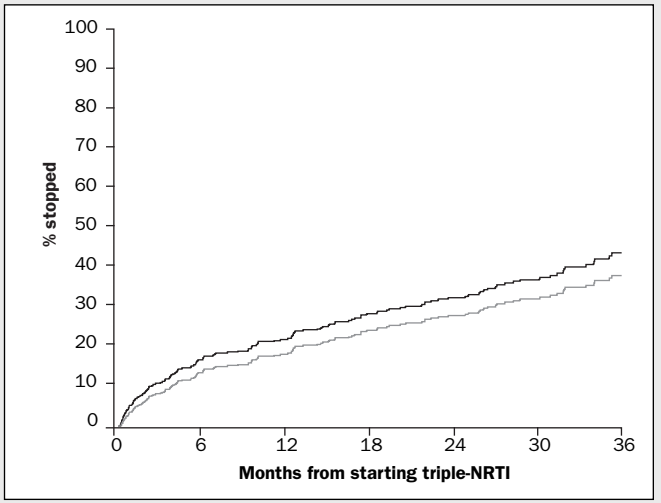

Figure 12.3: Kaplan-Meier estimates (95% CI) of the percentage of patients who discontinued using triple-NRTI combinations.

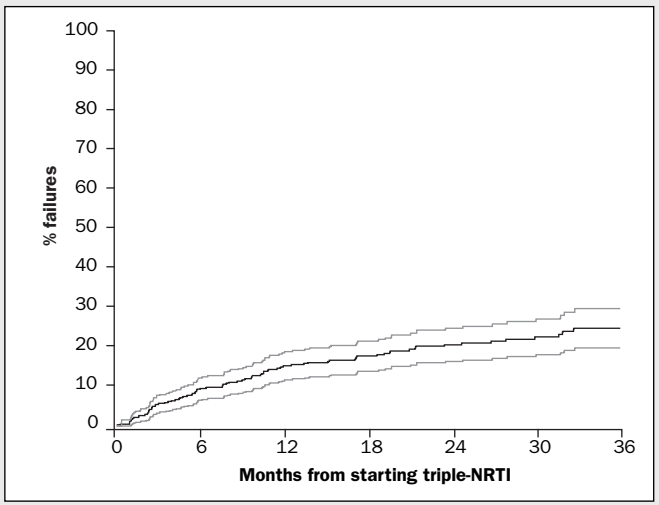

Figure 12.2: Kaplan-Meier estimates (95% CI) of the percentage of patients with virological failure who were still using triple NRTI.

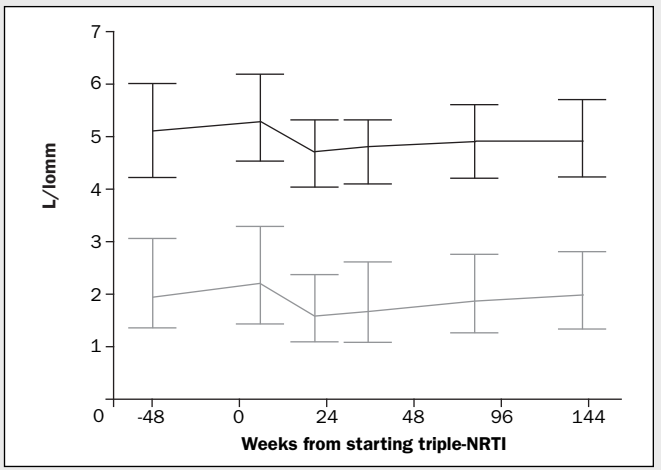

Figure 12.4: Median (IQR) of total cholesterol and triglyceride values before and after initiation of triple-NRTI therapy (black = total cholesterol; grey = triglycerides).


Viral

Blips

Frequency and characterisation of temporal viraemia during HAART

Ard van Sighem

Introduction

In a majority of patients, treatment with HAART results in sustained reduction of plasma HIV-RNA levels to below the limits of quantification. However, during follow-up many patients who achieve suppression of virus production have measurable, but transient, viraemia whilst on HAART[111-115]. Possible causes of these "viral blips" may be activation of latently infected cells and subsequent production of virus[116], release of virus from tissue reservoirs, or a rise in target-cell availability due either to vaccination or to co-infections[117, 118]. In contrast to short-term therapy interruptions, the effect of transient viraemia reportedly has a limited effect on treatment outcome, development of drug resistance, and clinical prognosis.[9, 111, 112, 114, 119, 120].

In this chapter, we present results from a study on viral load measurements taken after initial therapy success in patients treated with HAART. We focussed on a general description of those measurements, grouping them together in periods of therapy success and failure. Clinical events occurring during these periods were studied, and possible causes of viral blips were assessed.

Study population and methods

The study population consisted of HIV-1-infected patients receiving HAART. Initial virological success was defined by the finding of a viral load below 50 copies/ml in two consecutive measurements not more than 24 weeks apart. Patients were eligible for analysis from that moment onwards until end of follow-up or until a therapy interruption. HIV-RNA levels after success were classified into three categories: levels below 50 copies/ml, levels between 50 and 1000 copies/ml ('blips'), and levels above 1000 copies/ml. If a patient's CD4 and CD8 cells were not measured on the day of the viral load measurement, we used the CD4 and CD8 cell counts closest in time (within 28 days before or after the RNA measurement). CD4 and CD8 count slopes were calculated by subtracting the CD4 and CD8 counts taken at both the last and next-to-last viral load measurement, then dividing by the length of the time interval between these measurements.

Viral load measurements performed after initial HAART success were used to define periods of virological success and failure. A period of failure started when the viral load rose to a level above 50 copies/ml and ended when it returned to below 50 copies/ml. Analogously, a period of success started with a viral load below 50 copies/ml and ended when it rose above 50 copies/ml. Viral load measurements performed with assays having a limit of quantification above 50 copies/ml were excluded if the result was below the limit. Periods of failure were subdivided into periods of low-level viraemia (mean RNA between 50 copies/ml and 1000 copies/ml) and high-level viraemia (mean above 1000 copies/ml). The length of a period was calculated as the time between the first and the last RNA measurement that defined the period.

We assessed the occurrence of four kinds of events during each period of success or failure: therapy changes (excluding dosage changes), evidence of drug resistance, CDC-B and CDC-C events, and adverse events. Genotypic sequences were obtained as described in Chapter 15 and were scanned for the major resistance-associated mutations, as listed in the IAS-USA table[67].

The Poisson distribution was used to calculate 95% confidence intervals (CI) for frequencies of viral load measurements. Differences in those frequencies and in CD4 and CD8 cell counts were tested using Wilcoxon Mann-Whitney and $\chi 2$ non-parametric tests. For continuous variables, medians are reported together with the interquartile range (IQR). Changes over time in continuous variables were studied using analysis of variance. A multivariate cumulative logit model was used to identify covariates associated with observing the next viral load level after the most recent measurement in one the three aforementioned

categories. Results of the model are reported as odds ratios (OR) with 95% confidence intervals (CI).

Results

In total, 4838 patients who initiated HAART had an initial therapy success. The total follow-up after success until the last RNA measurement was 11,856 person-years, including 2986 person-years for the 956 pre-treated patients (19.8%) and 8870 person-years for the 3882 treatment-naïve patients (80.2%). Characteristics of the patient population are shown in Table 13.1.

During follow-up, 40,946 plasma viral load measurements were performed, corresponding with an average of 3.45 (95% CI 3.42–3.49) measurements per person-year of follow-up. For pre-treated patients, the mean number of measurements was slightly higher than for treatment-naïve patients, being 3.48 versus 3.44 measurements per person-year, but this difference was not statistically significant ($p=0.3$). In the treatment-naïve population, the incidence of viral load measurements in the range of 50 to 1000 copies/ml was 0.22 (0.21–0.23) per person-year; the incidence of measurements above 1000 copies/ml was 0.076 (0.070–0.082) per person-year. In the pre-treated population, these incidences were higher ($p<0.0001$), being 0.33 (0.31–0.35) and 0.10 (0.09–0.12) per person-year, respectively.

Of the 40,946 RNA measurements, 3891 (9.5%) were above 50 copies/ml, of which 2909 (7.1%) were between 50 and 1000 copies/ml and 982 (2.4%) were above 1000 copies/ml. In total, 3303 patients (68.3%) persistently had a viral load below 50 copies/ml, whilst 1220 (25.2%) had one or more viral load measurements between 50 and 1000 copies/ml but never exceeding 1000 copies/ml, and 315 (6.5%) had at least one measurement exceeding 1000 copies/ml. When the current, i.e. most recent, RNA measurement was below 50 copies/ml, the time to the next measurement was 100 days (84–126). When current RNA measurements were between 50 and 1000 copies/ml or above 1000 copies/ml, this period was shorter ($p<0.0001$), being 78 days (36–105) and 63 days (35–98), respectively. Between 1999 and 2004, the time between viral load measurements – when the current one was below 50 copies/ml – increased from 89 (56–101) to 112 days (91–137), an increase of 5.4 days per years ($p<0.0001$).

Table 13.2 shows the probability that a viral load measurement performed within 12 weeks after the current measurement will be observed in a certain one of the three viral load categories. When the current measurement was below 50 copies/ml, the probability that the next measurement was also below 50 copies/ml was 92.1%. In contrast, when the current measurement was above 1000 copies/ml, the probability of returning to below 50 copies/ml was only 18.1%, whilst the probability of again observing a viral load above 1000 copies/ml was 57.1%. For blips in the range 50 to 100 copies/ml, the probability of observing a viral load below 50 copies/ml at the next measurement was 74.0%; for blips between 100 and 1000 copies/ml, this probability was 51.0%. When the current viral load level was below 50 copies/ml, the probabilities of observing a blip at the next measurement in the range 50 to 100 copies/ml or 100 to 1000 copies/ml were 3.4% and 3.3%, respectively.

The multivariate model showed that a higher current RNA level, pre-treatment before initiation of HAART, and earlier calendar year were associated with a reduced probability of finding a lower RNA level at the next viral load measurement (Table 13.3). A higher CD4 count at the current RNA measurement was associated with a higher probability of measuring a lower RNA level at the next measurement (OR 1.26, 95% CI 1.16–1.37). In contrast, a higher CD8 count was associated with a lower probability (OR 0.77, 0.69–0.85). The time between the current and the next viral load measurement was

not significantly associated with the RNA level found at the next measurement.

The median CD4 slope between two consecutive viral load measurements below 1000 copies/ml was 0.11 x 10^6 cells/l per day (-0.59–0.82). This increase was larger ($p<0.0001$) when the first viral load measurement was above and the second one below 1000 copies/ml: 0.48 x 10^6 cells/l per day (-0.34–1.67). In contrast, when RNA levels rose from below to above 1000 copies/ml at two consecutive measurements, CD4 counts decreased at a rate of -0.27 x 10^6 cells/l per day (-1.19–0.36). This decrease was -0.16 x 10^6 cells/l per day (-1.19–0.83) if both measurements were above 1000 copies/ml. There was no significant difference in CD4 slopes when comparing viral load measurements below 50 copies/ml with measurements between 50 and 1000 copies/ml.

In the total population, there were 8974 periods of failure or success. The majority of the periods, 6730 (75.0%), were periods of success, whilst 1896 (21.1%) were marked with a mean viral load between 50 and 1000 copies/ml, and 348 (3.9%) had a viral load above 1000 copies/ml. For each period, the mean CD4 and CD8 count during the period was evaluated. As shown in Table 13.4, the medians of the mean CD4 counts were 467 x 10^6 cells/l (309–655) for periods of virological success; 470 (300–680) for periods with mean viral load between 50 and 1000 copies/ml ($p=0.4$, compared to periods of success), and 383 (253–560) for periods with mean load above 1000 copies/ml ($p<0.0001$, compared to each of the two other periods). Using the number of viral load measurements in each period of failure or success as markers of the duration of the period, we found that mean CD4 counts during periods of low-level viraemia with three or more viral load measurements were lower than during periods of success ($p=0.01$). Median CD8 counts were not significantly different between the low-level and the high-level periods of failure ($p=0.4$) but were lower during periods of success ($p<0.0001$, compared to periods of failure).

During 2912 (43.3%) periods of virological success, a therapy switch occurred. In 1629 (55.9%) of these periods, there was also at least one adverse event. Switching of therapy was less frequent during periods of failure with low mean viral load (19.1%) and more frequent (61.2%) when mean viral loads were above 1000 copies/ml. The incidence of CDC events was low during periods of both success and failure.

The majority (92.1%) of the periods of low-level failure were defined based on only one or two RNA measurements in the range 50-1000 copies/ml. Consequently, the median duration of these periods was short, 0.2 (0.1–0.3) years, and the number of periods without an event was high (73.5%). A genotypic sequence was obtained during 120 (34.5%) periods of high-level failures. In 96 (80%) sequences, one or more major resistance-associated mutations were found.

Discussion

During follow-up, 25% of our patients experienced at least one viral blip, a period of one or more viral load measurements between 50 and 1000 copies/ml, and 9% of patients had one or more measurements above 1000 copies/ml. These numbers agree with findings by other cohort studies[112, 114]. Of the total number of viral load measurements in our study, 9.5% was above 50 copies/ml, comparable with results obtained in a group of patients who were more frequently measured than in our study[113].

The majority of the blips observed in our study were isolated measurements. It has been estimated that the duration of episodes of transient viraemia is about three weeks. This was inferred from the higher probability of observing two consecutive blips when consecutive measurements were less rather than more

than one month apart[113, 121]. Likewise in the ATHENA cohort, we observed this higher probability (data not shown), but it was not statistically significant due to the limited number of measurements performed within one month after the current measurement.

In our study we found that a viral load below 50 copies/ml at the next measurement was less likely to be observed after a blip in the range 50 to 100 copies/ml than after a viral load below 50 at the last measurement. In addition, given a measurement below 50, the probability of seeing a blip of 50-100 copies/ml was equal to the probability of seeing a blip of 100 to 1000 copies/ml. Both findings suggest that blips cannot be explained by assay variation alone[122], although the extent to which such variation contributes to the occurrence of blips is not yet known[123].

Our model showed that earlier calendar year and pre-treatment with non-HAART therapies were associated with measuring higher viral loads during HAART. The association with calendar year was less significant when the model was limited to treatment-naïve patients or to patients who initiated HAART in or after 1998. Apparently, therapy regimens had become more potent or easier to adhere to, compared to the HAART regimens used before 1998, resulting in a more complete and more sustained suppression of viral load. This supposition is compatible with previous findings that intensification of therapy reduced residual replication of HIV and the frequency of viral blips[116, 117, 124].

CD4 cell counts during periods of low-level HAART failure did not differ from those observed in patients retaining RNA suppression below 50 copies/ml. Other studies found that the increase in CD4 cells after initiation of HAART was similar or even larger in patients with blips than in patients with persistently undetectable RNA levels[112, 125]. However, in patients with a period of low-level viraemia too long to be considered a blip, CD4 counts tended to decline[112, 115, 125]. According to our model, higher CD4 counts were associated with a lower probability of observing a blip at the next viral load measurement. This finding is compatible with reports that higher CD4 counts before initiation of HAART are associated with a lower frequency of blips during treatment with HAART[113, 120].

In contrast, we found that CD8 cell counts were higher during periods of low-level or high-level viraemia than during periods of RNA suppression. Others have found that the breadth and magnitude of the HIV-specific CD8 cell response is greater in patients with viral blips or with persistent viraemia in the range 50 to 1000 copies/ml[120]. It is not clear, however, whether intermittent viremic episodes were the cause or the consequence of a strong immune response.

For most periods of low-level HAART failure, we did not observe an event that could explain the occurrence of the failure. A study in three hospitals in London, England, showed that for 43% of the blips in that study, there was a documented prior period of poor adherence and drug interruption or change; for an additional 26% of the blips, there was an concurrent infection or vaccination[115]. We too observed therapy changes, but their timing suggested that they were more likely the response of the treating physician to therapy failure than the cause of failure. In 12% of our patients, there was a documented adverse event that might have led to a reduced adherence, whilst resistant HIV-1 virus strains were observed during 2.9% of the periods of low-level failure. On the basis of our results, we can only hypothesise on the role played by vaccinations and co-infections (including sexually transmitted infections) in the occurrence of viral blips. Several studies have examined this issue using mathematical models and have shown that exposure to antigen can result in a burst of viral replication[117, 118, 126].

	pre-treated, N=956		therapy naïve, N=3882		total, N=4838	
	N (%) / median (IQR)		N (%) / median (IQR)		N (%) / median (IQR)	
male gender	804	(84.1%)	3003	(77.4%)	3807	(78.7%)
region of origin						
the Netherlands	630	(65.9%)	2232	(57.5%)	2862	(59.2%)
sub-Saharan Africa	83	(8.7%)	733	(18.9%)	816	(16.9%)
transmission group						
MSM	614	(64.2%)	2066	(53.2%)	2680	(55.4%)
heterosexual	201	(21.0%)	1380	(35.5%)	1581	(32.7%)
IDU	62	(6.5%)	101	(2.6%)	163	(3.4%)
age at success (years)	42.3	(36.6–49.4)	39.2	(33.2–46.1)	39.8	(34.0–46.9)
CD4 count at success ($\times 10^6$ cells/l)	470	(320–670)	390	(250–577)	410	(260–590)
CD8 count at success ($\times 10^6$ cells/l)	994	(720–1330)	924	(650–1277)	940	(670–1290)
time T0 to success (years)	3.3	(2.0–4.5)	0.8	(0.5–2.0)	1.0	(0.5–2.8)
after initial success						
follow-up (years)	3.2	(1.6–4.6)	2.0	(0.7–3.7)	2.2	(0.8–4.0)
always < 50 copies/ml	552	(57.7%)	2751	(70.9%)	3303	(68.3%)
RNA not > 1000 copies/ml	315	(33.0%)	905	(23.3%)	1220	(25.2%)
RNA at least once > 1000 copies/ml	89	(9.3%)	226	(5.8%)	315	(6.5%)

IQR: inter quartile range; T_0: start of HAART; MSM: men having sex with men; IDU: intravenous drug use.

Table 13.1: Patient characteristics for the total patient population and for pre-treated and therapy-naïve patients who have initial HAART success.

	next RNA (copies/ml)		
current RNA (copies/ml)	**< 50**	**50–1000**	**> 1000**
< 50	92.1%	6.7%	1.1%
50–1000	60.3%	32.7%	6.9%
> 1000	18.1%	24.9%	57.1%

Table 13.2: Probability of observing the next viral load measurement in one of three categories (< 50 copies/ml, between 50 and 1000 copies/ml, or above 1000 copies/ml) when this measurement is performed within 12 weeks after the current, i.e. most recent, RNA measurement.

	OR	95% CI
current RNA		
< 50 copies/ml	1	
50-1000 copies/ml	4.14	(2.29–7.49)
RNA ($\log_{10}$ copies/ml) per unit increase	0.20	(0.15–0.26)
> 1000 copies/ml	0.17	(0.06–0.53)
RNA ($\log_{10}$ copies/ml) per unit increase	0.47	(0.35–0.64)
pre-treatment before HAART		
no	1	
yes	0.68	(0.60–0.77)
log CD4 ($\times 10^6$ cells/l) per unit increase	1.23	(1.13–1.34)
log CD8 ($\times 10^6$ cells/l) per unit increase	0.78	(0.70–0.86)
year of RNA measurement		
≥ 2003	1	
2001 or 2002	0.87	(0.80–0.96)
≤ 2000	0.73	(0.64–0.83)
non-Dutch origin (only if no pre-treatment)		
no	1	
yes	0.78	(0.69–0.89)

OR: odds ratio; CI: confidence interval. Odds ratios below 1 are associated with a higher probability of having a higher HIV-RNA level at the next viral load measurement.

Table 13.3: Covariates associated with measuring an HIV-RNA level falling in the same or a lower category at the first viral load measurement after the current one.

	period					
	success, N=6730		failure, low viral load, N=1896		failure, high viral load, N=348	
	N (%) / median (IQR)		N (%) / median (IQR)		N (%) / median (IQR)	
RNA measurements						
1	1130	(16.8%)	1478	(80.0%)	129	(37.1%)
2	937	(13.9%)	229	(12.1%)	78	(22.4%)
≥ 3	4663	(69.3%)	189	(10.0%)	141	(40.5%)
duration (years)	1.2	(0.4–2.6)	0.2	(0.1–0.3)	0.3	(0.1–0.7)
event during period						
none	2970	(44.1%)	1394	(73.5%)	114	(32.8%)
therapy change	2912	(43.3%)	363	(19.1%)	213	(61.2%)
genotype obtained	14	(0.2%)	62	(3.3%)	120	(34.5%)
≥ 1 RAMS	5	(0.1%)	55	(2.9%)	96	(27.6%)
CDC-B event	140	(2.1%)	18	(1.0%)	6	(1.7%)
CDC-C event	85	(1.3%)	6	(0.3%)	7	(2.0%)
adverse event	2422	(36.0%)	228	(12.0%)	68	(19.5%)
mean CD4 ($\times 10^6$ cells/l)	467	(309–655)	470	(300–680)	383	(253–560)
mean CD8 ($\times 10^6$ cells/l)	888	(600–1213)	960	(648-1320)	985	(635–1368)

RAMS: major resistance- associated mutation

Table 13.4: Characteristics of the periods of success (mean RNA < 50 copies/ml) and failure (mean HIV-RNA > 50 copies/ml) after initial therapy success. Periods of failure are subdivided in 'low viral load' (mean RNA between 50 and 1000 copies/ml) and 'high viral load' (mean RNA above 1000 copies/ml).

Death a

nd AIDS

Ongoing decline in mortality and incidence of AIDS after initiation of HAART

Ard van Sighem

Introduction

Treatment of HIV-infected patients with highly active antiretroviral therapy (HAART) slows down disease progression and reduces mortality directly attributable to HIV or AIDS[24, 127, 128]. In addition, the incidence of therapy-related and other non-HIV-related cases of death remains stable over time, indicating that the adverse effects of HAART are not yet a major cause of death[24, 127]. As HAART has been available since 1995, the oldest population has now been treated for up to ten years. However, as HAART treatment is further prolonged, there may be reduced efficacy, resulting in therapy failure and, ultimately, progression to AIDS or death.

This chapter provides an update on mortality and the incidence of AIDS in the HAART-treated population in the Netherlands. In addition, we will briefly describe a model that was developed in collaboration with the Association of Insurers in the Netherlands to explore the predicted life expectancies of HAART-treated patients based on their initial response to therapy.

Population and methods

The study population consisted of 8439 HIV-1-infected patients who initiated HAART between 1995 and 1 June 2005, the data-freeze date for this report. All deaths and AIDS cases occurring during this period were assessed. AIDS was defined as the first occurrence of a CDC-C event at least four weeks after initiation of HAART. Follow-up ended at the date of death or AIDS diagnosis or at the last follow-up visit. Patients were censored at their last follow-up visit, at closure of the database, or (for AIDS patients only) at time of death, whichever of these events came first.

Annual mortality and AIDS incidence were calculated as the number of deaths or AIDS cases per year divided by the total number of person-years of follow-up after initiation of HAART during that year. The Poisson distribution was used to calculate 95% confidence intervals (CI) for rates. Significance of changes in mortality over time was assessed by a $\chi 2$-test.

Of the 8439 patients, we selected 6191 who had started HAART with no previous ART and who had more than 24 weeks of follow-up and measurements of viral load and CD4 at 24 weeks (i.e., between 12 and 36 weeks) after initiation of HAART. In this group, progression to death was analysed using a multivariate hazards model; the hazard of death was calculated as the sum of an expected hazard and a function containing patient-specific covariates. The expected hazard depended on the patient's age and gender and was estimated from the annual mortality rate in the general population in the Netherlands [Actuarial Association, Woerden, 2002, available via http://www.ag-ai.nl]. Patient-specific covariates were retained in the model if their exclusion yielded a significantly less accurate model ($p<0.01$, likelihood ratio-test). The hazard ratio (HR) was calculated for each covariate together with a Wald 95% confidence interval (CI). The standardised mortality ratio (SMR) was defined as the one-year mortality of HIV-infected patients relative to the general population. Hence, a patient with SMRs had an *s* times higher probability of dying within one year than an uninfected individual of the same age and gender.

Results

For the total group (8439 patients with 39,969 person-years of HAART follow-up), there were 732 cases of death, corresponding with an average mortality of 1.83 (95% CI 1.70–1.97) deaths per 100 person-years. The mortality rate declined from 4.62 (3.09–6.63) in 1996 to a level of 1.55 (1.40–1.71) per 100 person-years after 2000 (see Figure 14.1). Thereafter, mortality did not change significantly over calendar time ($p=0.2$). In the therapy-naïve population (6191 patients with 25,211 person-years of follow-up), mortality was lower than in the pre-treated population (2248 patients with

14,758 person-years of follow-up), being 1.16 (1.00–1.32) compared to 2.50 (2.15–2.88) per 100 person-years after 2000.

In the total group, 957 AIDS diagnoses were registered after start of HAART during 36,657 person-years of follow-up. From 1996 onwards, there was a monotonous decline from 15.4 (12.4–18.9) AIDS diagnoses per 100 person-years in 1996 to 2.16 (1.73–2.66) in 2000 and 1.43 (0.96–2.05) in 2004. After 2000, AIDS incidence did not change significantly over calendar time (p=0.04). In the therapy-naïve population (23,538 person-years of follow-up), the incidence of AIDS after 2000 was similar to that in the pre-treated population (13,119 person-years of follow-up), being 1.84 (1.64–2.06) and 1.69 (1.39–2.04) per 100 person-years, respectively.

In total, 3678 of the 6191 patients were eligible for inclusion in the survival model, of which 126 (3%) died during 11,930 person-years of follow-up starting at 24 weeks after commencement of HAART. Of those patients, 590 (16%) had a 24-week CD4 count above 600 x 10^6 cells/l, and 2762 (75%) had a CD4 count above 200 x 10^6 cells/l. The only covariates significantly associated with survival were log-transformed CD4 count at 24 weeks (HR 0.50, 95% CI 0.40–0.61, per unit increase) and viral load at 24 weeks (HR 0.30, 95% CI 0.15–0.60, viral load $<$100,000 copies/ml versus $\geq$100,000 copies/ml) and infection by intravenous drug use (HR 0.16, 95% CI 0.10–0.26, non-IDU versus IDU). No statistically significant interactions between covariates and no interactions with time were found. The increasing risk of death associated with older age that is usually observed[24, 84] was, according to the model, fully compensated by the expected increasing hazard in the non HIV-infected population.

For 34-year-old HIV-infected men, the mortality was expected to be 20 (95% CI 14–29) times higher than in the general population when CD4 counts at 24 weeks were 50 x 10^6 cells/l, and 4.3 (3.3–5.8) times higher when CD4 counts were 600 x 10^6 cells/l. For women the same age, the expected mortality was 29 (20–42) and 5.9 (4.4–8.2) times higher, respectively. Figure 14.2 shows the predicted survival probabilities up to the age denoted on the horizontal axis for HIV-infected individuals still alive at the age of 34. The solid black line represents the survival probability for uninfected individuals. The dotted and grey lines are the corresponding survival probabilities for HIV-infected non-IDU patients who, at 24 weeks after starting HAART, had a CD4 count of 600 and 200 x 10^6 cells/l and a viral load below 100,000 copies/ml.

Discussion

The decline in mortality that had been observed since the wide-spread introduction of HAART in 1996 seems to have come to an end. Since 2000, the annual mortality has varied between one and two cases of death per 100 person-years of follow-up. In the HMF report for 2004, mortality for that year was said to be 1.95 (1.47–2.53), but in the present analysis, the finding for 2004 is 1.47[9]. Probably, last year's overestimation is due to the incomplete collection of data when the 2004 report went to press – a limitation that applies also to this report. Meanwhile, the incidence of AIDS still declined, although the apparent decrease in the last three years might partly be the result of a backlog in HMF registration of AIDS events. So far, there is no evidence that HAART is becoming less effective in preventing disease progression. In the pre-treated population, the incidence of AIDS was even less than in therapy-naïve patients, and neither mortality nor incidence of AIDS changed after 2000.

In the population used for the model, the only strong predictors for progression to death were the CD4 counts and HIV-RNA plasma levels measured after 24 weeks of initial HAART treatment and infection by drug use, with lower mortality observed in those with higher CD4 counts. This finding is consistent with recently published

results from a large international cohort[84]. In non-IDU patients with CD4 counts above 600 x 10^6 cells/l and viral load below 100,000 copies/ml, the mortality was, however, still higher than in the age- and gender-matched general population in the Netherlands, and only a minority of the study population had 24-week CD4 counts above 600. Moreover, patients who progressed fast and died before 24 weeks of HAART were excluded from the study.

One of the advantages of the model presented here is that it does not require information on cause-specific mortality, which can be hard to determine. Even if clinical data are available at time of a patient's death, it is often difficult to judge if death can be attributed directly to HIV or AIDS, to a side-effect of therapy, or to a non-HIV related cause of death[24].

Nevertheless, careful registration of mortality cases remains of utmost importance to permit early detection of potential increases in the number of deaths related, for example, to antiretroviral therapy[15, 24]. For that purpose, the CoDe classification system for causes of death in HIV-infected patients was developed by an international panel representing several large observational cohorts. The HMF evaluated this system early in 2005 and has been using it since May.

Other than being infected with HIV, there are differences between the HIV-infected population and the general population that may be underestimated by our model, even after correction for gender and age[129]. The male HIV-infected population consists mainly of homosexual men, who are likely to differ in lifestyle from men of the general Dutch population. For example, in the general population, around 40% of men and one third of women between 18 and 65 years smoke tobacco [Statistics Netherlands, available at http://www.cbs.nl]. In contrast, in a subset of our subjects for whom smoking was recorded, half of the homosexual men smoked, as did one third of both men and women who were heterosexual[89]. Therefore, part of the increased mortality in our subjects versus the general population will be due to life-style factors rather than HIV-infection. Furthermore, the expected mortality for the general population is based on all causes of death and thus includes HIV mortality. However, for the general population between 25 and 50 years of age, deaths due to HIV infection comprise at most 2% of the total number of deaths [Statistics Netherlands].

A proportion of the patients analysed in our study initiated HAART regimens that are generally no longer administered. Over calendar time, the composition of the first HAART combinations have shifted towards regimens without protease inhibitors. These newer regimens may be less toxic and hence easier to adhere to. The current response to HAART is therefore likely to be sustained for a longer time, resulting in a better prognosis and improved survival probabilities in the future.

Although mortality in HIV-infected patients responding well to HAART was still higher than in the general population, standardised mortality rates were comparable to those observed in patients with diabetes mellitus[129-131]. A large British cohort study on insulin-treated diabetic patients found rates of 3.7 and 4.9 in men and women, respectively, in the 30-39 year age category[131]. Likewise, the Swiss HIV Cohort Study showed that excess mortality amongst successfully treated HIV-infected patients is similar to that in successfully treated patients with cancer[132].

The model for progression to death described in this chapter has been used by the Association of Insurers in the Netherlands to estimate risks associated with life insurance for HIV-infected patients. It turned out that for a subgroup of patients, these risks are acceptable for insurance companies. Insurance is, however, only possible for patients treated with HAART, thus excluding

patients who are doing well without therapy. Currently, a model is being developed by HMF to predict survival probabilities from HIV diagnosis instead of from start of HAART, in order to be able to calculate risks associated with life insurance for those patients who do not yet need treatment.

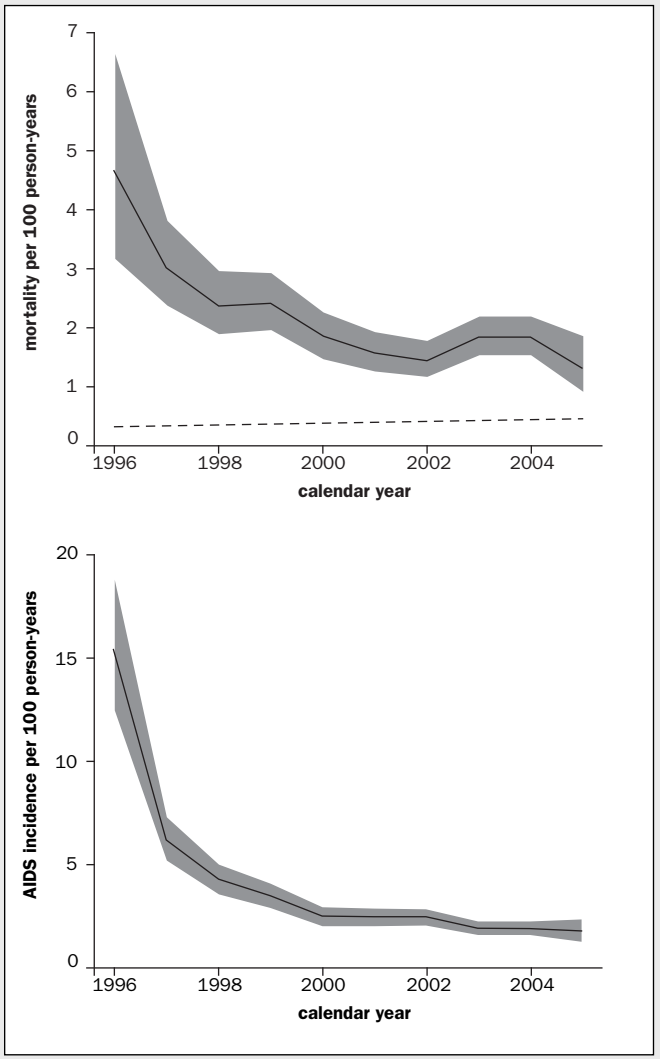

Figure 14.1: Mortality and incidence of AIDS as a function of calendar year. The black lines represent the incidence, whilst the grey areas are the 95% confidence intervals. The dotted line is the mortality expected in age- and gender-matched individuals from the general Dutch population.

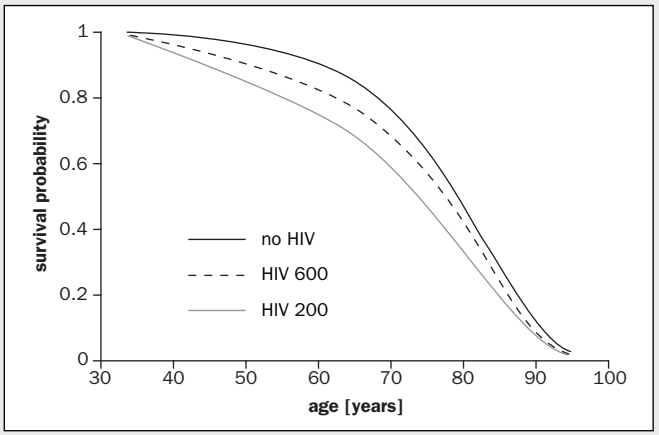

Figure 14.2: Predicted probabilities of surviving up to a specific age for 34-year-old uninfected individuals ("no HIV") as compared to HIV-infected individuals with a CD4 count of 600 x 10^6 cells/l ("HIV 600") or 200 x 10^6 cells/l ("HIV 200") after 24 weeks of HAART, who have a viral load below 100,000 copies/ml and were not infected by intravenous drug use.


Resis

tance

Limited transmission of drug resistant HIV, but high prevalence at therapy failure

Ard van Sighem

Introduction

Although treatment with HAART generally suppresses plasma HIV-RNA levels below the quantification limit of currently used assays, HIV is still replicating, albeit at a lower level[133, 134]. This strong but not complete suppression of HIV replication achieved with prolonged treatment with HAART, in combination with a non-optimal adherence, might lead to selection of HIV-1 viruses that escape HAART-induced suppression due to resistance[135, 136]. The presence of resistant virus strains limits future therapy options and might lead to a worsened prognosis. The prevalence of resistant virus in patients failing on therapy may be as high as 80%[137-139].

Resistant virus strains might also be transmitted to uninfected patients. In recent years, the prevalence of transmitted drug-resistant viruses in newly infected patients varied between 5% and 25% in Europe and North America[140-148]. Transmission of resistant virus strains was observed in 6% of newly infected participants of the Dutch Amsterdam Cohort Studies after 1998[149].

Study population and methods

Resistance was studied in 895 HMF-registered patients with recent infections or new diagnoses over the period 1994-2004. Resistance measurements were based on isolation of HIV-1 RNA in plasma of patients and amplification of the protease gene and part of the reverse transcriptase (RT) gene of the virus. Successful amplification was achieved only in patients with a viral load above 1000 copies/ml. HIV-1 RT and protease were genotyped by using the amplified genes in a sequencing procedure. Sequences were obtained in five different virological laboratories, as mentioned in Chapter 7: AMC-UvA in Amsterdam (Suzanne Jurriaans, Nicole Back, Lia van der Hoek, and Ben Berkhout), Erasmus MC in Rotterdam (Martin Schutten and Ab Osterhaus), UMCU in Utrecht (Charles Boucher and Rob Schuurman), LUMC in Leiden (Louis Kroes and Eric Claas), and VUMC in Amsterdam (Annika Petterson and Paul Savelkoul).

Sequences were compared to subtype B wild-type virus and scanned for specific mutations at codons known to be associated with resistance to the three major classes of anti-HIV drugs: nucleoside RT inhibitors (NRTI), non-nucleoside RT inhibitors (nNRTI), and protease inhibitors (PI). Mutations that can occur as natural polymorphisms were excluded, even if they contribute to resistance when present with other resistance-associated mutations.

Mutations conferring resistance to NRTI included M41L, E44D, A62V, K65R, D67N, T69D, K70R, L74V, V75T, F77L, Y115F, F116Y, V118I, Q151M, M184V/I, L210W, T215Y/F, T215D/N/S/C/E (denoted T215X), K219Q, and an insertion after position 69. Mutations conferring nNRTI resistance included L100I, K103N, V106A, V108I, Y181C/I, Y188C/L/H, G190S/A, P225H, M230L, and P236L. The PI resistance-associated mutations were D30N, M46I/L, G48V, I50V, V82A/F/T/S, I84V, and L90M. These three groups of mutations constitute a canonical set, though the set varies slightly in some reports[67, 141, 150, 151]. The NRTI-resistance-related mutations E44D and V118I occur also as natural polymorphisms. Therefore, we counted them as mutations only when they occurred in combination with other NRTI-resistance-related mutations[152].

Transmission of drug-resistant virus strains was studied in patients with either a recent infection or a new diagnosis, as two separate groups. Patients with a recent infection[251] were either diagnosed during acute infection or were tested HIV-1-positive less than two years after their last negative test. All other patients with a known HIV-1-positive test were assigned to the group of new diagnoses[644]. For both groups, a sequence had to be available within one year after diagnosis and before initiation of antiretroviral treatment. The sequences available from the HMF database were combined with those available from the Amsterdam cohort studies (ACS)[149], in which most HMF patients are participants.

Data on viral load measurements were used to define the start and the stop of failures that occurred after initiation of antiretroviral treatment. For the present study, failure was defined as at least two consecutive viral load measurements of > 500 copies/ml. A period of failure started at the midpoint of the interval between the last measurement of ≤500 copies/ml and the first one above that level. Analogously, the period of failure ended at the midpoint of the interval between the last measurement of > 500 copies/ml and the first one below. It should be noted that this definition of failure did not take into account the use of therapy.

For each calendar year, we counted the number of persons in whom failure occurred (N_{fail}) and the number of persons in follow-up (N_{total}) in that year. In addition, the total number of person-years of follow-up (PY_{total}), failure (PY_{fail}), and therapy ($PY_{therapy}$) per year was determined. The number of patients with failure periods whilst on therapy was estimated by reweighting N_{fail} by $PY_{therapy}/PY_{fail}$. In those patients, we counted the number of sequences obtained per year and the number of sequences with one or more resistance-associated mutations. The fraction of patients with such a sequence was determined by dividing the resulting number by N_{fail}.

Results

Transmission of drug-resistant virus

Amongst the 251 recently infected patients (Table 15.1), resistance-associated mutations were found in 21 (8.4%), of whom nine were infected in or before 1996. Of all HIV transmissions, the percentage of resistant virus strains per year of infection dropped from 24% in 1994 to 6% in 1996. Due to a limited number of recent infections, the percentage fluctuated thereafter between 0% and 15% (Figure 15.1). Overall, the percentage was 18% (95% CI 9–31) in patients infected in or before 1996 and 6.0% (95% CI 3.2–10.3) in patients infected thereafter.

Of the recently infected patients, two harboured a M46I mutation at codon 46 in protease as their only resistance-associated mutation. In three patients, only mutations conferring nNRTI resistance were found. As to NRTI resistance, one patient harboured a M184V mutation that confers resistance to 3TC[153]. Eleven other patients had one or more mutations associated with resistance to AZT. Those found most frequently were M41L (6 patients), K70R (4 patients), T215Y/F (4 patients), and T215X (4 patients)[154-156]. For the first time in the ATHENA cohort, a recently infected patient was found to harbour a virus strain that was resistant to more than one drug-class. Infected in 2004, this patient harboured resistance mutations to all three drug-classes.

In the group of 644 new diagnoses, resistance was found in 38 patients (5.9%). The majority of the resistant sequences (33 of 38) were obtained in or after 2002. The annual percentage of transmissions of resistant virus strains varied between 0% and 8% (Figure 15.1). In 2003 and 2004, 25 transmissions of resistant virus were observed amongst the 366 new diagnoses of those two years, yielding a proportion of 6.8% (95% CI 4.5–9.9). As shown in Table 15.1, 333 homosexual men and 213 heterosexual persons had new diagnoses. Of the former, 8.4% (28/333) were infected with a resistant virus strain, whilst this proportion was 3.3% (7/213) in the heterosexual group (p=0.02). Of the 644 patients with new diagnoses, most of those harbouring resistant viruses were infected with a subtype B virus: 35/460 (7.6%) versus 3/184 (1.6%) non-B subtypes (p=0.004).

In three of the 38 patients, mutations associated with PI resistance were found: M46I in all three and, in one of them, a L90M mutation as well. Eleven patients harboured mutations conferring nNRTI resistance to nevirapine and efavirenz. Of these, K103N was found in 4 patients, Y181C in 2 patients, and G190A in 2 patients[157, 158]. In five patients, the only mutation found

was V108I in RT, conferring resistance to nevirapine but not to efavirenz in the absence of other mutations[159].

In 30 patients, mutations were found that conferred NRTI resistance, mainly to AZT, d4T, and 3TC. In 15 patients, a mutation T215X was found at codon 215, which reflects evolution from a transmitted AZT-resistant virus[160]. Other mutations were the AZT-resistance-related mutations M41L (18 patients), K219Q (4), D67N (3), T69D (2), and K70R (2). In three patients, the 3TC-resistance-associated mutation M184V was found.

In three of the 38 patients, resistance to both NRTI and nNRTI was observed. One of the three harboured mutations conferring resistance to all three drug classes.

Resistance during treatment

The fraction of pre-treated patients on HAART who failed virologically declined from 39% in 1996 to 18% in 2005 (Figure 15.2). During the same period, the fraction of failures amongst therapy-naïve patients on HAART increased from 7% in 1997 to 10% in 2005. In the group of pre-treated patients, the fraction of failing patients from whom a sequence was obtained increased from 11% in 1996 to 28% in 2003. More than 90% of these sequences harboured one or more resistance-associated mutations. In the therapy-naïve group, the fraction of failing patients for whom sequences were available increased from a few percent before 1998 to 24% in 2003. In the years after 2000, 80% to 85% of the sequences obtained from therapy-naïve patients harboured mutations.

The nature of resistance-associated mutations observed per year of sequencing in the population with failing therapy changed over time (Figure 15.3). The proportion of sequences with NRTI-resistance-associated mutations decreased from 92% in 1996 to a level between 70% and 80% from 2000 onwards. In general, there was a decline in the prevalence of mutations associated with resistance to AZT. For example, between 1996 and 2004 the prevalence of M41L declined from 59% to 23%, L210W from 49% to 12%, K219Q from 17% to 10%, and T215Y/F from 67% to 25%. In contrast, the prevalence of K65R and L74V, associated with resistance to the NRTIs abacavir and tenofovir[161], rose from 0% and 1%, respectively, to 5% and 10%, respectively. In addition, an increase was observed in nNRTI-resistance-associated mutations from 1% in 1996 to 47% in 2004. The prevalence of K103N increased from 0% in 1996 to 28% in 2004, withV108I going from 1% to 7%, Y181C/I from 0% to 13%, and G190S/A from 0% to 10%. The prevalence of mutations associated with PI resistance increased from 13% in 1996 to a level between 50% and 60% between 1998 and 2000. Thereafter, their prevalence declined to 27% in 2004.

As of July 1, 2005, a total of 9019 ATHENA patients were still in follow-up. In the case of 1025 (11.4%), a sequence had been obtained in which resistance-associated mutations were found. The number of patients found with resistance to only one drug class was 319 (35.4%). Resistance to two drug classes was found in 487 (54.0%), whilst 219 (24.3%) turned out to be resistant to all three drug classes. Mutations conferring resistance to NRTIs, nNRTIs, and PIs were found in 977 (10.8%) patients, 544 (6.0%) patients, and 432 (4.8%) patients, respectively.

Discussion

The levels of transmission of drug-resistant HIV-1 virus strains remain low in the Netherlands. Last year, 6.5% of the recently infected patients who were diagnosed after 1996 harboured a strain containing at least one major resistance-associated mutation[9]. In the current analysis, we observed the transmission of resistant strains in 6.0% of the recently infected patients. A slightly higher percentage was found amongst newly diagnosed patients. These percentages are comparable with those observed in other western countries[140, 148, 162]. Decreasing levels of drug-resistance in newly HIV-infected patients

is correlated with the decreasing amount of virus circulating in the chronically infected population[148].

Since 2002, it is standard care in some hospitals in the Netherlands to obtain a protease and RT sequence in all newly diagnosed patients with HIV infection. This is illustrated in Figure 15.1, in which the dashed lines show an increasing number of sequences obtained in each year after 2002. Only since that year do we have accurate estimates of the percentage of resistant transmissions amongst newly diagnosed patients. For patients with a sequence at diagnosis before 2002, it is unknown whether the sequence was obtained immediately at diagnosis or retrospectively, e.g., when a therapy regimen failed. Moreover, the number of patients from whom a sequence was obtained at diagnosis was very limited before 2002.

The percentage of transmissions of resistant virus differed amongst risk groups and was higher in homosexual men than in the heterosexual population. Currently, the Kwaliteitsinstituut voor de Gezondheidszorg CBO is formulating guidelines that will recommend obtaining a sequence at diagnosis only in those populations that have an increased risk of being infected with a resistant virus strain. Whilst this recommendation will reduce the strain on hospital and laboratory resources, it will also reduce the chances of observing a future increase in resistant transmissions that might occur in populations now at low risk.

The fraction of patients in failing therapy from whom a sequence was obtained increased over time. Of those patients with a sequence obtained whilst on therapy, 80% to more than 90% harboured resistance-associated mutations[137-139]. These figures indicate that determining the genotypic resistance profile is becoming an integrated part of routine clinical care for HIV-infected patients in the Netherlands. Still, the fraction of patients from whom a sequence was obtained in 2003 was only around 25%, suggesting that the perceived necessity to obtain a sequence was not always pressing.

As observed previously, the prevalence of specific resistance-associated mutations changed over time[9], in correlation with changes in antiretroviral drug use[163]. Initially, only nucleoside analogues were used, whilst after 1996, protease inhibitors became available. After 1998, non-nucleoside RT inhibitors were introduced and quickly replaced PIs as the initial HAART regimen.

We found that 11.4% of the ATHENA population now in follow-up harbours virus strains that are resistant to one or more drug classes. A recent study in the UK showed that the risk of one or more of the major mutations listed by IAS-USA was 27% after six years of HAART[164]. In the HOMER cohort, resistance was found in 25% of the patients with a viral load above 1000 copies/ml during the first 30 months after they started HAART[136]. Hence, the actual resistance level in the ATHENA cohort is probably higher than the level found in this study.

	new diagnoses, N=644		recent infections, N=251	
	N (%) / median (IQR)		N (%) / median (IQR)	
male gender	482	(75%)	228	(91%)
born in NL	390	(61%)	171	(68%)
transmission group				
homosexual	333	(52%)	157	(63%)
heterosexual	213	(33%)	32	(13%)
IVD	8	(1%)	9	(4%)
other/unknown	90	(14%)	53	(21%)
CD4 ($\times 10^6$ cells/l)	290	(110–500)	490	(360–680)
RNA ($\log_{10}$ copies/ml)	4.9	(4.3–5.3)	4.9	(4.2–5.5)
years of age	37.1	(30.7–43.5)	34.0	(30.0–41.5)
non-B subtype	184	(29%)	22	(9%)
resistant	38	(5.9%)	21	(8.4%)

Table 15.1: Percentage of transmissions of resistant virus as a function of time amongst recently infected (A) and newly diagnosed patients (B). The black line represents the percentage whilst the grey areas are the 95% confidence intervals. The dashed line is the number of sequences that was obtained in each year (right axis).

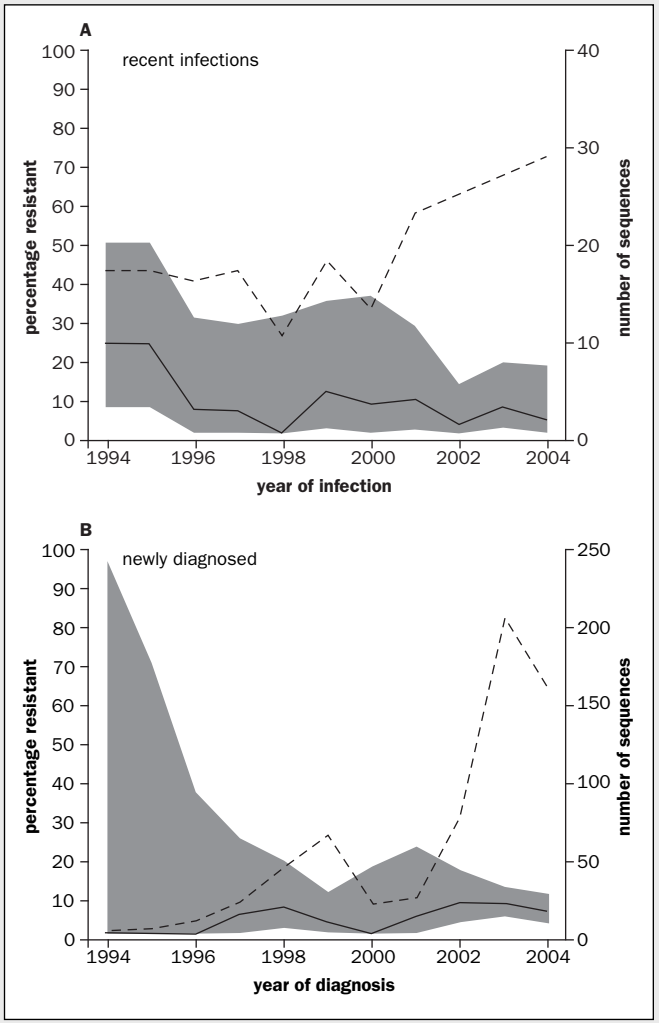

Figure 15.1: Percentage of transmissions of resistant virus as a function of time amongst recently infected (A) and newly diagnosed patients (B). The black line represents the percentage whilst the grey areas are the 95% confidence intervals. The dashed line is the number of sequences that was obtained in each year (right axis).

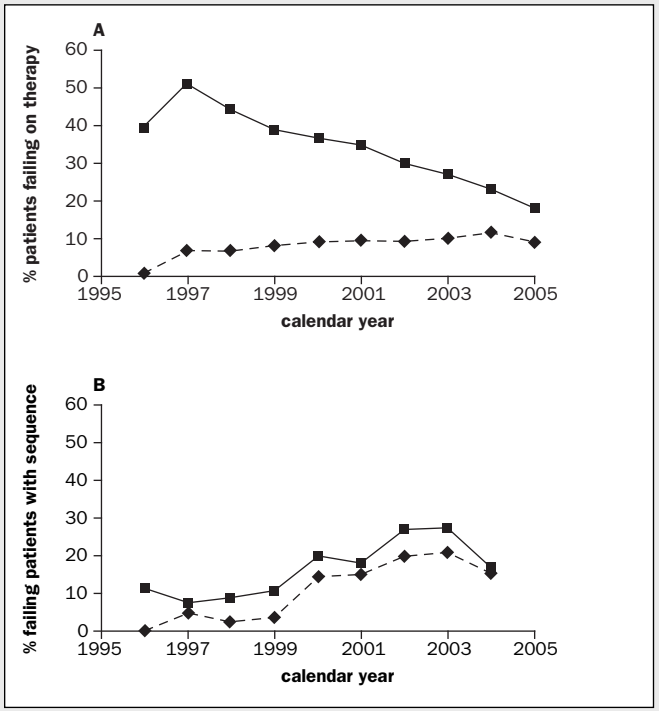

Figure 15.2: The fraction of pre-treated (solid line) and therapy-naïve (dashed line) patients virologically failing per year (A) and the fraction of failing patients in whom a sequence was obtained (B).

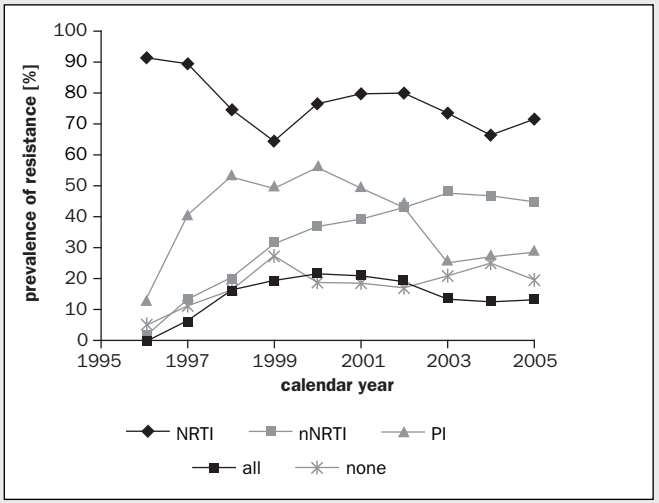

Figure 15.3: Annual relative prevalence of sequences harbouring mutations associated with resistance to nucleoside reverse transcriptase (RT) inhibitors (NRTI), with resistance to non-nucleoside RT inhibitors (nNRTI), and with resistance to protease inhibitors (PI). Also shown are the prevalences of sequences with mutations conferring resistance to all three drug classes ('all') and of sequences with no mutations ('none').

Conclusi

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Frank de Wolf

The ATHENA national observational cohort

At present, the ATHENA national observational cohort has included a total of 10,854 HIV-infected patients with a follow-up of almost 70,000 person-years. These patients are registered and monitored in 23 HIV Treatment Centres. Patients have a median follow-up period of 5.4 years (IQR 2.2-9.6). The median time between healthcare visits is approximately 3 months.

Since 2002, the number of new HIV diagnoses seems to have stabilised at around 800 per year. Until 2002, the distribution of HIV-infected men and women per year of diagnosis showed a slow but steady increase of infected women. After 2002, the increase of HIV-infected women was stable, in contrast to an absolute as well as a relative increase in HIV-infected men. This finding might reflect an increase in high-risk sexual behaviour amongst homosexual men[37] in combination with a recent decrease in heterosexual immigrants coming from HIV-endemic areas, especially sub-Saharan Africa.

Homosexual men still form the largest HIV-infected group in the Netherlands[9, 11]. This group is mainly of Dutch origin and is infected in the Netherlands with a subtype B strain. Their age and CD4 counts at diagnosis indicate that homosexual men are diagnosed sooner after infection and are infected at older ages than patients in other risk groups.

HIV transmission through heterosexual contact occurs mainly amongst patients originating from sub-Saharan Africa and, to a lesser extent, from Latin America and the Caribbean. The overwhelming majority of these patients are infected in their region of origin, a finding confirmed by the high prevalence of non-B HIV subtypes found in this group. Clearly, a substantial proportion of heterosexually transmitted HIV is acquired outside the Netherlands. Most heterosexual patients of Dutch origin are infected in the Netherlands and in sub-Saharan Africa, although a considerable number of heterosexual men are infected in South/Southeast Asia, mainly in Thailand.

In the heterosexual group, men are generally diagnosed at an older age and later stage of infection than women. HIV-RNA plasma levels are lower in women than in men when CD4 cell counts are high, but higher when CD4 counts are low, i.e., typically below 200 x 10^6 cells/l[46]. This finding is consistent with our current observation that women with high median CD4 counts have lower median viral load levels than men.

The rate of new HIV infections in Eastern Europe is amongst the highest in the world[47], and these infections occur mainly in intravenous drug users (IDUs). Although several countries in Eastern Europe are now part of the European Union and migration to Western Europe is easier, introduction of Eastern European HIV variants into the epidemic in the Netherlands seems limited. Reduced intravenous drug use in the Netherlands may contribute to this result. However, importation of HIV from Eastern Europe may be underestimated, since the ATHENA database does not encompass some pertinent data, such as infection rates amongst commercial sex workers moving from Eastern European countries to the Netherlands.

More than 80% of the patients registered with HMF are treated with HAART. Of the rest, only very few are on an ART regimen that cannot be classified as HAART, whilst a relatively stable percentage of 18.5% receive no antiretroviral agents at all. The majority of these untreated patients were diagnosed with HIV during or after 2000. Their relatively recent diagnosis plus their relatively high CD4 cell numbers and low HIV-RNA plasma concentrations point to recent infection, which makes them HAART-ineligible by the current Dutch treatment guidelines.

The long-term effect of treatment with highly active antiretroviral therapy (HAART)

Patients starting HAART below the CD4 cell count threshold of 200 cells/mm^3 are at an increased risk of death or developing AIDS-defining events. Patients lacking these measurements are likewise at an increased risk of death or AIDS, suggesting that low CD4 levels or other risk factors were present, albeit undetected. No significant differences in the risk of progression to AIDS or death were seen in patients starting HAART with 200-350 CD4 cells/mm^3 versus patients starting with a higher CD4 cell count. These results support the national guidelines that recommend starting HAART as soon as CD4 cell counts have dropped to levels between 200 and 350 cells/mm^3.

A significant finding is that the increase in CD4 cell count to levels that are normal for non-HIV-infected individuals seems possible, irrespective of baseline cell count, although the rise may take more time when HAART is deferred until CD4 cell count has declined to <350 cells/mm^3. Our study shows the largest increases from baseline in patients who commence HAART whilst having a CD4 cell count of <50 cells/mm^3. However, the absolute number of CD4 cells in these patients after five years remains significantly lower than in patients commencing HAART with a higher number of CD4 cells.

In contrast to the finding by Kaufmann and colleagues[82], restoration of CD4 cells in the ATHENA patient group with >500 CD4 cells/mm^3 at HAART initiation seemed not to increase beyond a median of 800 cells/mm^3. Within this subgroup, it might be of interest to evaluate the characteristics of patients whose CD4 cell count continues to increase to >800 cells/mm^3 and compare them to patients who do not experience further increases.

The virological success of HAART is reflected in the HIV-RNA levels measured over 5 years of follow-up. Nearly 60% of the patients achieved plasma levels <500 copies/ml in all measurements taken within the first 5 years after the start of HAART. Furthermore, 75-80% of the patients at 1, 2, 3, 4 and 5 years had HIV-RNA levels <50 copies/ml. These high percentages are of importance, as higher HIV-RNA levels during therapy are strongly associated with progression of disease[84, 85].

The effect of changes in the HAART regimen

Since antiretroviral treatment of HIV-infected patients is continuous and life-long, studies of HAART changes to prevent serious side effects are of increasing interest. In the ATHENA national observational cohort, the effect of a regimen change to atazanavir was examined. This new protease inhibitor (PI), given in a once-daily dose in combination with two nucleoside reverse transcriptase inhibitors (NRTI), has been associated with significant improvement of lipid parameters in patients switching from nelfinavir to atazanavir[95]. Even patients with hyperlipidemia who switch to ritonavir-boosted atazanavir have had improvement of lipid levels in plasma[96-98]. Preliminary results from the atazanavir-switch study in ATHENA patients indicate an improvement of the total cholesterol and triglyceride plasma levels at 24 weeks after the switch. However, no firm conclusion can be drawn from this preliminary analysis as to the ability of such a strategy to maintain pVL below 50 copies/ml.

Another strategy for reducing the side effects of PI- and nNRTI-encompassing HAART regimens is to switch to triple-NRTI therapy. In the ATHENA cohort, patients who switched to a triple-NRTI HAART combination consisting of non-thymidine analogues experienced a high virological failure rate, as reported before[108]. Although patients using AZT+3TC+ABC were at lower risk of virological failure, AZT+3TC+TDF and the 'other' non-AZT+3TC+ABC regimens did not offer significantly lower risk than the non-thymidine analogues. This finding may reflect the small sample size. Only 14

patients initiated triple NRTI with AZT+3TC+TDF, whilst 24 used 'other' combinations.

The rate of virological failure with triple NRTI was lower with higher CD4 counts at its commencement. Overall, 75% of the patients switching to triple NRTI combinations were still virological successful three years after the switch. Our results indicate that the risk of virological failure is low in patients with high CD4 cell count who are switching to triple NRTI after successful PI- or NNRTI-based HAART. Moreover, switching to triple NRTI has a beneficial effect on total cholesterol and triglycerides levels.

The effect of transient viraemia during HAART on the outcome of HIV infection

In one third of ATHENA patients successfully using HAART, a temporary burst of low-level virus production occurs after the achievement of HIV-RNA plasma levels <50 copies/ml. In contrast to short-term therapy interruptions, these "viral blips" reportedly have a limited effect on treatment outcome, development of drug resistance, and clinical prognosis.[9, 111, 112, 114, 119, 120]

In the ATHENA cohort, we found that an HIV-RNA plasma level <50 copies/ml at the next measurement is less likely to be observed after a viral blip in the range 50 to 100 copies/ml than after a HIV-RNA level <50 at the last measurement. In addition, given a measurement below 50, the probability of seeing a blip of 50-100 copies/ml was equal to the probability of seeing a blip of 100 to 1000 copies/ml. Both findings suggest that viral blips cannot be explained by assay variation alone[122], although the extent to which such variation may influence their occurrence is not yet known[123].

Earlier calendar year of starting HAART and pre-treatment with non-HAART therapies were both associated with the occurrence of viral blips during HAART. The association with calendar year was less significant when only treatment-naïve patients or patients who initiated HAART in or after 1998 were taken into account. This indicates that HAART regimens have become more potent and/or easier to adhere to, compared to the regimens used before 1998, resulting in a more complete and more sustained suppression of viral load. This supposition is compatible with previous findings that intensification of therapy reduces residual replication of HIV and the frequency of viral blips[116, 117, 124].

CD4 cell counts observed during transient periods of low-level HAART failure did not differ from those observed in patients who consistently retained RNA suppression below 50 copies/ml. However, when the viraemia lasted too long to be considered a blip, CD4 counts tended to decline[112, 115, 125]. In our study, a higher CD4 observed at the most recent measurement was associated with a lower probability of observing temporary viraemia at the next pVL/CD4 measurement. This finding is compatible with reports that higher CD4 counts before initiation of HAART are associated with a lower frequency of viral blips during HAART treatment[113, 120].

For most periods of low-level HAART failure, we did not observe an event that could explain their occurrence. We observed therapy changes, but their timing suggested that they were more likely the response of the treating physician to therapy failure, not the cause of failure[115]. In 12% of blips, there was a documented adverse event that might have led to a reduced adherence, whilst resistant HIV-1 virus strains were observed during 2.9% of the periods of low-level failure. On the basis of our results, we can only hypothesise on the role played by vaccinations and infections, including sexually transmitted infections, in the occurrence of temporary viraemia. Several studies have examined this issue using mathematical models and have shown that exposure to antigen can result in a burst of viral replication[117, 118, 126].

The prevalence and incidence of infection with HIV strains which are resistant to one or more classes of antiretroviral drugs

The levels of transmission of drug-resistant HIV-1 virus strains remain low in the Netherlands. In 2004, 6.5% of the recently infected patients who were diagnosed after 1996 harboured a strain containing at least one major resistance-associated mutation[9]. In the current analysis, transmission of resistant strains is seen in 6.0% of the recently infected patients. A slightly higher percentage is found amongst newly diagnosed patients. These percentages are comparable with those observed in other western countries[140, 148, 162]. Decreasing levels of drug-resistance in newly HIV-infected patients is correlated with the decreasing amount of virus circulating in the chronically infected population[148].

The proportion of patients failing therapy from whom a sequence was obtained increased over time. Of those patients from whom a sequence was obtained at therapy failure, 80% to more than 90% harboured resistance-associated mutations[137-139]. As observed previously, the prevalence of specific resistance-associated mutations changed over time[9], in correlation with changes in anti-retroviral drug use[163]. Initially, only nucleoside analogues were used, whilst after 1996, protease inhibitors became available. After 1998, non-nucleoside RT inhibitors were introduced and quickly replaced PIs in the initial HAART regimen.

We found that 11.4% of the ATHENA population now in follow-up harbours virus strains that are resistant to one or more drug classes. In contrast, a recent study in the UK showed that, after six years of HAART, 27% of patients harboured one or more of the major mutations listed by IAS-USA[164]. In the HOMER cohort in the US, resistance was found in 25% of the patients with a viral load above 1000 copies/ml during the first 30 months after they started HAART[136].

In the Netherlands, more accurate estimates of the percentage of resistant transmissions amongst newly diagnosed patients have been possible only since 2002, when measuring resistance through genotyping of the HIV reverse transcriptase and protease genes became standard of care in some treatment centres. The percentage of transmissions of resistant virus differed amongst risk groups and was higher for homosexual men than in the heterosexual population. New guidelines will recommend obtaining a sequence at diagnosis only in those populations with a high risk of being infected with a resistant virus strain. This recommendation will reduce the strain on hospital and laboratory resources. However, it will also reduce the chances of observing a future increase in resistant transmissions that might occur in populations now at low risk. Hence, the actual resistance level in the ATHENA cohort is probably higher than we are able to report.

Changes over time in the HIV-infected subpopulation of immigrants

Within the ATHENA observational cohort, the four largest immigrant populations are differently distributed over the main HIV transmission risk groups. In the homosexual and IDU groups, there are few if any patients from Ghana and Cape Verde; however, patients originating from Suriname and the Netherlands Antilles are well represented in all three risk groups.

Most of the HIV-infected Surinamese and Antillean homosexual men and drug users were infected in the Netherlands. Amongst the heterosexually infected immigrants, the number of patients who entered the Netherlands already HIV-infected was largest for patients from Ghana, and next (in descending amount) from the Netherlands Antilles, Suriname, and Cape Verde. HIV-infected patients from Cape Verde were mainly women and mainly infected in the Netherlands.

The ranking of the Netherlands Antilles, Suriname, and Cape Verde after Ghana is consistent with the frequency of travel to these countries (e.g., most frequent for Antilleans) and might be related to differences in sexual behaviour during travel[48]. A study now being conducted in patients originating from Suriname and the Netherlands Antilles seeks to discover, amongst other things, the extent to which infections are imported by these individuals who live in the Netherlands and regularly visit their country of origin (HMF research project I04031).

The population of patients that have survived despite being infected with HIV for a long period of time, in some cases more that 20 years

Insight into the characteristics of these patients may be of importance in evaluating antiretroviral therapy strategies for patients in general. In the Netherlands, patients who were HIV-positive for at least 15 years on 1 January 2003 constituted 6% of the HIV-infected population at that time. Of these so called "long-term survivors," 10% are considered "long-term non-progressors"[50]. Non-progressors have survived in relatively good health with little or no treatment for HIV infection whereas, in contrast, long-term survivors have suffered from a broad range of CDC-C and adverse events despite treatment.

Non-HIV-related causes of death that are not fully explained by the older age nevertheless influence death rates after 1 January 2003 in the long-term survivors and especially in the subgroup diagnosed in or before 1987. Maybe the life-style of the subgroup differs from that of more recently diagnosed patients.

It has been shown that non-progressors are the extreme cases in a continuum of progression rates[51], although immunological and host genetic factors surely play a role. Significant correlations of human lymphocyte antigen (HLA) genes with progression rates[55, 56] and with susceptibility to HIV-infection[57] have been found. In particular, allele B27 is associated with non-progression[58, 59]. However, the underlying cause of non-progression cannot be determined from the data collected by the HMF.

The baseline characteristics of the population of HIV-infected children in the Netherlands

As of 1 June 2005, data on 112 HIV-infected children were available in the ATHENA national observational cohort. The total number of HIV-infected children in the Netherlands for whom data will be entered by the end of 2005 is estimated to be around 200. The majority of the children now registered were born in the Netherlands. Most have at least one parent born outside the Netherlands. Transmission from mother to child is the most important route of transmission, indicating that HIV-prevention activities in the Netherlands are not fully reaching immigrant populations with a high prevalence of HIV. Infection by sexual contact is limited to girls 14-17 years of age who almost all belong to immigrant populations and are infected in their region of origin.

A total of 221 pregnant women tested HIV-positive during routine prenatal screening between 2003 and mid-2005, and all have given birth to children not infected with HIV. This suggests that the HIV-infected infants registered in these years were born of mothers who were not HIV-tested or not adequately treated during pregnancy. It is also possible that the children were infected only after birth, through breast-feeding.

The success rate after 24 weeks of treatment with HAART appears to be similar for children and adults. However, the proportion of children harbouring virus strains with one or more resistance-associated mutations is almost three times as high as this proportion in the total HIV-

infected population. This higher prevalence of resistance is partly due to the larger number of children, compared to adults, from whom genotypic resistance data are obtained. But it may also reflect transmission of resistant HIV-strains to newborns following inadequate treatment of HIV-infected mothers. In addition, selection for drug-resistant virus strains may result from the treatment difficulties and suboptimal adherence in very young children, in combination with their high viral load.

Recommendations

A prerequisite for the analyses of the data of the ATHENA national observational cohort is to ensure the quality of the data collected from individual patients by individual HIV- treating physicians in each of the HIV Treatment Centres in the Netherlands. Data quality could be improved by implementing 100% source-data verification for a number of crucial data items that are entered manually. Direct entry of authorised laboratory data from laboratory databases into the HMF database is also recommended, as is ongoing quality control and improvement of the way data are organised and maintained in the database. Overall, special attention must be paid to keeping the data anonymous and without connection to personal details of the patient.

Ideally, all treatment centres and patients should participate in an all-inclusive and consistent programme to determine in each individual the HIV-1 subtype and its pre-existing resistance to antiretroviral drugs. This may not be feasible, but improvements can surely be made in existing practice. At this time, only about 30% of the patients failing on HAART are tested to determine HIV resistance to the antiretroviral drugs. The resulting lack of data creates difficulties on the individual level and also on a far more general level. As it stands now, the HMF database still cannot provide sufficiently reliable data on the level of transmission of resistant strains or the development of resistance in the HIV-infected source population in the Netherlands.

It is therefore recommended that a programme be designed by HMF specifically to monitor resistance. With the aim of collecting resistance data from a representative selection of patients now in follow-up, the programme should be restricted to those HIV Treatment Centres committed to active participation in the programme.

Of course, differences in outcome of HIV-infection, as well as response to antiretroviral therapy – in terms of anti-HIV effect, and the immunologic, pharmacologic and toxic response – may be influenced by genetic host factors as well as by drug resistance. To support studies in the genetics area, the collection and storage of host DNA is crucial. Proposals are now being developed within and beyond the framework of HMF to study host genetics, using HMF data. International collaborations are increasingly paying attention to host genetics in HIV-infection. It is therefore recommended that HMF develop a programme specifically intended to collect and preserve patient DNA throughout the HMF system of Treatment Centres.

Finally, it becomes clear that the monitoring of specific groups – such as pregnant women, HIV-exposed and -infected children, and immigrant populations at risk for HIV – requires specific arrangements and protocols for the collection, monitoring, and analysis of data. Moreover, the observational approach so far allows for the determination of trends, but the results of observational research need confirmation through data that are obtained from patients participating in a prospective cohort. This holds especially true for studies comparing the course of HIV infection when it is continuously treated with antiretroviral drugs and when it is untreated.

It is therefore recommended that HMF should participate actively in the development of a prospective clinical cohort whilst continuing to participate in collaborations to improve analytical and mathematical models for use in observational studies.

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Over

view

Overview of ongoing research projects

Overview of ongoing research projects

Research projects whose progress report has been submitted

I04034: The Data Collection on Adverse events of Anti-HIV Drugs (D:A:D)

Date of approval by HMF Advisory Board: June 8th, 2004.

International coordination by Copenhagen HIV Programme (CHIP) under leadership of Dr. Jens Lundgren. Principal investigator for the Netherlands: Dr. Peter Reiss.

The D:A:D Study is now embarking in its 6th year and is projected to continue at least through 2006. Eleven cohorts worldwide are participating, representing 188 clinics in 21 countries in Europe, USA and Australia. An additional 12,000 HIV-infected persons have been added (D:A:D Cohort II) to the original study population of 23,441 persons (D:A:D Cohort I). Enrolment into cohort II is ongoing, and Athena is expected to enrol > 3000 patients into this cohort in 2005. At present time, the study has contributed with important information on the association of combination antiretroviral therapy (cART) and the risk of cardiovascular disease. The study continues to follow patients prospectively and focuses on monitoring the risk of cardiovascular disease and its association with extended exposure to cART. The central research question to be solved in the future is to identify which mechanisms can explain this observed increased risk. Furthermore, the study now also collects detailed information on causes of death by implementing a standardized coding system of causes of death (CoDe), which has been developed jointly by all participating cohorts as well as a number of clinical trial networks.

Participation in D:A:D and CoDe has provided the opportunity and incentive for the HMF to implement and improve its datacollection on cardiovascular risk factors and morbidity/mortality and on causes of death in general within the Athena cohort as a whole. Furthermore, by harmonizing the way such data are collected with other HIV cohorts, it also continues to allow Athena to importantly contribute to international cross-cohort collaborations.

For additional information, please see www.cphiv.dk

I04014A: Long-term follow up of trizivir compared to standard NNRTI containing Regimens in antiretroviral naïve patients

Date of approval: April 20th, 2004.

G. van den Berk, L. Gras, R. Vriesendorp, C. Richter, M. van Kasteren, F. de Wolf and K. Brinkman on behalf of the ATHENA cohort.

Background

The use of 3-NRTI as initial treatment is discouraged, after trizivir? showed inferior results in naives compared to efavirenz containing regimens at week 26. Between 2000 and 2004, several patients have started with trizivir?. This study evaluates the long-term outcome of these patients in comparison to NNRTI containing regimens.

Methods

In the ATHENA cohort, all naïve patients were selected who started AZT-3TC, combined with ABC, nevirapine (NVP) or efavirenz (EFZ). Over time, virological success and other parameters were analysed, using multivariate. accel. failure time models with a log-logistic survivor distribution.

Results

Between 2000 and 2004, 1079 naive patients started HAART with AZT-3TC-ABC (n=200), AZT-3TC-EFZ (n=384) or AZT-3TC-NVP (n=495). At baseline, a significantly higher proportion of patients in the EFZ group had CDC-C criteria, with higher BL viral loads and lower CD4 counts. Within a median follow-up of 29.4 months (IQR: 16.7, 41.4), 534/1079 patients changed/ stopped the initial treatment. with no significant difference in time to regimen change between the three groups. Most important reason to stop/change treatment within 2 years was toxicity (ABC-group = 36/90 (40%), EFZ group = 89/164 (54%), NVP group =108/216 (50%), but time to such change did not differ significantly between treatment groups.

Time to virological suppression <50 cps/ml was not significantly different between groups. Time to viral rebound >50 copies/ml was sign. shorter in patients starting trizivir compared to NVP (acceleration factor 3.19 (1.24, 8.33, p=0.02) but not to EFZ. When time was not censored at regimen-change, the difference with NVP was not longer significant.

Conclusion

Virological success between the three regimens was not significantly different, but there was a higher virological failure rate in ABC vs NVP arm.

I04014B: Maintenance Treatment With Triple NRTIs after Successful Anti-retroviral Therapy: Long-term Follow-up

Date of approval: April 20th, 2004.

G. van den Berk, L. Gras, R. Vriesendorp, C. Richter, M. van Kasteren, F. de Wolf and K. Brinkman on behalf of the ATHENA cohort

Background

Data on switch from PI- or NNRTI- to 3-NRTI containing regimens are limited. In this study we analysed the long-term virological efficacy of maintenance 3 NRTI treatment and determined predictors for stopping 3-NRTI therapy and virological failure.

Methods

In the ATHENA cohort all patients were selected who switched from successful (viral suppression, defined as VL <500 c/ml) first-line not 3-NRTI containing ART to 3-NRTI treatment. During longitudinal 5 year follow-up, reasons for virological failure (sustained VL >500 c/ml) were analysed. Time to stop 3-NRTI treatment and virological failure were analysed using parametric survival models.

Results

In total, 539 patients were selected (88% prior PI exposure, 12% prior NNRTI exposure), with a median follow-up of 23 months (IQR 15-33). Simplification

was the most recorded reason for switching to a 3-NRTI regimen (30%), followed by toxicity (27%). In total, 213/539 (39,5%) patients stopped with the triple NRTI combination during follow-up. Virological failure occurred in 130/539 of patients. Predictors for virological failure were: a pVL>50,000 in the 6 months before switch, HR vs <500 copies/ml 3.03 (95% CI 1.77, 5.15, p<0.0001), not all pVL after initial suppression below 500 copies/ml, HR 1.75 (1.09, 2.82, p=0.02), 2 NRT+1 NNRT in the regimen prior to the switch, HR compared to a PI including regimen 1.60 (1.02- 2.50, p=0.04), toxicity as reason to stop the previous regimen, HR compared to simplification 1.81 (1.08, 3.03, p=0.04) and lower CD4 at time of switch HR 50-200 vs 350-500 cells/mm^3 1.943 (1.039, 1.634, p=0.04).

Conclusion

Simplification as reason for switch to triple NRTI, a more sustained viral load suppression prior to switch and a previous PI containing regimen were associated with a longer time on triple NRTI therapy and more sustained viral suppression after the switch.

I04046: Predictors of frequencies; key charcateristics of observational data obtained from Hiv-infected patients participating in the national cohort on AIDS therapy evaluation in The Netherlands

Date of approval: July 8th, 2004.

Luuk Gras, Jamie Griffin, Azra Ghani, Ard van Sighem, Jan Prins, Frank Kroon, Frank de Wolf.

Objectives

The goal of the project was to identify determinants of follow-up frequency (clinical visits, CD4 and plasma viral load measurements). Given these determinants we aimed to study the effect of ignoring differences in follow-up frequency on estimates of standard performed analyses in HIV research such as time to an increase in CD4 cells count/mm^3 or time to plasma viral load below detectable levels. Another possibility is to study differences in AIDS/mortality and viral rebound rates between hospitals with low-high follow-up frequency as identified in the analyses described below. A lower rate of viral rebound in hospitals with a high follow-up frequency would then suggest that a high follow-up frequency is of benefit to the patient. The design of such a comparison needs more discussion.

Methods

All visits to the out-patient clinic of (un)treated adult HIV infected patients included in the ATHENA observational cohort from one year after entry until 31 December 2003 were selected. For the analysis of time between CD4 and viral load measurements, measurements from one year after start HAART until 31 December 2003 were selected. The number of days between visits/ measurements was modeled using log-logistic accelerated failure time models including a gamma frailty term for each patient. Possible predictors were: demographic characteristics, the year of visit/measurement and year of registration/start HAART, CD4 cell count and plasma HIV-RNA level at the previous visit, CDC-C status, clinical trial participation, therapy status, time since HIV diagnosis and treatment centre.

Results

In total 50141 visits by 5605 patients and 75197 CD4 and 79467 viral load measurements by 5918 patients were analyzed. Reported results apply to the analysis of time between clinical visits but predictors acted in a similar manner on time between viral load/CD4 measurements. Median time between visits (MTBV) was 91 days. MTBV was 0.65 times shorter (95% CI 0.63-0.68) during trial participation than between regular visits.

The MTBV was 1.07 (1.02-1.12) times longer for men than for women and for IDU 1.11 (1.03-1.19) times longer than for MSM. Follow-up frequency was not significantly different with respect to region of origin or age. Lower CD4 cell count and a higher plasma viral load at the previous visit was associated with shorter MTBV, whereas never being diagnosed as having symptomatic HIV with longer MTBV. MTBV was 0.76 (0.75-0.78) times shorter when regimens had changed and interruption of HAART resulted in a MTBV 1.16 (1.11-1.22) times longer than when HAART was used continuously. On the other hand, time between CD4 measurements was shorter during therapy interruptions than when HAART was used continuously.

Calendar year of registration and of visit independently resulted in a lower MTBV in the more recent calendar years, with a MTBV in 2000 of newly registered patients being 0.73 times shorter than in 2002. Considerable differences in time between clinical visits between hospitals were found. Finally, some hospitals had a policy to measure CD4 every visit whilst viral load was measured every other visit.

Conclusions

Follow-up frequency of HIV-infected patients in out-patient clinics and frequency of CD4 and viral load measurements declines in later calendar years. Moreover, gender, route of transmission, disease status, (dis)continuous HAART use and treating hospital are associated with differences in follow-up. Observation of events such as undetectable plasma viral load or increase in 100 CD4 cell counts from baseline depend on follow-up frequency. Comparisons of time to follow-up frequency dependent endpoints between patients with lower vs. higher CD4 cell counts or between patients in earlier vs. later calendar years could result in biased estimates when interval censoring is not taken into account.

I04016 The Genotypic Inhibitory Quotient (GIQ) for Lopinavir

Date of approval: March 1st, 2004.

D.M. Burger, J.G.M. Hoefnagel, M.J. van der Lee, P.P. Koopmans, J.M.D. Galama

Objectives

To determine the predictive value of the Genotypic Inhibitory Quotient (GIQ) for lopinavir, and to set cut-off values.

Methods

Baseline genotypic susceptibility was determined in protease inhibitor (PI)-experienced patients starting lopinavir-ritonavir therapy. The GIQ was calculated as the lopinavir trough level divided by the number of mutations. Three sets of mutations were explored, the PI-associated mutations (PAMs),

the lopinavir-associated mutations (LAMs) and the Lopinavir Mutations Score (LMS). Cumulative numbers of mutations, using previously performed genotypic tests, were also studied. Virological response was defined as a viral load <500 cps/mL after 12 months.

Results

95 included patients had a median viral load of 4.4 $\log_{10}$ cps/mL and a median CD4-cell-count of 240 cells/mm^3 at baseline. The median lopinavir through level was 5.2 mg/L (IQR 3.7-6.3), the median number of PAMs, LAMs and LMS was 4 (IQR 2-7), 3 (IQR 1-6) and 3 (IQR 1-6), respectively. The median GIQ based on PAMs (GIQPAM) was 1.2 (IQR 0.7-2.3), the GIQLAM was 1.9 (IQR 0.8-3.7) and GIQLMS was 1.8 (IQR 0.8-3.8). 76% of the intention-to-treat population were responders. All three GIQs and all three mutation sets were significantly associated with virological outcome (p-values ≤0.003). The GIQ did not show a greater predictive value than the number of mutations. Cut-off values were set at 0.9, 1.1 and 1.5 for GIQPAM, GIQLAM and GIQLMS, respectively. Calculation of the GIQ with cumulative mutation sets including previous genotypic tests showed significant better association with response.

Conclusions

The predictive value of the lopinavir GIQ is not greater than that of the number of mutations. Cut-off values were set.

I10303: Triestan (Treatment Interruption in Early STArters in The Netherlands)

Date of approval: February 19th, 2003.
K. Brinkman, J.M. Prins, F. Kroon, F.W. Wit, Dr. J.M.A. Lange, K. Pogány.

Objectives

To evaluated the safety, efficacy and benefit of discontinuing highly active antiretroviral therapy (HAART) in HIV-1 positive patients who initiated HAART at a CD4+ T-lymphocyte count (CD4 count) >350 cells/mm^3, which is higher than advised in current guidelines.

Methods

TRIESTAN is a prospective, non-randomised, multi-center study. All patients who had initiated HAART at a CD4 count >350 cells/mm^3 were identified from the Dutch ATHENA national observational cohort. Patients were offered the choice to either interrupt or continue HAART. Data on clinical and virological parameters, toxicity and plasma drug concentrations.

Results

In total, 71 patients were enrolled of whom 46 (64%) interrupted and 25 (36%) continued HAART. The median CD4 count at start HAART was 476 (IQR:420-570) and 510 cells/mm^3 (IQR:440-637) among patients who interrupted or continued HAART.
At inclusion, i.e. the moment HAART could be stopped, the median CD4 count was 905 cells/mm^3 (IQR:730-1150) and 850 cells/mm3 (IQR:659-1070), respectively. Duration of HAART use was similar in both groups: 69 months (IQR:12.9-87.8) in patients who interrupted and 57.2 months (IQR:42.4-73.4) in patients who continued.
In the group that interrupted, no serious clinical or adverse events occurred after interruption. At the time of analysis, 45 patients of the STOP-group had reached week 48. At that time, the median plasma HIV-RNA in this group was 4.58 $\log_{10}$ copies/ml (IQR:4.2-4.94). The median CD4 count at 48 weeks still exceeded the pre-HAART count: 559 cells/mm^3 (IQR:450-710). Six patients reinitiated HAART for personal reasons. None of the patients restarted HAART because of a decline in CD4 count or a new AIDS diagnosis. CD4 counts and HIV-RNA levels in the group who continued HAART remained stable until 48weeks

Conclusions

Our results indicate that patients who started HAART above 350 CD4+ T-cells/mm^3 can interrupt HAART safely for at least 48 weeks. Most importantly, CD4 counts remained above CD4 levels at start HAART.

Other research projects

I10003: Differential treatment response in patients using Zidovudine or Stavudine first-line HAART regimens
Date of approval: June 17th, 2003.
Ferdinand Wit, Joep MA Lange.

I03347 HIV-TB co-infection treatment in the Netherlands from 1997 till 2004
Date of approval: April 20th, 2004.
J.G. den Hollander, R. van Aalsburg, M. Bakker, S. de Marie, M.E. van der Ende, F. de Wolf, L. Gras, P. Koopmans.

I04015 Hiv-1 and HIV-2 infection in West African residents in the Netherlands: Epidemiology and missed diagnosis
Date of approval: April 20th, 2004.
M. Schutten, M.E. van der Ende, F. de Wolf, A.D.M.E. Osterhaus.

I04031 Heterosexual HIV transmission among migrants originating from Surinam, The Netherlands Antilles and Aruba: the role of travelling to the country of origin
Date of approval: June 8th, 2004.
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Mission
The HIV Monitoring Foundation is appointed by the Dutch Minister of Health, Welfare and Sports (Ministerie van Volksgezondheid, Welzijn en Sport) as the national executive organization for the registration and monitoring of HIV infected patients in follow-up in one of the Dutch Treatment Centres. Our mission is to further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection.

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