REPORT 2009

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

STICHTING HIV MONITORING

Luuk Gras
Ard van Sighem
Colette Smit
Sima Zaheri
Hanneke Schuitemaker
and Frank de Wolf
on behalf of
the Netherlands
collaborative
HIV treatment
centres

HIV treatment centres

Medisch Centrum Alkmaar

Flevoziekenhuis Almere

Academisch Medisch Centrum bij de Universiteit van Amsterdam

Onze Lieve Vrouwe Gasthuis Amsterdam

Sint Lucas Andreas Ziekenhuis Amsterdam

Slotervaart Ziekenhuis Amsterdam

Stichting Medisch Centrum Jan van Goyen Amsterdam

VU Medisch Centrum Amsterdam

Ziekenhuis Rijnstate Arnhem

HAGA ziekenhuis Den Haag

Medisch Centrum Haaglanden Den Haag

Catharina Ziekenhuis Eindhoven

Medisch Spectrum Twente Enschede

Universitair Medisch Centrum Groningen

Kennemer Gasthuis Haarlem

Medisch Centrum Leeuwarden

Leids Universitair Medisch Centrum

Academisch Ziekenhuis Maastricht

Universitair Medisch Centrum Sint Radboud Nijmegen

Erasmus Medisch Centrum Rotterdam

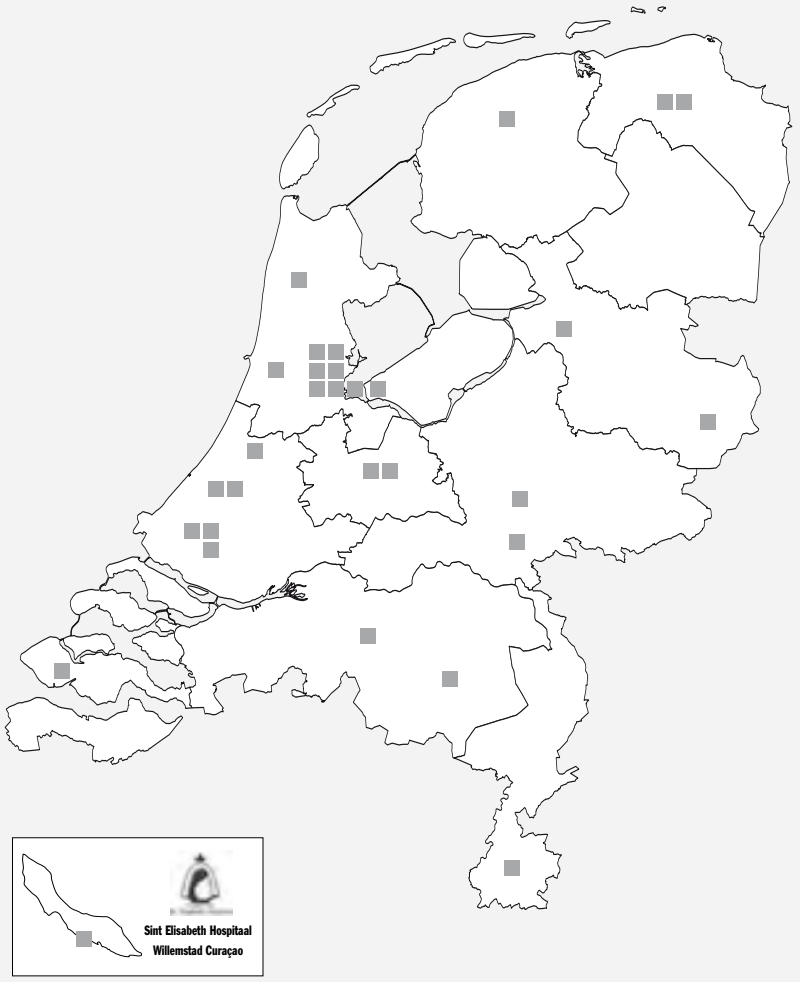
Maasstad Ziekenhuis Rotterdam

Sint Elisabeth Ziekenhuis Tilburg

Universitair Medisch Centrum Utrecht

Ziekenhuis Walcheren Vlissingen

Isala klinieken Zwolle



Sint Elisabeth Hospitaal Willemstad Curaçao

Paediatric HIV treatment centres

Emma Kinderziekenhuis AMC Amsterdam

Beatrix Kinderkliniek Universitair Medisch Centrum Groningen

Erasmus Medisch Centrum-Sophia Rotterdam

Wilhelmina Kinderziekenhuis Universitair Medisch Centrum Utrecht

table of

contents

introduction

In its annual report on the HIV monitoring programme in the Netherlands, the Stichting HIV Monitoring (SHM or HIV Monitoring Foundation) provides information on trends over time in the epidemic and the effect of treatment on HIV. This year's report confirms the ongoing increase in the number of HIV diagnoses amongst men who have sex with men. The extent to which combination antiretroviral treatment (cART) effectively suppresses virus production in the monitored populations has increased, and the incidence of toxicity-driven treatment changes has declined over time. Changes in mortality patterns confirm the increase in non-AIDS-related causes of death in the chronically HIV-infected population who receive lifelong treatment.

The Stichting HIV Monitoring is assigned by the Dutch Minister of Health, Welfare and Sport not only to monitor HIV in the Netherlands but also to contribute to the quality of HIV care. Its target groups are primarily the HIV-treating physicians who work in 1 of the 25 hospitals throughout the country that are acknowledged as HIV treatment centres. Treating physicians have access to the data provided by each centre to the SHM, and, when research proposals are approved, to all the data available from all the centres. Other HIV research groups have access under the same conditions.

The overview of the characteristics of the population living with HIV in the Netherlands that is provided through the SHM's yearly report contributes to the development of HIV care and prevention policies, enables clinicians to model their clinical work on that of the all HIV treatment centres, and allows research groups to determine the usefulness of the monitoring data for their purposes.

The report, after the summary and recommendations, includes a section on the quality of the data that the HIV Monitoring Foundation collects, with a chapter on the prediction of missing data on liver fibrosis by use of the alanine aspartyl transferase-to-platelet ratio index (APRI) as an indicator for source data verification for liver fibrosis. A section on the HIV monitoring programme follows, with more detailed descriptions of the findings on the number of new HIV diagnoses registered, the changes over time of the characteristics of the infected population at time of diagnosis, the effects of cART, and the development of resistance to antiretroviral drugs. Also in this section are chapters on HIV infection amongst pregnant women and children and co-infection with hepatitis B and hepatitis C virus. The Special Reports section includes a chapter on HIV in Curaçao and the Netherlands Antilles and one on results from the Amsterdam Cohort Studies. Tables and figures are included at the end of each chapter; references can be found in a separate section following Special Reports.

The approach to HIV monitoring in the Netherlands has been made possible through the ongoing efforts of the HIV-treating physicians, HIV nurse-consultants and staff of various diagnostic laboratories and facilities in the HIV treatment centres, and data collecting and monitoring staff both in and outside the Stichting HIV Monitoring. The help of the people living with HIV who are in the care of one of the HIV treatment centres and who provide the data is unprecedented. I wish to acknowledge both professionals and patients for their contribution.

Professor Frank de Wolf, MD
Director, Stichting HIV Monitoring

summary & recommendations

Frank de Wolf

Trends in the epidemic

Since June 2008, when 14,960 individuals were included in the SHM database[1], the registered population in the Netherlands has increased by 1,169 patients, or 7.8%, to 16,129. Newly registered patients with diagnoses in 2007 or later accounted for 87.5% of the increase, with the large majority (97%) of patients infected with HIV-1. As of 1 June 2009, 12,405 (79,3%) were still in follow-up in one of the 25 HIV treatment centres in the Netherlands, including 12,258 (98.8%) adults and 147 (1.2%) children.

The annual number of newly registered HIV-infected individuals has varied in previous years by approximately 1,200, and, in contrast to 2008, this year's increase fits well into the overall trend. However, the fraction of recently diagnosed patients appears higher than in previous years. When taken together with a low percentage of patients showing signs or symptoms of HIV-related disease and a growing percentage of patients with a known last HIV-1 antibody negative test date, this indicates that the time between infection and diagnosis and entry into care has been shortened. However, a further decrease needs to be achieved, since CD4 cell counts at diagnosis, although higher than in 1996, are still at a median of 380 cells/mm^3 in those without a recorded negative test.

Shortening the time between HIV transmission and diagnosis plays an important role in containing ongoing HIV transmission[2]. Another factor in ongoing transmission may be the amount of virus circulating in an individual unaware of his or her infection. A higher HIV-1 plasma RNA concentration at set point is known to be associated with a shorter time of disease progression and higher transmission efficiency[3,4]. This year we present results of our study of the changes over time of HIV-1 RNA concentration at viral set-point in a large group of men with a known date of an HIV-negative test result before becoming positive. We investigated the concentration of HIV-1 RNA in plasma at 9 to 27 months after the estimated date of seroconversion for HIV-1 and before antiretroviral therapy was started. We found an increase of HIV-1 RNA plasma concentration at this so-called viral set-point in those men who seroconverted in more recent years as compared to that in men who seroconverted in the beginning of the HIV epidemic. Simultaneously, CD4 counts measured at viral set-point decreased. These results could indicate an increase in viral fitness over time[5] and could be contributing to an increase in the transmission rate of HIV amongst men having sex with men (MSM) in more recent years.

The epidemic in the Netherlands is predominantly an epidemic amongst men, with homosexual contact as the most important risk factor for acquiring HIV. Heterosexual contact is the second most important risk factor amongst men and by far the most important one amongst women. Almost half of women with HIV now originate from Sub-Saharan Africa and a quarter from the Netherlands; approximately one-third of men originate from Sub-Saharan Africa and one-third from the Netherlands. The differences in region of origin are reflected in the distribution of HIV-1 subtypes, with MSM almost exclusively infected with subtype B and Sub-Saharan Africans with various non-B subtypes.

The age of the population living with HIV in the Netherlands has increased, and 28% of the population currently in follow-up is 50 years of age or older. The life expectancy of infected patients has increased significantly, especially since the introduction of combination antiretroviral therapy (cART). Before 1996, a 25-year-old infected person had a 5% chance of becoming 50 years old; currently that chance is 80%[6]. Previously, we showed that survival of infected patients on cART has reached a level comparable to the rate for patients with diabetes[7]. Next to the increased life expectancy, the age at infection, reflected in the age at

diagnosis, seems to increase. In the coming years, the age of the population will continue to increase, and by 2015, an estimated 41% of the patients in follow-up will be more than 50 years old[8]. It is expected that treatment of HIV will be complicated by the increasing age of the population due to the appearance of age-related diseases and other non-AIDS-related illnesses. The total costs of HIV treatment are expected to increase from 110 million euro annually at present to 230 million in 2015.

Homosexual men are currently the largest group of patients with hepatitis C virus (HCV)-HIV co-infection in the Dutch population of HIV-infected patients, and most of the new HCV diagnoses in HIV-infected patients have been among homosexual men. Several studies have reported an increased death risk in the HCV-HIV co-infected population[9,10]. In contrast to the higher mortality rates by HCV co-infection reported earlier[1], we presently no longer find an increased risk of death in HCV co-infected patients in the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort.

This improved mortality rate amongst HIV-HCV co-infected individuals may be the result of an increased awareness of HCV. A more active screening policy for HCV co-infection among HIV-infected patients is in place, providing a diagnosis earlier in HCV co-infection among homosexual men who are well treated for HIV. This may, in turn, result in a greater chance of spontaneous clearance of HCV, since clearance is associated with high CD4 cell counts and treatment of HIV is likely to contribute to a higher level of CD4 cell counts[11]. In addition, the number of patients treated for HCV co-infection has increased, which may contribute to a lower mortality rate.

Most HCV infections among homosexual men are recently acquired infections[12] in which progression to liver fibrosis has not yet occurred. If HCV treatment is initiated very shortly after diagnosis, then successful treatment rates from 71% to 80% can be achieved in newly diagnosed patients with HCV-HIV co-infection[13,14]. Successful treatment of HCV infection, in combination with the increased number of recently diagnosed HCV infections, may have resulted in a decreased impact of HCV on the all-cause mortality in the ATHENA population of HIV-infected patients. However, the success of HCV treatment is determined by genotype, and genotypes 1 and 4 are hard to treat[15]. Most of the homosexual men are infected with genotype 4, although the incidence of liver-related disease and mortality are still low.

So far, we have been unable to study the effect of HCV genotypes on treatment success, since the number of treated HCV-HIV co-infected patients in ATHENA is too small. Larger studies are needed to further evaluate the impact of HCV treatment on the decrease of all-cause and liver-related mortality and the impact of the different HCV genotypes on population level. Stichting HIV Monitoring (SHM) is coordinating such a study within the framework of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), a large cohort collaboration.

Trends in treatment

Amongst the 15,236 adults with a known year of HIV-1 diagnosis, 12,297 (80.7%) started cART. Of these patients, 2,328 (18.9%) had been treated with mono- or dual antiretroviral therapy before starting cART, whilst 9,969 (81.1%) started cART as therapy-naïve patients. The median time between diagnosis and start of cART for patients diagnosed in 1996 or later was 15 weeks for men and 12 for women.

The median CD4 cell count in men at the start of cART was 200 (Interquartile range [IQR], 80-300) cells/mm^3; the median CD4 count in women at the start was 210 (100-340) cells/mm^3. After 24 weeks of cART, CD4

counts had increased to 320 (IQR, 190-470) cells/mm^3 in men and 344 (210-509) cells/mm^3 in women. The median CD4 count increased further to 370 (IQR, 240-520) cells/mm^3 in men and 380 (260-548) in women at 48 weeks after the start of cART.

At 24 weeks, 85.5% (6,975 of 8,157) of men and 80.5% (1,801 of 2,237) of women whose RNA levels were measured reached levels below 500 copies/ml. At 48 weeks after the start of cART, these proportions were 84.1% (6,427 of 7,639) for men and 75.5% (1,557 out of 2,062) for women. For therapy-naïve patients, 90.8% of the men and 83.1% of the women had levels below 500 copies/ml at 24 weeks, whilst these levels were obtained for 63.1% of men and 65.8% of women in the pre-treated population (p=0.4 for difference between men and women).

The most frequently used first-line cART combination in 2008-2009 was tenofovir + emtricitabine + efavirenz, which was prescribed in 55.4% of cases, compared to 48.3% of cases in 2007-2008. Overall, the prescription of tenofovir increased from 78.2% (817 cases) in 2007-2008 to 86.3% (635 cases) in 2008-2009 ($p<0.001$). Emtricitabine was part of 790 (75.6%) initial regimens in 2007-2008 and 628 (85.3%) in 2008-2009 ($p<0.001$), whereas the use of lamivudine decreased from 254 (24.3%) to 107 (14.5%) cases ($p<0.001$). Also, zidovudine was a less frequent option; 124 (11.9%) patients in 2007-2008 received it, compared to 66 (9.0%) patients in 2008-2009 (p=0.05).

The most frequent additions in 2008-2009 were efavirenz (468 patients, 63.6%), nevirapine (125, 17.0%), lopinavir (123, 16.7%), and atazanavir (37, 5.0%). Compared to 2007-2008, the proportion of patients using nevirapine (15.6%, p=0.4), lopinavir (19.9%, p=0.09), and atazanavir (6.7%, p=0.1) did not differ. The proportion of patients starting efavirenz (58.9%, p=0.05) was marginally smaller in 2007-2008 than in 2008-2009.

Virologic response

The Kaplan-Meier estimate of the proportion of patients with viral suppression <50 copies/ml was 64.8% within 12 weeks of starting cART and 78.7% within 36 weeks. Patients starting cART in 2008 had a significantly longer time to viral suppression than patients starting in 2005. In concordance with other studies[16], time to suppression was significantly longer in patients younger than 30 years as compared to those who were 30-40 years. Time to suppression was also longer in patients starting with CD4 counts ≥500 cells/mm^3 and in patients starting on a protease inhibitor (PI)-based regimen.

Poor adherence might play a role, as has been shown by other studies[17]. Patients who started with PI-based regimens also had a lower probability of viral suppression, as did patients who started with CD4 counts >350 cells/mm^3. Also, patients from Sub-Saharan Africa had a lower probability of having <50 copies/ml compared to patients from the Netherlands, as did injecting drug users (IDU) and patients infected through heterosexual contact when compared to MSM. When the analysis was restricted to those measurements obtained whilst patients were using cART, the probability of viral suppression was no longer significantly different between different age groups. These results suggest that as long as patients are able to stay on cART, virological efficacy of PI-based and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based initial regimens is not significantly different.

However, the lower probability of viral suppression remained in IDU and heterosexually infected patients as compared to that in MSM and in patients from Sub-Saharan Africa as compared to that in Dutch patients. Also, patients starting cART in 2003-2004 had a lower probability of viral suppression (<50 copies/ml) compared to those starting in 2005. Keeping viral load at levels below 50 copies/ml is crucial, because patients

with low viral load contribute less to transmission of HIV infection[18,19]. Although, it is hotly debated whether or not transmission occurs when plasma viral loads are below 50 copies/ml[20-23].

Immunologic response

The higher CD4 threshold of 350 cells/mm^3 recommended in the current guidelines[24,25] for the initiation of cART is reflected in a higher CD4 count at the start of cART in 2008 compared to that in previous years. The median CD4 count at the start of cART was 250 cells/mm^3 in 2008 compared to 200 cells/mm^3 between 2004 and 2007 ($p<0.0001$). The percentage of patients with a CDC-C diagnosis prior to starting cART was also lower in patients starting in 2008 as compared to patients starting between 2004 and 2007 ($p<0.0001$).

Ultimately, cART should result in CD4 counts comparable to those found in uninfected persons (reported to be 1,050, 840, and 800 cells/mm^3 for women, heterosexual men, and MSM, respectively[26]), with likely geographic variation in normal CD4 ranges[27]. In therapy-naïve patients with more than 9 years of continuous viral suppression to <50 copies/ml, increases in CD4 count ranged from 480 cells/mm^3 for patients starting cART with <50 cells/mm^3 to 330 for patients starting cART with 350-500 cells/mm^3. After 9 years of viral suppression, patients starting cART at CD4 counts ≥500 cells/mm^3 had a median increase of 220 cells/mm^3. These results show that even after 9 years of continuous viral suppression, CD4 cell counts in patients who started cART according to current guidelines are still lower than those in uninfected individuals. Therefore, it might be beneficial to start cART at even higher CD4 cell counts, for instance, when CD4 cell counts drop to <500 cells/mm^3.

cART toxicity-driven regimen change

During the first 3 years of cART, the overall incidence of toxicity-driven regimen changes was 22.8 per 100 person-years on cART. Patients could change the regimen more than once in a period. During follow-up, 7,388 of the 11,268 patients (65.6%) did not change the regimen because of toxicity. The maximum number of changes because of toxicity in a single patient was 14. The incidence was higher amongst women and highest in the first 3 months of cART.

We found a strong decreasing trend in the adjusted relative risk for toxicity-driven therapy change with later calendar year of starting cART. With the exception of the year 2000, the risk was always lower compared to the previous year. In accordance with results from other studies[28-30], we found that female gender was associated with a 1.5 times higher risk of toxicity-driven therapy changes. This has been attributed to a lower body mass index[31] and a higher drug concentration in plasma in women[32], but in our study differences in men and women remained after adjusting for weight. The risk of toxicity-driven changes increased also with older age at the start of cART and in patients with an AIDS diagnosis at the start of cART, in patients with hepatitis C co-infection and in patients with a plasma HIV RNA concentration above 4 $\log_{10}$ copies/ml. Finally, patients with a CD4 cell count at the start of cART ≥500 cells/mm^3 had a higher risk for toxicity-driven therapy changes compared to patients with lower CD4 cell counts; this finding is in agreement with earlier reports on the loss of quality of life caused by treatment of HIV at an early stage of the infection[28,33]. However, other studies did not find that higher CD4 cell counts before the initiation of highly active antiretroviral therapy (HAART) had an effect on the discontinuation of antiretroviral drugs because of toxicity[30, 34].

Trends in resistance

Sub-optimal adherence to antiretroviral treatment may result in incomplete suppression of HIV replication and subsequently selection of HIV virus strains that are resistant to one or more of the drugs used in the therapy

regimen. Resistance limits future therapy options and may lead to a worsened prognosis. Resistant strains can be transmitted to uninfected patients, restricting therapy options from the start.

Resistance following treatment failure

The annual proportion of patients pre-treated with non-cART regimens who failed on cART declined from 49% in 1997 to 11% in 2008. During the same period, the proportion of previously therapy-naïve patients who experienced failure remained between 6% and 8%. In the group of pre-treated patients, the fraction of failing patients from whom an HIV-1 pol sequence was obtained increased from 9% in 1997 to levels between 20% and 30% between 2000 and 2007. In the therapy-naïve group, the fraction of patients with a sequence was 35% in 2003, and it decreased to 19% in 2005 and thereafter.

In the total HIV-infected population, 3,211 sequences were obtained after the patients started cART. Of these sequences, 1,393 (43.4%) were obtained from pre-treated patients and 1,818 (56.6%) from previously therapy-naïve patients; 2,321 (72.3%) contained at least one resistance-associated mutation, and the rest, 890 (27.7%), contained none. Resistance was found in 1,227 (88.1%) sequences from pre-treated patients and in 1,094 (60.2%) sequences from therapy-naïve patients.

As of 1 June 2009, a total of 12,258 HIV-1-infected adults were still being actively followed. In 1,380 (11.3%) of those patients, at least one sequence with resistance-associated mutations had been obtained, and 1,078 (78.1%, or 8.8% of the population in follow-up) had high-level resistance to at least one antiretroviral drug. These percentages most likely underestimate the true prevalence of resistance in the total population, since a resistance test was performed in only 20% to 30% of the patients failing on treatment. Besides, other cohorts have found higher prevalences. For example, in Switzerland, the prevalence of resistance in 2007 was estimated to be between 37% and 45%, whilst in British Columbia, Canada, resistance was found in 28% of the patient population[35,36].

The number of patients with high-level resistance to drugs from one class was 491 (35.6%). Resistance to drugs from two classes was found in 511 (37.0%) patients, whereas 168 (12.2%) were found to be resistant to drugs from all three classes. High-level resistance to at least one nucleoside reverse transcriptase inhibitor (NRTI) was found in 1,000 (72.5%) of the patients; of those patients, 883 (88.3%) were resistant to lamivudine and emtricitabine, and 454 (45.4%) to other NRTI's. High-level resistance to at least one PI was found in 317 (23.0%) patients and to at least one NNRTI in 700 (50.7%).

Transmission of resistance

Since 2003, treatment guidelines recommend obtaining a genotypic sequence at HIV diagnosis to assess whether patients are infected with a drug-resistant virus strain, since the presence of resistant virus will limit future therapy options. Between 2003 and 2008 6,387 new HIV diagnoses were registered, and a pol sequence was available within one year after diagnosis and before the start of antiretroviral treatment from only 2,238 (35%). The prevalence of resistance-associated mutations found in the total population diagnosed in or after 2003 was estimated to be 7.6%.

Of the 2,238 patients, 671 (30.0%) were recently infected, i.e., they were diagnosed either during the acute phase of the infection or they had tested positive for HIV-1 less than 1.5 years after their last negative test. Resistance-associated mutations were found in 53 (7.9%). The annual percentage of patients with resistance-associated mutations did not change over time. In total, 651 patients were fully susceptible to all PI's, 631 to all NRTI's, and 651 to all NNRTI's.

Five patients (0.7%) had intermediate or high-level resistance to at least one PI, 16 (2.4%) to at least one NRTI, and 8 (1.2%) to at least one NNRTI. Overall, 24 patients had intermediate or high-level resistance to at least one drug, corresponding to a prevalence of 3.6% (95% CI, 2.3-5.3), which was lower than the prevalence of major resistance-associated mutations. Apparently, the presence of resistance-associated mutations was not necessarily a sign of full resistance. Two patients had intermediate or high-level resistance to all three drug classes and one patient to two drug classes. Resistance-associated mutations were found in 120 (7.7% [95% CI, 6.4-9.8]) of the remaining 1,567 newly diagnosed patients. Intermediate or high-level resistance to PI's was found in 7 (0.4%) patients, to NRTI's in 34 (2.2%), and to NNRTI's in 38 (2.4%). In total, 68 patients had intermediate or high-level resistance to at least one antiretroviral drug, corresponding to a prevalence of 4.3%. Two patients had high-level resistance to drugs from all three classes. The prevalence of intermediate or high-level resistance to at least one drug in the total population diagnosed in or after 2003 was also estimated to be 4.3%.

The proportion of patients with evidence of transmitted drug resistance in the Netherlands was similar to proportions found in other European countries[37-39]. In the EuroSIDA study, the prevalence of transmitted drug resistance between 1996 and 2004 was 11.4%[38]. In Switzerland, the prevalence was 7.7% during the same period, and no changes over time were observed[37]. These relatively low levels of transmitted resistance may be the result of a limited reservoir of infectious patients in whom resistance developed during treatment. On the other hand, transmission of drug-resistant strains would also be low if HIV infections were predominantly transmitted by infected individuals who were untreated or not yet aware of their infection at the time of transmission. The latter scenario is likely for the group of homosexual men in the Netherlands[2].

Trends in causes of death, AIDS, and serious non-AIDS events

The life expectancy of patients infected with HIV-1 has increased significantly since the introduction of cART, although still not to the level of the age- and gender-matched general population[7]. AIDS is still diagnosed, but to a lesser extent and often as a result of delayed HIV testing. As the HIV-1 infected population ages, non-AIDS diseases are increasingly more common.

Mortality and incidence of AIDS

From the group of 15,602 patients with an HIV-1 infection and a known date of diagnosis, 15,591 patients were selected who were diagnosed before 1 June 2009. Amongst this group, 1,419 cases of death were recorded from 1996 onwards, corresponding to an average mortality of 1.35 deaths per 100 person-years (py). The mortality decreased over time from 1.92 in 1997 to 0.91 per 100 person-years in 2009.

For the total group of 15,591 patients, 4,366 AIDS diagnoses were registered at or after HIV diagnosis. There were 2,573 new AIDS diagnoses recorded 6 weeks or longer after an HIV diagnosis, of which 2,109 (82.0%) were recorded in or after 1996, yielding an average AIDS incidence of 2.34 per 100 person-years. From 1996 onwards, there was a decline ($p<0.001$) in AIDS diagnoses from 9.0 per 100 person-years in 1996 to 1.27 in 2008.

In the population of patients starting cART in 1995 or later, the overall mortality rate declined from 4.5 per 100 person-years in 1996 to 1.21 in 2008 and 1.09 in 2009. It should be noted, however, that this decline in mortality should be interpreted with care. The decline is partly due to a survival effect in which patients who do not die contribute to the total number of person-years in each calendar year, whereas patients who die contribute only to the number of deaths in one year.

On average, the mortality after 2000 was 1.43 per 100 person-years, being 1.16 in the therapy-naïve population and 2.31 in the pre-treated population. Between 1996 and 2009, the overall mortality in the naïve population was 1.19 per 100 person-years and did not change over time. When patients with an AIDS diagnosis in the year prior to the start of cART were excluded, the mortality rate was 0.87 per 100 person-years in the previously therapy-naïve population and 2.12 in the pre-treated population, and both rates did not change over time.

In the total group who ever started cART, 1,439 AIDS diagnoses were registered in 1996 or later during 70,807 person-years of follow-up after the start of cART. The incidence of new AIDS diagnoses decreased dramatically from 14.8 in 1996 to 1.19 per 100 person-years in 2008. In the therapy-naïve population the overall incidence of AIDS was 1.81 and in the pre-treated population 2.62. The AIDS incidence after 2000 was similar in the pre-treated and therapy-naïve populations, being 1.56 and 1.59 per 100 person-years, respectively.

Early diagnosis and prognosis

Several prognostic models have been developed to estimate survival probabilities of HIV-infected patients[7,40-43]. Some of these models considered patients at the start of cART, whereas other models took into account the initial response to treatment. In order to develop a prognostic model for patients who were untreated at the time of assessment of the prognosis, 4,174 patients were selected who were diagnosed between 1998 and 2007, who were not yet treated at 24 weeks after diagnosis, and who did not have AIDS at that time.

The only covariates associated with progression to death were age at 24 weeks and being in CDC stage B. Further analysis showed that patients of older age were no further advanced in their HIV infection than patients of younger age, because CD4 counts and CDC stage at 24 weeks were similar. Also, there were no differences in causes of death between older and younger patients. These findings are compatible with a model in which ageing is accelerated in HIV-infected patients[44].

The model was used to predict the expected age reached by HIV-infected patients and the number of remaining life years given the patients' age at 24 weeks after diagnosis. The median number of remaining life years for individuals 25 years of age from the general population was 53.1 years for men and 58.1 for women. For HIV-infected patients who were 25 years of age at 24 weeks after diagnosis, the expected median number of remaining life years was 52.5 for men and 57.5 for women. The number of life years lost increased from 0.7 years at age 25 to 1.9 years at age 55 for HIV-infected men and from 0.7 to 2.2 years for women. Hence, the life expectancy of HIV-infected individuals is, at most, a few years less than that of non-infected individuals. For patients with a CDC-B event at 24 weeks, however, the number of life years lost was larger: 3.4 years for men and 3.6 years for women 25 years of age and 8.9 and 11.6 years, respectively, for individuals 55 years of age.

Although life expectancies of HIV-infected individuals can be almost equal to those of non-infected individuals, this holds true only for patients who are still relatively early in their infection (at 24 weeks after diagnosis), i.e., they have high CD4 counts and are not yet eligible for treatment. About half of the patients with an HIV diagnosis between 1998 and 2007 were already treated after 24 weeks after diagnosis, whilst one sixth of the patients already had AIDS. Hence, a substantial proportion of the patients are diagnosed with HIV late in their infection, which considerably worsens the prognosis compared to that for patients presenting early in their infection[40-42]. Traditionally, the Netherlands has one of the lowest HIV testing rates in

the industrialised world[45]. This situation is changing, however, and amongst newly diagnosed HIV-positive men, the proportion of patients who ever had an HIV-negative test increased from 23% in 1996 to 62% in 2008. Nevertheless, in order to trace infections as early as possible, testing rates should increase amongst those who are at high risk for HIV, thus enabling a maximum beneficial effect of cART on prognosis.

Cause of death

The proportion of deaths due to AIDS after the start of cART between July 1996 and December 2008 showed a decreasing trend over time; it was 45% between 1996 and 2000, 33% between 2001 and 2004, and 28% between 2005 and 2009. The proportion of deaths due to non-AIDS cancers increased from 7% between 1996 and 2000 to 18% between 2005 and 2009. The proportion of deaths due to cardiovascular disease between 2001 and 2004 was similar to that between 2005 and 2009 and was higher than between 1996 and 2000 (10.4% vs. 4.5%).

The median CD4 count prior to death caused by an AIDS-defining infection was 50 cells/mm^3, which was lower than the 100 cells/mm^3 found in cases of an AIDS-defining malignancy. The same trend was seen in non-AIDS-defining infections (median last CD4 count, 125 cells/mm^3) and in non-AIDS-defining malignancies (210 cells/mm^3). The highest median CD4 counts were seen in patients prior to death caused by an accident or violence (380 cells/mm^3) and by cardiovascular disease (320 cells/mm^3). The AIDS-related mortality was 155.8/1000 person-years for patients with a latest CD4 count of less than 50 cells/mm^3, compared to 2.9 for those with a count between 200 and 350 cells/mm^3. Non-AIDS related mortality was also higher, with lower CD4 cell counts of 71.8/1000 person-years for patients with a latest CD4 count of less than 50 cells/mm^3 and 9.5 for patients with CD4 counts between 200 and 350 cells/mm^3.

The mortality rate due to non-AIDS-defining cancer was 3.04 (95% CI, 2.22-4.07) for pre-treated male patients and 1.55 (0.50-3.63) per 1000 py for female patients. This compares to 1.31 and 0.60 per 1000 py for the male and female age-standardized general population. In men, the incidence of death after starting cART was due to cardiovascular disease, myocardial infarction, and suicide, and it was higher compared to the age-standardized population, both in pre-treated and therapy-naïve patients. Other studies have also reported this result for myocardial infarction and certain non-AIDS-defining cancers, even after adjustment for other risk factors[46-50].

AIDS and serious non-AIDS morbidity

Serious non-AIDS events in the ageing HIV-infected population are the same as the events associated with older age in uninfected subjects, such as non-AIDS-defining malignancies and cardiovascular, renal, and hepatic disease, but they are seen more often in infected individuals than in uninfected controls[46,48-52]. Apart from the well known risk factors of older age and antiretroviral therapy, there is increasing evidence that HIV infection itself is associated with a higher incidence of these events[44]. In ATHENA, data are collected routinely for 7 serious non-AIDS events: renal insufficiency (chronic and acute disease), hepatic steatosis, diabetes mellitus, myocardial infarction, cerebrovascular accident (CVA), osteoporosis, and non-AIDS defining malignancies. The incidence of AIDS in the first year after the start of cART was 79.6/1000 person-years and of non-AIDS events 32.3. From 3 years after the initiation of cART onwards, the incidence of serious non-AIDS events was higher than that of AIDS events. All serious non-AIDS events clearly showed an increasing incidence with older age.

The increasing number of older patients living with HIV-1 partly explains the increasing trend of serious non-AIDS morbidity over time. Cardiovascular disease,

osteoporosis, malignancies, and renal disease are associated with older age in the general population. However, the higher number of older aged patients living with HIV alone does not completely explain the increasing trend of certain events with more recent calendar years. The incidence of non-AIDS malignancies is higher in HIV-infected patients than in the general population across all age groups, except for women between 60 and 65 years of age. The incidence among men is higher than among women, and risk factors such as smoking and lifestyle might play a role. Although the number of smokers may be higher in the HIV-infected population than in the general population, other studies that adjusted for age and other risk factors still found a higher incidence of non-AIDS malignancies, renal disease, and myocardial infarction[46,48-52] in patients infected with HIV-1 compared to uninfected controls. This has led to the hypothesis that HIV is associated with an accelerated ageing process, further supported by a study showing an increased frailty amongst HIV-infected patients compared to uninfected individuals[53].

Finally, serious non-AIDS mortality and morbidity is higher when CD4 cell counts are lower. Likewise, prevention of AIDS, early identification of infected patients at risk for co-morbidities, and a timely start of cART may help stop progression to non-AIDS diseases.

General conclusions and recommendations

The HIV epidemic in the Netherlands is a concentrated one and is still growing amongst homosexual men. HIV testing policies have improved, and the effect is obvious: with the increasing proportion of recently HIV-infected patients, the time from infection to diagnosis has been shortened. Last year and in previous years, we stressed repeatedly the need for new preventive approaches in order to be able to further contain the spread of HIV in the MSM population. Those measures should focus on risk behaviour from the time of infection to diagnosis[2]. That particular period contributes substantially to transmission of HIV[2], and thus, changing risk behaviour especially during that period is crucial for containing the epidemic.

Changing risk behaviour not only in the infected population but also in non-infected risk groups, together with an active testing policy amongst the latter, is important because a protecting vaccine is not yet available nor will it be available in the coming years. This is despite the hopeful, but somewhat confusing, results of the US-Thai ALVAC-HIV vCP1521 + AIDSVAX vaccine trial (Rerks-Ngarm S, et al. N Engl J Med 2009;361. Published 22 October 2009, at NEJM.org).

Finally, this year we present data on the increase over calendar time of viral load at set-point. Such an increase is worrying, as it implies a higher transmissibility of HIV, especially in that period during which infected individuals are yet not treated. SHM in collaboration with other groups needs to confirm these results and to further investigate the heritability of set-point viral load. This would point towards HIV adapting itself so that optimal transmission continues to occur[54,55]. In addition, SHM should initiate research regarding transmission networks, aiming at better insight into the patterns of transmission and other factors that impact the efficiency of transmission. To be able to perform such studies, it is essential to obtain an HIV-1 pol sequence for each newly diagnosed patient before initiation of cART. It would simultaneously improve HIV care because pol sequencing is the well established method for determining resistance of HIV to the three antiretroviral drug classes that are currently used for the first-line response to infection. In view of HIV care and of HIV public health, pol sequencing in only 35% of the recently infected population seems inappropriate.

Since the population of HIV-infected individuals who are being monitored through HIV care and who have

access to cART is growing, prediction of outcome becomes more relevant for the development of both HIV health care and public health policies. For instance, important parameters such as predicting time to entry into heath care, to start and failure of therapy, to AIDS and non-AIDS events, to death, as well as prediction of the distribution over time of CD4 cell counts, of viral load peaks, and of risk groups, including migrants, need to be analysed and used in modelling the progression of HIV, the effect of cART, and subsequently, the estimates of people living with HIV. SHM should further data analyses and model development[7] and continue to contribute to the understanding and predictions of the changes in the HIV-infected population in the Netherlands. Together with our modelling partners at Imperial College[56] and in collaborations with groups such as The European Coordinating Committee for the Integration of Ongoing Coordination Actions Related to Clinical and Epidemiological HIV Research (EuroCoord), SHM can help keep issues of prevention, diagnosis, and treatment of HIV on the agenda in Europe.

data quality

1. Prediction of missing data on liver fibrosis

Sima Zaheri, Bianca Slieker, Colette Smit

Data (Appendix 1) of all HIV-infected patients who are registered at the Stichting HIV Monitoring (SHM) are collected by data collectors in the 25 HIV treatment centres in the Netherlands. Data are obtained directly from the patients' medical files, electronic laboratory results, and complementary diagnostic reports, according to the data collections protocols and entered on site in the ATHENA (AIDS Therapy Evaluation in the Netherlands) database. Data monitors at the SHM supervise the quality of the data and maintain the accuracy and completeness of the data set by comparing it to source documents and by verifying its protocol compliance.

Controlling the quality of data obtained from patients is crucial for all clinical research, irrespective of the setting in which the collection takes place [57-61]. Usually, source data verification (SDV) is the approach of choice. However, given the large population size of the ATHENA cohort, a 100% source data verification is not feasible. Therefore, customized procedures for continuous monitoring of data quality and resolving the discrepancies were implemented [62-64]. These procedures include effective data selections for SDV in order to identify missing data that have a marked influence on the data analysis. The use of clinical markers as a predictor for data on clinical events is one approach.

Non-AIDS events have become the most frequent clinical events in HIV-infected patients with highly active antiretroviral therapy (HAART). More than 60% of all deaths in HIV-positive persons receiving combination antiretroviral treatment (cART) are from causes other than AIDS [65-71]. Untreated HIV, as well as several other immunodeficiency disorders, can lead to acceleration of liver disease seen in patients chronically infected with either the hepatitis B virus (HBV) or hepatitis C virus (HCV) [10,72-74]. Long exposure to cART is associated with a slight increase in the risk of liver-related mortality [10]. Because the number of patients co-infected with HBV and HCV is high, it is important to further investigate if continued exposure to cART may ultimately lead to significant progression of liver failure. Also, the progression of liver disease associated with HBV, HCV, or both is known to be accelerated by HIV [75]. Since the availability of cART, the life expectancy of HIV-infected individuals has improved, and the prevalence of liver disease is therefore likely to increase. Therefore, longer follow-up and correct registration of non-fatal outcomes of liver disease are highly important.

Progression of hepatic fibrosis is usually used as a marker for progression of liver failure in HIV studies [76,77]. Therefore, the diagnosis of liver fibrosis is one of the main data collection items for the ATHENA cohort. In our observational setting, various clinical information sources such as physicians' notes and letters in the medical files, liver biopsy, and reports of CT scans, MRI, and abdominal echography should be consulted by the data collectors to completely and correctly abstract data on liver fibrosis. Therefore, the registration of liver fibrosis is prone to missing data. This was also noticed during routine SDV by the data monitors of the SHM.

The alanine aspartyl transferase (AST)-to-platelet ratio index (APRI) is shown to be a good predictor for the development of fibrosis in HCV-infected patients. The predictive value of the APRI score is even higher in patients with an HIV-HCV co-infection [76]. In this study, we assessed whether the APRI score can be used as

a predictor for missing data on liver fibrosis in the ATHENA database.

Methods

APRI score is defined as: 100 x (AST/upper limit of normal)/platelet count (10^9/L). The APRI score >1.5 is found to be predictive for liver fibrosis[76]. Conforming to our protocol for manual data collection, we enter AST measurements > 3 x upper limit of normal and platelets < 150 (10^9/L) into the ATHENA database. Lab results that are entered directly into the ATHENA database by means of an automated link, a so-called "lab link", contain all AST and platelets values available in the hospitals' computerized information system. For this study, we selected data from patients with an APRI score >1.5. The lower limit of the APRI scores in the manually collected part of the ATHENA dataset counted 2. The selection yielded 1043 patients, and data collected for 826 patients of those was verified by means of SDV at the time of the analysis. During the SDV, the values on which the APRI scores are based were checked, and subsequently all available data sources (physicians' notes and letters in the medical files, liver biopsy, and CT scan, MRI, and abdominal echography reports) were consulted for verifying data on liver fibroses. The numbers of missing and incorrect records were determined by the data monitors. The results of SDV were entered into a Microsoft Access database for further analysis.

Results

Of all patients with data, 7% had an APRI score >1.5. The percentage of patients with APRI >1.5 was 3.2 times higher in the HIV-HCV co-infected patients, compared with that in the HIV mono-infected patients.

Data obtained from 826 patients with an APRI score >1.5 showed 100 diagnoses of liver fibrosis, a prevalence of 12% before SDV. Eight patients with an APRI score based on incorrect lab values were excluded from the analysis (Table 1.1). SDV revealed 57 (7%) missed diagnoses in the remaining patients (818) and resulted in a significantly higher prevalence (19%) of diagnoses of liver fibrosis (12% difference; 95% confidence interval [CI] of the difference, 3-10). The prevalence of diagnoses of liver fibrosis in the HIV-HCV co-infected patients was significantly higher than in the HIV mono-infected group, 34% and 14%, respectively; the difference in the prevalence of fibrosis between mono- and co-infected patients was 21% (95% CI, 14-26). The percentage of a missing diagnosis of liver fibrosis in the HIV-HCV co-infected patients was 2.2 times higher than that in HIV mono-infected patients (95% CI of the difference, 1-10). The liver fibrosis diagnoses were missed by the data collectors mainly because the pathology and radiology reports were overlooked. None of the collected diagnoses of liver fibrosis was found to be surplus after SDV, and 47% of all patients with a fibrosis diagnosis had an APRI score >1.5.

In order to investigate the number of missing APRI scores <1.5 on account of limitations of our protocol for manual data collection, APRI scores based on AST measurements > 3 x upper limit of normal and platelets < 150 (10^9/L) were selected and compared with APRI scores based on all available measurements in the Academic Medical Center (AMC) hospital, which has an automated link to the hospitals' computerized information system ("lab link"). This comparison showed that 66% of all APRI scores >1.5 (329) would be missed if laboratory data were manually collected (AST measurements > 3 x upper limit of normal and platelets < 150 [10^9/L]). Consequently, 21% of the missing diagnoses of liver fibrosis (18) that were found as a result of SDV would not have been found if the selection had been based on the manually collected data (Table 1.2).

Discussion

The results of analyses of liver failure as an endpoint in HIV studies depend on the quality of the collected data on liver fibrosis. Data may be missing from the collection on diagnoses of liver fibrosis in an observational setting

such as ours, because data collectors extract diagnostic data from various sources and checking all sources may not be possible. Efficient use of SDV in addition to training data collectors can improve the quality of those data. One possible approach for improvement is focusing on source data verification of data likely to have a higher frequency of discrepancies.

Like other researchers[76], we show that the percentage of patients with an APR >1.5 is higher in the HIV-HCV co-infected patients compared with that in HIV mono-infected patients. The percentage of missing liver fibrosis diagnoses was significantly higher in patients with HIV-HCV co-infection than in patients with HIV mono-infection. This could be explained by the fact that the prevalence of liver fibrosis was also significantly higher in the HIV-HCV co-infected group compared with the HIV mono-infected group. The objective of this study was to find a predictor for missing data on liver fibrosis. Source data verification of data from patients with an APRI score >1.5 resulted in a significant increase of the number of liver fibrosis diagnoses and thus seems to be an effective predictor for missing data on liver fibrosis. However, this finding was based mainly on manually collected data on AST and platelet values, which are limited to extreme values. To further analyze the predictive value of the APRI score, all available AST and platelet values of patients in the study should be taken into account. Furthermore, the number of missing diagnoses of liver fibrosis in patients with an APRI score >1.5 compared to patients with an APRI score <1.5 should be investigated.

In conclusion, SDV of data from all patients with an APRI >1.5 should be included in our procedures for data quality improvement. Furthermore, in order to define more laboratory data markers as predictors for missing data, we recommend the implementation of automated links to all hospitals' computerized information systems to upload laboratory data directly into the ATHENA database.

Table 1.1: Results of source data verification (SDV): APRI score as a predictor for missing data on fibrosis diagnoses. APRI: alanine aspartyl transferase (AST)-to-platelet ratio index

	Total	HIV mono-infected	HIV-HCV co-infected
Before SDV			
Patients with data (n)	14960	13552	1408
Patients with APRI >1.5 (n)	1043	782	261
Fibrosis diagnoses records in the database (n)	275	144	131
Fibrosis diagnoses records in patients with APRI >1.5 (n)	100	50	50
After SDV			
Verified patient's medical files (n)	826	610	216
Patients with correct APRI >1.5 (n)	818	604	214
Fibrosis diagnoses records in the database (n)	332	177	155
Fibrosis diagnoses records in patients with APRI >1.5 (n)	157	83	74
Missing fibrosis diagnoses records (n)	57	33	24
Missing fibrosis diagnoses records in the verified population (%)	7%	5%	11%

Table 1.2: Comparison of available APRI scores >1.5 in "lab link" data versus manually collected data in the Academic Medical Centre (AMC) hospital. SDV: source data verification; APRI: alanine aspartyl transferase (AST)-to-platelet ratio index.

	Number of patients	Number of fibroses diagnoses after SDV	Number of fibroses diagnoses before SDV
Before SDV			
Patients with APRI > based on "lab-link" data	497	84	42
Patients with APRI >1.5 based on manual data collection	126	24	
Missing APRI scores >1.5 in manually collected part of data	329	18	

Appendix 1: Data

Upon patient entry into the Stichting HIV Monitoring 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, location of testing and health care body that referred pt to specialist	
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, injecting drug use (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	
Intoxication	Data on smoking, alcohol consumption and drug intake	
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, congenital defects, perinatal exposure to antiretroviral (ARV) therapy and co-medication, antenatal complications	
Additional data for HIV-infected pregnant women		
Demographic data	Nationality and country of birth of patient's parents Patient's ethnicity *('Asian', 'Caucasian', 'Black', 'other', or 'unknown)*	
Screening	Was the patient found to be HIV-positive at the national pregnancy screening?	
Visits to the gynaecologist	Visit date, Blood pressure	
Obstetric data	Has there been a delivery/abortion? Date of delivery/abortion Sex of the baby Duration of pregnancy Child number Prophylactic antibiotics? Intra-uterine infection Duration of dilation Duration of expulsion	Duration of ruptured membranes Mode of delivery Caesarean section? Fetal scalp electrode Episiotomy or rupture Birth weight of the baby Apgar scores after 1 minute/5 minutes Duration of stay in the incubator Perinatal mortality Breast-feeding?
Complications during pregnancy	Complications during and/or after birth? Blood loss during the first half of pregnancy? Blood loss during second half of pregnancy? Intercurrent infection? Version (attempt) with breech presentation? Pre-eclampsia?	Intra-uterine retardation of growth (sonography<p5%)? PPROM (preterm premature rupture of outer membranes) at how many weeks? Abdominal trauma at how many weeks?

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 by 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	Rash
	Myopathy	Abacavir hypersensitivity
	Lactate acidosis	Sexual dysfunction (loss of libido, erectile dysfunction)
	Hepatic fibrosis / cirrhosis	Non-AIDS malignancies
	Osteopenia / Osteoporosis	Anal dysplasia
	Hepatic steatosis	Diabetes mellitus
	Hepatic encephalopathy	Myocardial infarction
	Oesophagus varices	Hypertension
	Hepatorenal syndrome	Arrhythmia
	Liver transplantation	Heart failure
	Pancreatitis	Cardiomyopathy
	Nephrolithiasis	Stroke
	Renal insufficiency and failure	Coronary artery by-pass grafting
	Kidney dialysis	Coronary angioplasty / stenting
	Kidney transplantation	Carotid endarterectomy
	Lipodistrophy, fat loss in extremities	Pregnancy
	Lipodistrophy, central fat accumulation	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	Newly available medication
	Immunological failure	As a precaution
	Patient's decision	Pregnancy wish
	Toxicity	Pregnancy
	New CDC-B and or CDC-C events	End of pregnancy
	Interaction with co-medication	Compliance problems
	Simplification of the regimen	Other
	Related to blood concentration of ARV	Unknown
	Structured treatment interruption	

Items collected at every follow-up visit for HIV-infected adults		
Co-medication	CDC events, prophylaxis	Anti-diabetic agents
Start and stop date and the	CDC events, treatment	Insulin and its derivatives
medication status at current visit	Anti-epileptic agents	Anabolic steroids and appetite stimulants
(ongoing: yes or no)	Anti-coagulant agents	Hepatitis B treatment
	Platelet aggregation inhibitors	Hepatitis C treatment
	Anti-hypertensive agents	Medication that interacts with antiretroviral therapy
	Anti-arrhythmic agents	Miscellaneous: megestrol acetate, dranabinol and methadone
	Lipid lowering agents	
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 x N*	
	ASAT/SGOT>3 x N*	
	Alkaline phosphatase >3 x N*	
	Gamma GT >3 x N*	
	Lactate>N*	
	Creatinine always collected	
	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 10^9/l	
	Thrombocytes <150 10^9/l	
	Other viral infections:	
	Value (positive or negative), laboratory, sample date for the following determinates:	
	HBsAg, HBsAb, HBcAb, HBeAg, HBeAb, HBV-DNA (quantitative and qualitative values),	
	HCV-Ab, HCV-RNA (quantitative and qualitative values), CMV-IgG, CMV-IgM	

Items collected at every follow-up visit for HIV-infected adults	
	Sexually transmitted diseases: Value, units, laboratory and sample date for the following determinates: Chlamydia Condylomata accuminata Gonorrhoea Human Papilloma virus Syphilis
	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
Additional data for HIV-infected children	
Clinical examination	Skull circumference, puberty stage
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 by standard protocol. In addition to CDC-B and –C events, CDC-A events are also collected.
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
	Other viral infections: Value (positive or negative), laboratory, sample date for the following determinates: In addition to Hepatitis and CMV, Toxoplasmosis and Varicella Zoster Virus are collected.

monitoring programme report

2.The HIV epidemic in the Netherlands

Ard van Sighem, Luuk Gras, Colette Smit

Total population

As of June 2009, the total HIV-infected population registered by the SHM consisted of 16,715 patients (see Figure 2.1). Of these patients, 586 (3.5%) were registered in an HIV treatment centre in Willemstad on Curaçao, and this particular group of patients is discussed in more detail in chapter 8. The other 16,129 patients had been or were still in follow-up in a treatment centre in the Netherlands. The total follow-up for this group was 119,290 person-years since diagnosis. The majority of the 16,129 patients (15,651 [97.0%]), were infected with HIV-1, and 83 (0.5%) were infected with HIV-2. Seroreactivity to both HIV-1 and HIV-2 was found for 47 (0.3%) patients, and serologic results were inconclusive or not yet known for 348 (2.2%). Of the 16,129 patients who had been registered in a treatment centre in the Netherlands, 12,405 (79.3%) were still in follow-up as of 1 June 2009, including 12,258 (98.8%) adults and 147 (1.2%) children and adolescents.

Last year the SHM database included 14,960 patients; since then, the registered population in the Netherlands has increased by 1,169 patients, or 7.8% [1]. The number of HIV-1-infected patients increased by 8.6% (2008: 14,407 patients), whilst the number of HIV-2-infected patients increased by 5% (2008: 79). On the other hand, the number of patients with seroreactivity to both HIV-1 and HIV-2, which was 112 last year, decreased this year by 58%, whilst the number of patients without serologic results remained nearly the same, 362. Patients with HIV diagnoses newly registered in 2007 or later accounted for 87.5% of the increase, patients diagnosed between 1996 and 2006 accounted for 9.6%, and those diagnosed before 1996 accounted for 4.0%.

The 15,651 patients in the Netherlands infected with HIV-1 constitute the basic population on which all analyses in this report are based, unless stated otherwise. For 49 (0.3%) patients, the year of the first positive HIV test was unknown; the total HIV-1-infected population with a known year of diagnosis consisted of 15,602 patients. Of the 15,602 patients, 15,236 (97.7%) were diagnosed at the age of 18 years or older, including 12,090 (79.4%) men and 3,146 (20.6%) women, and these patients will be described later in section 'Trends over time – diagnosis'. The other 366 patients included 208 (56.8%) children 12 years of age or below at diagnosis and 158 (43.2%) patients 13 to 18 years of age, and are discussed in section 'HIV-infected children and adolescents'.

Amongst the 3,146 HIV-1-infected women with a known year of infection, 797 became pregnant at least once after being infected with HIV. In total, 1,055 pregnancies were recorded amongst these women (section 'Pregnant women'). Another group of patients frequently referred to in later chapters is that of the 12,297 (80.7% of the 15,236) patients who were ever treated with combination antiretroviral therapy (cART). In total, 2,328 (18.9%) patients had been treated with non-cART regimens before they started cART, whilst 9,969 (81.1%) patients started cART without prior exposure to antiretroviral medication. Finally, amongst the 15,236 patients, there were 992 patients with an HBV co-infection, 1,452 with an HCV co-infection, whilst 157 patients were co-infected with both HBV and HCV (see Chapter 6).

Population currently in follow-up

As of June 2009, 12,258 adult patients were still in follow-up (Figure 2.1). This number is probably an

underestimation, because for some patients there was a backlog in data collection of more than one year. The majority of the 12,258 patients were men who originated from the Netherlands and were infected via homosexual contact (Table 2.1). The median age of the population was 44.3 (Interquartile range [IQR], 37.6-51.1) years, and men were generally older than women, that is, 45.4 (39.0-52.2) years of age compared to 39.4 (33.2-46.5) years for women. The age of the population increased over calendar time (Figure 2.2).

cART was administered to 9,757 (79.6%) patients, whilst 42 (0.3%) patients received a non-cART regimen, and 2,459 (20.1%) were not yet treated. The number of patients not yet treated was higher amongst men than women, 2,112 (21.8%) and 347 (13.6%), respectively. The four most frequently used regimens were tenofovir + emtricitabine + efavirenz, tenofovir + emtricitabine + nevirapine, zidovudine + lamivudine + nevirapine, and tenofovir + emtricitabine + ritonavir-boosted atazanavir, accounting for 43.2% of all regimens (Table 2.2). As of 1 June 2008, these regimens accounted for 36.0% of all those given. Between 1 June 2008 and 1 June 2009, the proportion of patients using tenofovir increased from 57.0% to 62.5%, and the proportion using emtricitabine increased from 36.1% to 46.6%. On the other hand, the use of lamivudine decreased from 53.3% to 44.5%, and zidovudine use decreased from 22.9% to 19.6%. As of 1 June 2009, the most frequent additions to the backbone were nevirapine (28.1%, 2008: 28.6%, p=0.4), efavirenz (32.8%, 2008: 30.2%, p<0.001), lopinavir (16.0%, 2008: 16.8%, p=0.1), and atazanavir (12.5%, 2008: 12.0%, p=0.3).

The most recently measured CD4 cell counts were 490 (IQR, 360-660) cells/mm^3 for the male population and 500 (360-690) cells/mm^3 for the female population (p=0.08). CD8 cell counts were 930 (IQR, 670-1289) cells/mm^3 for men and 820 (590-1128) cells/mm^3 for women (p<0.001). In the total population, 9088 (74.1%) patients had a plasma viral load <500 copies/ml. One or more AIDS-defining events had been diagnosed in 2,894 (23.6%) patients; of those patients, about half (1,537; 12.5% of the total population) had an AIDS diagnosis at or within 4 weeks after their HIV diagnosis.

The HIV-1 subtype could be determined for 4,147 (33.8%), including 3,375 men and 772 women. The majority (3,253, 78.4%) were infected with a subtype B strain. This subtype was more frequently observed in men (2,932, 86.9%) than in women (321, 41.6%). Other frequently observed subtypes were AG (265, 6.4%), C (204, 4.9%), A (115, 2.8%), and AE (93, 2.2%).

The median time since diagnosis was 6.9 (IQR, 3.2-12.2) years for men and 6.9 (3.9-10.9) years for women (p=0.6). In total, 2,674 (21.8%) patients were diagnosed in the 3 years before 1 June 2009; this proportion was higher for men (22.8%) than for women (18.1%, p<0.001). Also, a larger proportion of men (3,259, 33.6%) than women (743, 29.1%) received their HIV diagnosis more than 10 years ago (p<0.001).

A total of 11,359 (92.7%) patients were tested for hepatitis B co-infection and 861 (7.8%) tested positive. HBV was most prevalent amongst injecting drug users (IDU), of whom 32 (10.4% of 309 tested) were co-infected. The HBV prevalence was 8.1% (533 of 6,589 tested) amongst homosexual men (p=0.2 compared to IDU). Amongst heterosexually infected patients, the overall prevalence was 6.4%, and it was significantly higher amongst men (8.2%) than amongst women (5.1%) (p<0.001). The prevalence of HBV was 2.7% (32 of 1,164 patients tested) amongst heterosexually infected patients originating from the Netherlands, 5.4% (19 of 353 tested) for patients from Latin America, 9.5% (146 of 1,530 tested) for patients from Sub-Saharan Africa, and 9.6% (7 of 73 tested) for patients from Central or Eastern Europe.

The HCV status was known for 10,820 (88.3%) patients, of whom 1,150 (9.4%) were HCV-positive. Co-infection with both HBV and HCV was found in 98 patients. The HCV prevalence was highest amongst injecting drug users, of whom 299 (91.7% of the 326 tested) were co-infected with HCV. In the population infected via heterosexual contact, the HCV prevalence was 5.7% for men and 4.8% for women (p=0.2). The prevalence was higher amongst homosexual men (p<0.001), of whom 515 out of 6,367 tested (8.1%) were HCV-positive. In the group of homosexual men, the HCV prevalence was 9.9% in patients seen in hospitals in Amsterdam and 6.3% in patients followed in other hospitals (p<0.001). The HCV prevalence was higher amongst those infected by blood-blood contact (30%; 43% for men, 9% for women) and amongst those for whom the route of transmission was unknown (19.7%; 15.2% for men, 41.8% for women).

Trends over time – diagnosis

Of the 16,129 HIV-infected patients registered in one of the 25 HIV treatment centres, 15,236 (94.5%) had a known year of HIV-1 diagnosis and were diagnosed at 18 years of age or older (Figure 2.1). Of these patients, 12,090 (79.4%) were men, and 3,146 (20.6%) were women. The majority of the patients, 8,688 (57.0%), originated from the Netherlands, whilst 2,445 (16.0%) were of Sub-Saharan African origin. In total, 3,441 (22.6%) patients were diagnosed in or before 1995.

Men having sex with men (MSM)

For 8,553 (70.7%) of the 12,090 men with an HIV-1 diagnosis, the reported mode of transmission was homosexual contact. Of these patients, 6,416 (75.0%) were diagnosed in 1996 or later. The annual number of diagnoses increased from 371 in 1996 to 710 in 2008 (Table 2.3), whilst the annual proportion of MSM in the annual tally followed a parabolic curve with nadir in 2003 and increasing to 68.2% in 2008 (Figure 2.3). In 2009, the proportion of MSM has appeared to shrink to 61.8%, but only 157 HIV-1-infected patients were diagnosed and included up to 1 June. Most MSM, 6,235 (72.9%), were of Dutch origin, whilst 810 (9.5%) originated from other European countries, 559 (6.5%) from Latin America, 251 (2.9%) from the Caribbean, and 231 (2.7%) from South and Southeast Asia. The proportion of MSM of Dutch origin increased from 72.5% in 1996 to 77.2% in 2008 (p=0.005).

For patients diagnosed in or after 1996, median HIV-1 plasma RNA levels at diagnosis were 4.9 (IQR, 4.3-5.3) $\log_{10}$ copies/ml, and CD4 and CD8 counts were 370 (173-560) and 930 (620-1346) cells/mm^3, respectively. Patients originating from the Netherlands had higher RNA levels than other patients, that is, 4.9 (IQR, 4.3-5.3) $\log_{10}$ copies/ml for patients of Dutch origin compared to 4.7 (4.1-5.2) for other patients (p<0.001). CD4 counts were higher in Dutch patients, 371 (IQR, 182-570) cells/mm^3, compared with those in other patients, 340 (151-540) cells/mm^3, (p<0.001). Also, CD8 cell counts were higher in Dutch patients, 940 (IQR, 640-1370) cells/mm^3, compared with those in patients from other countries, 900 (600-1260) cells/mm^3, (p<0.001). Median CD4 cell counts increased from 240 (IQR, 85-415) cells/mm^3 in 1996 to 412 (250-570) cells/mm^3 in 2008. Median CD8 cell counts did not change over time (p=0.2), whilst median HIV RNA levels decreased by a minute 0.01 $\log_{10}$ copies/ml per year (p=0.003).

The median age at diagnosis was 37.9 (IQR, 31.7-45.0) years; for patients of non-Dutch origin it was 33.9 (28.8-39.9) years, which was lower than the median age of patients originating from the Netherlands, which was 39.3 (33.2-46.4) years. For Dutch patients, the median age at diagnosis increased from 37.0 (IQR, 31.7-45.5) years in 1996 to 40.3 (32.7-46.6) years in 2008, whereas for patients from other countries it increased from 32.9 (29.8-39.2) to 35.1 (29.2-40.8) years.

In 1996, the proportion of patients who were in CDC stage C, i.e. who had an AIDS-defining event, at diagnosis was 20.5%, whilst 7.8% were diagnosed in CDC stage B. Thereafter, these proportions decreased, and in 2008, 3.7% of the MSM diagnosed in that year were in CDC stage B and 7.8% were in CDC stage C.

In total, 1,381 (21.5%) patients diagnosed in 1996 or later had a negative HIV-1 test in the 18 months prior to diagnosis (classified as "recent infection"). Since 1996, there has been a steady increase in the proportion of MSM with a recent infection, increasing from 36 out of 371 (9.7%) in 1996 to 245 out of 710 (34.5%) in 2008. The proportion of patients with a recent infection was higher amongst patients of Dutch origin (22.6%) than amongst patients from other countries (18.4%). A recent infection was found in 621 out of 3,184 (19.5%) patients who were 38 years of age or older at diagnosis. In 3,232 patients younger than 38 years, a recent infection was more common, occurring in 760 (23.5%, $p<0.001$).

For patients with a recent infection, median CD4 and CD8 counts at diagnosis were 518 (IQR, 370-680) and 1,010 (710-1480) cells/mm^3 and did not change over time ($p=0.8$). CD4 and CD8 counts were lower for patients who were not diagnosed with a recent infection, specifically, 311 (IQR, 130-500) and 900 (600-1300) cells/mm^3, respectively. For patients without recent infection, CD4 counts increased from 210 (IQR, 72-398) cells/mm^3 in 1996 to 360 (190-520) cells/mm^3 in 2008, whereas CD8 counts did not change over time ($p=0.4$). The number of patients who ever had a negative HIV test increased from 85 (22.9%) in 1996 to 441 (62.1%) in 2008.

For 6,771 (79.2%) patients, the most likely country of infection was known. A majority, 5,997 (88.6%), were infected in the Netherlands. The proportion of patients infected in the Netherlands increased from 263 out of 304 (86.5%) in 1996 to 526 out of 558 (94.3%) in 2008. For 5,074 (96.2%) of the 5,272 Dutch patients for whom the country of infection was known, the reported country of infection was the Netherlands. The country of infection was known for 145 of 210 (69.0%) patients originating from the Netherlands Antilles or Aruba and for 163 of 238 (68.5%) patients from Suriname. Of the 145 from the Antilles, 27 (19%) were infected there, and 111 (77%) were infected in the Netherlands, whilst of the 163 from Suriname, 17 (10%) were infected in Suriname and 143 (88%) in the Netherlands.

The HIV-1 subtype could be determined for 3,080 (36.0%) MSM. Of these, 2,943 (95.6%) were infected with a subtype B virus strain, and the proportion of patients infected with a subtype B strain decreased from 99% in 1996 to 90% in 2008 ($p<0.001$). Other subtypes found in homosexual men were AE (39 patients, 1.3%), AG (34 patients, 1.1%), C (29 patients, 0.9%), A (21 patients), G (4 patients), and other subtypes (10 patients).

Heterosexual men and women

Of the 4,861 patients infected via heterosexual contact, 2,121 (13.9% of the total HIV-1-infected population with a known year of diagnosis and 43.6% of the heterosexual group) were men, and 2,740 (18.0% of the total population and 56.4% of the heterosexual group) were women. The proportion of heterosexual men and women in the annual number of diagnosed patients reached a maximum in 2003 and decreased thereafter to 12.7% and 13.6%, respectively, in 2008 (Figure 2.3). From 1996 onwards, the annual number of diagnoses amongst men increased to 174 in 2003, whilst the number of diagnoses amongst women increased to 261 (Table 2.3). From 2005 on, the number of diagnoses decreased and for 2008, 132 diagnoses amongst men and 142 amongst women have been reported so far.

The most frequently reported regions of origin for heterosexual men were the Netherlands (823 patients, 38.8%) and Sub-Saharan Africa (725, 34.2%). Other

regions were Latin America (2,114 patients, 10.1%), Europe excluding the Netherlands (142, 6.7%), and the Caribbean (112 patients, 5.3%). Almost half of the heterosexual women originated from Sub-Saharan Africa (1,338 patients, 48.8%), whilst 668 (24.4%) patients were from the Netherlands. The proportion of women originating from the Caribbean (161, 5.9%) and Latin America (251, 9.2%) was similar to that of men, whilst 163 (5.9%) female patients originated from South and Southeast Asia and 117 (4.3%) from Europe excluding the Netherlands. After 1996, there were almost twice as many diagnoses amongst women than amongst men from Sub-Saharan Africa, that is, 673 diagnoses amongst men and 1,244 amongst women. The men-to-women ratio was more balanced amongst heterosexuals from other regions: 1,189 diagnoses amongst men and 1,128 amongst women.

The number of diagnoses amongst patients from Sub-Saharan Africa increased from 53 in 1996 to 241 in 2004. Thereafter, the number of diagnoses declined to 130 in 2006. This is consistent with the reduction in the number of people emigrating from Sub-Saharan Africa to the Netherlands, as reported by Statistics Netherlands (http://statline.cbs.nl). According to Statistics Netherlands, after 2004 the number of immigrants from Sub-Saharan Africa stabilised. This was probably reflected in the data by an apparent stabilisation of the number of diagnoses amongst Sub-Saharan Africans from 2006 onwards; in 2007, 136 patients from Sub-Saharan Africa were diagnosed, and in 2008, 115 patients.

The median CD4 cell counts at diagnosis were 200 (IQR, 52-410) cells/mm^3 for heterosexual men and 290 (120-490) cells/mm^3 for heterosexual women. Median CD8 cell counts were 790 (IQR, 500-1140) cells/mm^3 and did not differ between men and women (p=0.6). Plasma viral load at diagnosis was 4.9 (IQR, 4.3-5.3) $\log_{10}$ copies/ml for men and was lower for women, 4.4 (3.6-5.0). Women were younger at diagnosis than men, with a median age of 31.3 (IQR, 26.3-37.9) years, compared to 37.6 (31.7-45.1) years for men.

Men and women from Sub-Saharan Africa were generally younger and had lower CD4 counts than their Dutch counterparts. The median age was 29.7 (IQR, 25.2-34.9) years for women from Sub-Saharan Africa and 34.3 (28.6-39.6) years for men, whereas for Dutch women the median age was 35.7 (28.4-46.2) years and for Dutch men the median age was 40.9 (34.1-50.2) years. CD4 counts were 250 (IQR, 121-410) cells/mm^3 for Sub-Saharan African women and 169 (62-330) cells/mm^3 for Sub-Saharan African men, whereas they were 420 (170-650) cells/mm^3 for women from the Netherlands and 280 (65-490) cells/mm^3 for heterosexual men from the Netherlands. Viral load and CD4 and CD8 cell counts at diagnosis for men and women did not differ between Dutch patients and patients from other European countries. However, patients from other European countries were generally diagnosed at a younger age, that is, 36.7 (IQR, 32.5-48.1) years for men and 31.5 (28.2-37.7) years for women ($p<0.001$). Median CD4 counts in patients from countries other than the Netherlands, Europe, and Sub-Saharan Africa were 160 (IQR, 40-360) cells/mm^3 for men and 280 (77-474) cells/mm^3 for women. Their median age at diagnosis was between that for Dutch and sub-Saharan African patients, specifically, 39.3 (IQR, 33.6-46.6) for men and 32.1 (27.4-39.3) for women. CD8 cell counts and viral load were similar for patients from different regions, taking into account gender differences.

In general, no significant changes occurred in RNA levels and CD8 counts between 1996 and 2008. Median CD4 cell counts increased (p=0.002) from 100 (IQR, 30-380) cells/mm^3 in 1996 to 250 (70-440) cells/mm^3 in the male population. In the female population, CD4 counts were 280 (IQR, 150-433) cells/mm^3 in 1996 and 306 (90-479) cells/mm^3 in 2008, but this increase was not statistically significant (p=0.5). The median

age at diagnosis of the entire heterosexual population increased from 33.1 (IQR, 27.4-38.4) years in 1996 to 37.4 (28.6-46.0) years in 2008 ($p<0.001$).

Between 1996 and 2008, 742 (17.7%) patients presented with an AIDS-defining event, whereas 296 (7.1%) patients had a CDC-B event. The proportion of male patients with AIDS was 22.3% (409 out of 1,831), which differed from the proportion of female patients, 14.1% (333 out of 2,354). Proportions did not change over time ($p>0.4$).

Of the 4,234 heterosexuals diagnosed in 1996 or later, 227 (5.4%) had a negative HIV test within 18 months prior to HIV diagnosis, whilst 695 (16.4%) ever had a negative test. These proportions were similar for men and women ($p>0.3$). Of the 1,407 patients originating from the Netherlands and the rest of Europe, 120 (8.5%) had a negative test in the 18 months prior to diagnosis and 324 (23.0%) ever had a negative test, whereas for the 2,827 patients born outside Europe, 107 (3.8%) had a recent infection and 371 (13.1%) ever had a negative test. The proportion of patients with a recent infection tended to increase over time from 4.9% in 1996 to 7.3% in 2008 ($p=0.03$). Likewise, the proportion of patients with a negative HIV test at any time before diagnosis increased from 16.0% in 1996 to 25.5% in 2008 ($p<0.001$).

The most likely country of infection was recorded for 3,743 (77.0%) patients, including 1,580 (74.5%) men and 2,163 (78.9%) women. Of the 3,743 patients, 1,678 (44.8%) were infected in the Netherlands, and 1,444 (38.6%) in Sub-Saharan Africa. The majority of the patients infected in the Netherlands (996, 59.4%) also originated from the Netherlands, whilst 209 (12.5%) originated from Sub-Saharan Africa, 178 (10.6%) from Suriname, and 81 (4.8%) from the Netherlands Antilles or Aruba. Of the patients who were infected in Sub-Saharan Africa, 1,319 (91.3%) were also born in Sub-Saharan Africa, whereas 109 (7.5%) originated from the Netherlands. Of the 161 patients from the Netherlands Antilles or Aruba, 73 (45.3%) were infected in their home country, as were 78 (30.0%) of the 261 patients from Suriname. More men than women of Dutch origin were infected abroad: 191 (29.1%) men compared to 72 (12.0%) women. Of these 263 patients, 72 (27.4%, 70 men) were infected in Thailand, 20 (7.6%) in Kenya, and 12 (4.6%) in Spain.

Of the 1,440 (29.6%) patients with a known HIV-1 subtype, 629 (43.7%) originated from Sub-Saharan Africa and 811 (56.3%) from other countries. The most prevalent subtype amongst patients from other countries was B (581 patients, 71.6%). Other reported subtypes were AE (59 patients, 7.3%), AG (50, 6.2%), C (38, 4.7%), A (28, 3.5%), G (18, 2.2%), D (9, 1.1%), F (9, 1.1%), and other non-B subtypes (19, 2.3%). Subtype B was found in only 15 (2.4%) patients from Sub-Saharan Africa. The most frequent subtypes other than B amongst Sub-Saharan Africans were AG (203, 32.3%), C (159, 25.3%), A (83, 13.2%), G (44, 7.0%), D (37, 5.9%), F (14, 2.2%), and other non-B subtypes (70, 11.1%).

Injecting drug users (IDU)

For 664 (4.4%) patients, including 485 (73.0%) men and 179 (27.0%) women, the reported mode of transmission was injecting drug use. The majority of these patients (395, 59.5%) were infected before 1996; only 126 (19.0%) patients were infected in or after 2000. Of the IDUs, 416 (62.7%) of the patients originated from the Netherlands, and 129 (19.4%) were born in other Western European countries. Of the 269 patients diagnosed in or after 1996, 88 (32.7%) were followed in a hospital in Amsterdam, 84 (31.2%) in another hospital in the Randstad, and 64 (23.8%) patients in the southern part of the Netherlands, in particular, Maastricht (49 patients, 18.2%).

Median CD4 counts, CD8 counts, and viral load at diagnosis were 268 (IQR, 90-504) cells/mm^3, 805 (485-1180) cells/mm^3, and 4.6 (3.9-5.1) $\log_{10}$ copies/ml, respectively. There were no differences between men

and women nor between patients of Dutch origin and patients born elsewhere. However, patients from outside the Netherlands were younger than those of Dutch origin ($p<0.001$); the age of non-Dutch patients was 34.0 (IQR, 27.5-41.0) years compared with 39.3 (35.1-43.4) years for those born in the Netherlands. An AIDS event was found in 35 (13.0%) of the diagnosed IDUs in 1996 or later, whereas 214 (79.6%) were asymptomatic at diagnosis.

The most likely country of infection was reported for 573 (86.3%) patients. The majority (486, 84.8%) were infected in the Netherlands, whereas 52 (9.1%) patients were infected in other Western European countries. Of the IDUs diagnosed from 1996 on, 12 (4.5%) patients had a recent infection, whereas 47 (17.5%) patients ever had a negative test. Subtype B was the most frequently reported HIV subtype; 154 (90.6%) of the 170 with a known subtype were infected with this strain.

Trends over time – start of cART

Amongst the 15,236 adult patients with a known year of HIV-1 diagnosis, 12,297 (80.7%) started cART (Figure 2.1). Of these patients, 2,328 (18.9%) had been treated with mono- or dual antiretroviral therapy before starting cART, whilst 9,969 (81.1%) started cART as therapy-naïve patients. For the total population, the median age at the start of cART was 38.3 (32.3-45.5) years, but the 9,608 (78.1%) men were generally older than the 2,689 (21.9%) women: men were 39.6 (33.9-46.6) years of age compared to 33.1 (28.0-39.3) years for women. The median time between diagnosis and start of cART for patients diagnosed in 1996 or later was 0.29 (IQR, 0.11-1.46) years for men and 0.23 (0.09-0.93) years for women.

The median CD4 cell count in men at the start of cART was 200 (IQR, 80-300) cells/mm^3 and the median CD8 cell count was 870 (560-1271) cells/mm^3; the median CD4 count in women at the start was 210 (100-340) cells/mm^3, and their median CD8 count was 764 (490-1110) cells/mm^3. After 24 weeks of cART, CD4 counts had increased to 320 (IQR, 190-470) cells/mm^3 in men and 344 (210-509) cells/mm^3 in women. In previously therapy-naïve patients, CD4 cell counts rose from 200 (IQR, 80-298) cells/mm^3 at start of cART to 340 (200-480) in men and from 210 (100-330) to 350 (220-510) in women. The median CD4 count increased further to 370 (IQR, 240-520) cells/mm^3 in men and 380 (260-548) in women at 48 weeks after the start of cART. After 24 weeks, CD8 counts were 950 (IQR, 680-1300) cells/mm^3 in men and 840 (610-1190) cells/mm^3 in women, whereas they were 951 (680-1310) cells/mm^3 in men and 850 (610-1180) in women after 48 weeks.

In the therapy-naïve population, median CD4 cell counts at start of cART were 200 (IQR, 90-310) cells/mm^3 in 1996, and they decreased to 180 (70-320) in 2000 ($p<0.001$). Between 2000 and 2005, CD4 cell counts were 180 (IQR, 70-284) cells/mm^3. Thereafter, CD4 counts increased to 240 (IQR, 150-305) cells/mm^3 in 2008 ($p<0.001$). Median HIV RNA levels at start of cART were 5.0 (IQR, 4.5-5.4) $\log_{10}$ copies/ml and did not change over time ($p=1.0$).

At 24 weeks, 85.5% (6,975 of 8,157) of men and 80.5% (1,801 of 2,237) of women whose RNA levels were measured reached levels below 500 copies/ml. At 48 weeks after the start of cART, these proportions were 84.1% (6,427 of 7,639) for men and 75.5% (1,557 out of 2,062) for women. For therapy-naïve patients, 90.8% of the men and 83.1% of the women had levels below 500 copies/ml at 24 weeks, whilst these levels were found for 63.1% of men and 65.8% of women in the pre-treated population ($p=0.4$ for difference between men and women).

The most frequently used first-line cART combination in 2008-2009 was tenofovir + emtricitabine + efavirenz which was prescribed in 55.4% of cases, compared to 48.3% in 2007-2008 (Table 2.2). Overall, the prescription

of tenofovir increased from 78.2% (817 cases) in 2007-2008 to 86.3% (635 cases) in 2008-2009 ($p<0.001$). Emtricitabine was part of 790 (75.6%) initial regimens in 2007-2008 and 628 (85.3%) in 2008-2009 ($p<0.001$), whereas the use of lamivudine decreased from 254 (24.3%) to 107 (14.5%) cases ($p<0.001$). Also, zidovudine was a less frequent option; 124 (11.9%) patients in 2007-2008 received it, compared to 66 (9.0%) patients in 2008-2009 ($p=0.05$).

The most frequent additions in 2008-2009 were efavirenz (468 patients, 63.6%), nevirapine (125, 17.0%), lopinavir (123, 16.7%), and atazanavir (37, 5.0%). Compared to 2007-2008, the proportion of patients using nevirapine (15.6%, $p=0.4$), lopinavir (19.9%, $p=0.09$), and atazanavir (6.7%, $p=0.1$) did not differ. The proportion of patients starting efavirenz (58.9%, $p=0.05$) was marginally smaller in 2007-2008 than in 2008-2009.

Changes in viral set-point over time

During the asymptomatic phase of HIV-1 infection, virus production and clearance are believed to reach a balance, reflecting a relatively stable level of HIV-1 RNA concentration in plasma. Whether this balance, or viral set-point, is reached in all patients remains open to debate[1,2]. It is agreed, however, that with a higher HIV-1 RNA plasma level, progression to AIDS is more frequent[3], as is the rate of HIV-1 transmission[4]. A rising trend over time in plasma HIV-1 RNA concentration at set-point might imply an increase in the efficiency of transmission[18,55]. Three observational studies found no evidence for such a change[78-80], whereas two studies did[81,82]. Contrasting results likewise come from studies of HIV-1 RNA replicative fitness at viral set-point, thought to be positively correlated with HIV-1 RNA concentration in plasma[83,84]. One study suggested a lower replicative fitness in HIV-1 isolates obtained from patients infected in 2002-2003 compared to isolates from patients infected between 1986-1999[85], but samples were not matched for time since seroconversion. A similar study, using isolates obtained from participants of the Amsterdam Cohort Study and samples matched for time since seroconversion, found an increase in replicative fitness over time [5].

Here we present a study of changes between 1984 and 2007 in the mean HIV-1 RNA concentration and CD4 cell count at viral set-point.

Patients included in the SHM database who became seropositive between 1996 and 2007 were selected. In addition participants of the Amsterdam Cohort Studies (ACS) were included. In total 612 patients with a maximum interval of one year between the last negative and first positive HIV-1 antibody test were selected. The day of seroconversion was estimated as the midpoint between the last seronegative and the first seropositive test. Patients with negative or indeterminate Western Blot results in the presence of HIV-1 p24 antigen or RNA were also selected, in which case the day of seroconversion was set one month prior to the date of the first positive antibody test. All 612 patients were male, had homosexual contact recorded as the most likely transmission route, and originated from western Europe or North America. Because disease progression has been shown to differ among patients with subtype A, C, D and G infection[86-88], we excluded patients known to be infected with a subtype other than B. In 297 patients (49%) infection with subtype B was found via nucleotide sequences of the pol region obtained for HIV-1 drug-resistance testing. The remaining 315 patients with no information on subtype were likely to be infected with subtype B and were included in all further analyses. Of 282 patients tested before antiretroviral therapy was started, 20 (7.1%) had at least one resistance mutation. CD4 cell counts were available for 578 (94%).

In all patients with seroconversion before 1996, the HIV-1 RNA concentration at set-point was measured

with assays using the nucleic acid sequence-based amplification (NASBA) technique. Overall, reverse transcription-polymerase chain reaction (RT-PCR) was the type of assay technique used most often (in 42% of the 612 total). HIV-1 RNA plasma concentrations measured at set-point were below the lower quantitation limit of the assay in 23 of 612 (4%) patients. In 17 patients (3%), HIV-1 RNA concentrations were above the upper quantitation limit of the assay.

The mean HIV-1 RNA concentration at set-point in all 612 patients was 4.54 $\log_{10}$ copies/ml. It was 4.34, 4.27, and 4.71 $\log_{10}$ copies/ml in patients with an estimated seroconversion date between 1984-1995, 1996-2002, and 2003-2007, respectively. Compared to patients with an estimated seroconversion date in or after 2003, the adjusted mean HIV-1 RNA concentration among patients seroconverting between 1996 and 2002 and before 1996 was lower by 0.41 $\log_{10}$ copies/ml (95% CI 0.27-0.67; $p<0.0001$) and 0.34 (0.17-0.51; $p<0.0001$), respectively (Table 2.4). Figure 2.4 shows the HIV-1 RNA concentration at set-point and at 12, 18, and 24 months after seroconversion as well as the estimated mean HIV-1 RNA concentration by calendar year of seroconversion. The dashed line in Figure 2.4a shows that the mean set-point HIV-1 RNA concentration at the start of 1985 was 4.46 $\log_{10}$ copies/ml (95% CI 4.27-4.65). It was 4.21 $\log_{10}$ copies/ml (4.09-4.33) at its lowest value in 1995 and 4.88 $\log_{10}$ copies/ml (4.76-5.01) in 2007.

We looked separately at plasma HIV-1 RNA levels at 12, 18, and 24 months after seroconversion and found mean HIV-1 RNA concentrations of 4.50, 4.48, and 4.40 $\log_{10}$ copies/ml, respectively. Differences in mean HIV-1 RNA concentration at 12 and 18 months according to estimated year of seroconversion were similar to those obtained through models that included the first HIV-1 RNA concentration between 9 and 27 months after seroconversion.

Our results agree with those of the Concerted Action on SeroConversion to AIDS and Death in Europe (CASCADE) study[81] and a recent study of the epidemic in Italy[82]. The CASCADE study found an increase in mean HIV-1 RNA concentration at viral set-point of 0.035 $\log_{10}$ copies/ml/year over the period 1985-2002, although our study found an increase only from 1996. Three other studies found no evidence for an increase[78-80]. Differences in patient selection, study period, and outcome definitions across these five studies might explain the discrepancies. In a study from the Swiss HIV Cohort Study (SHCS) and the Italian cohort study[79,82], all patients with a confirmed HIV-1 infection were selected. Other studies restricted patient selection to seroconverters with a maximum seroconversion interval of 6 months[80] or 12 months[78,81]. Herbeck et al.[78] looked at HIV-1 RNA concentration at set-point in 384 homosexual patients with known seroconversion dates between 1985 and 2005, but most were infected before 1996. The study period in both the study of Herbeck et al. and the SHCS[79] might have been too short to find an increase in HIV-1 RNA concentration at set-point over time. Outcome definitions of the five studies ranged from the first available measurement of HIV-1 RNA plasma concentration after seroconversion[80,81] to measurements at a later stage[78,79,82]. Because the exact moment of seroconversion is unknown, the former definition has the disadvantage of not knowing whether the measurement was taken: during the peak HIV RNA concentration phase following infection, during the phase shortly before or after the peak, or during the set-point phase. This type of measurement error most likely hampers the detection of significant changes over time. Admittedly, the use of measurements at a later stage can introduce bias, because patients who have started antiretroviral therapy early are censored from the analysis. With the assumption that patients with a high HIV-1 RNA concentration and a low CD4 cell count will start therapy earlier than patients with a lower concentration and a higher cell count,

results may be biased towards a lower HIV-1 RNA concentration and higher CD4 cell count at viral set-point from 1996 onwards, especially in measurements taken 24 months after seroconversion. Therefore, we performed a sensitivity analysis, including 751 patients with a maximum seroconversion interval of 6 months. The mean of the first HIV-1 RNA concentration taken after seroconversion was 0.48 $\log_{10}$ copies/ml (95% CI, 0.26-0.71; $p<0.0001$) lower for seroconverters before 1996 and 0.17 (0.00-0.35; $p=0.05$) lower between 1996-2002 compared to that from 2003-2007. The mean was 0.31 $\log_{10}$ copies/ml (95% CI, 0.06-0.56; $p=0.02$) lower for seroconverters before 1996 compared to that from 1996-2002. So, although these two approaches lead to different estimates, both analyses show an increasing HIV-1 RNA concentration over time.

The HIV-1 RNA plasma concentration was measured with several assays. The distribution of the assays has changed over the years, and we did not perform batch-wise re-testing of samples using only one assay. To test whether the increase in viral set-point could reflect changing use of various quantitative HIV-1 RNA assays over time, we added type of assay to the model. The differences in mean HIV-1 RNA concentration between different periods of seroconversion increased slightly (Table 2.4). Relative to seroconverters between 2003 and 2007, the mean HIV-1 RNA concentration was 0.44 $\log_{10}$ copies/ml (95% CI, 0.28-0.60; $p<0.0001$) lower for seroconverters between 1996 and 2002 and 0.55 (0.29-0.82; $p<0.0001$) lower for those seroconverting before 1996. The difference in HIV-1 RNA concentration measured with RT-PCR assays was on average -0.12 $\log_{10}$ copies/ml (95% CI, -0.30, 0.07; $p=0.21$) compared to NASBA assays and 0.04 (-0.09, 0.17; $p=0.54$) compared to branched DNA signal amplification (bDNA) assays. The HIV-1 RNA concentration was on average 0.16 $\log_{10}$ copies/ml (95% CI, -0.03, 0.35; $p=0.10$) higher when measured with the NASBA technique compared to samples tested with assays using bDNA. The same ranking has been described in the literature[89-92] and might explain the more pronounced differences after adjusting for type of assay between seroconverters from 1984-1995 and from 2003-2007. In concordance with previous reports, the mean HIV-1 RNA concentration at set-point was slightly higher when measured using assays with a lower detection limit of 1000 or 400 copies/ml compared to ≤50 copies/ml[93], but adjustment for assay sensitivity did not appreciably change our results (results not shown). The changing distribution of assays is thus unlikely to explain the increase over time in mean HIV-1 RNA concentration at viral set-point.

In samples obtained before 1996, quantitation followed storage at -80°C. No significant effect of freezing, storage, and thawing on HIV RNA recovery with use of the Amplicor HIV-1 Monitor and NASBA HIV-1 RNA QT assay has been reported[92,94,95]. Moreover, we observed an increase in mean HIV-1 RNA concentration at set-point between periods 1996-2002 and 2003-2007.

In 578 patients with CD4 cell counts available between 9 and 27 months after seroconversion, the median count at viral set-point was 530 cells/mm^3 (Interquartile range [IQR], 390-680). Table 2.5 shows results of the linear regressions of CD4 cell count at viral set-point. Mean CD4 cell count at viral set-point declined throughout the period 1984-2007 by 0.028 cube root cells/mm^3/year (95% CI, 0.014, 0.041; $p<0.0001$), a decline of approximately 5 CD4 cells/mm^3/year. The mean decrease over time at 12, 18, and 24 months after seroconversion was 0.025 (95% CI, 0.011, 0.038), 0.027 (0.013, 0.041), and 0.021 (0.004, 0.038) cubic root cells/mm^3/year, respectively. Figure 2.5 shows the estimates back-transformed to the original scale. Mean CD4 count at 12 months was 592 (562-653), 563 (523-605) and 502 cells/mm^3 (479-527) for seroconverters between 1984-1995, 1996-2002, and 2003-2007, respectively. The decreasing trend in CD4 cell count at viral set-point over time complements the increasing trend in

HIV-1 RNA concentration. A similar decrease in CD4 cell count over time was found in other studies[81,96,97]. Evidence of an increasing trend[98] or a stable level[78,99] in CD4 cell count might reflect a shorter study period.

Techniques for measuring CD4 cell counts changed over time as well, leading to less test variability. Absolute CD4 cell counts were traditionally assessed via a dual-platform technique that has been gradually replaced by a single-platform technique introduced in the late 1990s. Others changes in flow cytometry techniques over time include changes in the gating strategy and sample preparation. There is some evidence to suggest that CD4 cell counts turn out lower when measured with the single-platform technique. Also, CD45-SSC gating, more frequently used in later calendar years, may yield higher CD4 cell counts than CD45-CD14 gating, which was more often used in earlier calendar years[100]. For our study, these two potential biases may outweigh each other.

Bias through systematic inclusion of correlated transmission networks is unlikely, because active enrolment of related partners was never in place during our entire study period. The level of awareness of physicians and patients to symptoms of acute HIV-1 infection has improved in recent years and could have influenced our findings. Set-point HIV-1 RNA concentration has been shown to increase with the number of symptoms after recent HIV-1 infection[101,102]. In times when patients without symptoms were overlooked, the mean HIV-1 RNA concentration at set-point was most probably overestimated. However, since data on symptoms were not collected, we could not investigate this further.

The increasing number of patients included in our study over time positively correlated with increasing set-point viral load levels. The contribution of resulting selection of higher viral load at set-point in facilitating the spread of HIV is a cause for alarm. However, other reasons for the higher number of study patients in more recent years include increased sexual risk behavior[103,104], more HIV-negative subjects who repeatedly test for sexually transmitted infections (STIs)[104-106], and a higher incidence of STIs[107]. Also, the start in 2003 of a randomized study of patients with primary HIV-1 infection has raised physician awareness. Therefore, the higher number of new infections in recent years included in our study cannot be ascribed solely to a higher set-point viral load in those years. In addition, an ongoing phylogenetic study has found no indications that newly imported HIV-1 strains are responsible for the changes in set-point HIV RNA levels.

Some evidence suggests that HIV-1 RNA concentration at viral set-point is an adaptive trait and may change under the influence of selection[55]. Transmission of HIV-1 is thought to happen most efficiently very early, during primary infection, and late, during the symptomatic phase[4, 108]. During the asymptomatic phase after primary infection, the probability of transmission may be smaller, but given the long duration of this phase, its contribution to the number of newly infected patients is probably substantial. Successful antiretroviral therapy, usually started some years after primary infection, suppresses HIV-1 RNA plasma concentration to levels at which the probability of transmission is considered minimal. Thus, the period of infectiousness may largely be confined to the very early phase of infection, in which viruses that reproduce at a high level are selected. Such viruses could establish a high HIV-1 RNA concentration at set-point in a new host[109]. For this hypothesis to hold, set-point viral load between transmitter and recipient needs to be correlated. This correlation will be investigated in a future study, using data from transmission networks.

A significant increase in HIV-1 replication fitness over time has been described for the Amsterdam epidemic[5].

Follow-up molecular analysis should reveal which changes in the viral components are responsible for this increased replication capacity. An increase in HIV RNA concentration at set-point may be also the result of adaptation of HIV to particular HLA molecules in the population. Kawashima et al. have shown that HLA molecules associated in 1983 with slow disease progression did not protect against disease progression in Japanese patients infected between 1997-2008[110].

In conclusion, we found an increase in the HIV-1 RNA plasma concentration measured at viral set-point and a decrease in CD4 cell count in non-treated MSM from western Europe North America with a confirmed HIV-1 seroconversion during the last decade of the HIV epidemic in the Netherlands. The higher HIV-1 RNA concentration could not be attributed to changes in subtype or assay used, but it coincides with a higher proportion of treated HIV-1-infected patients. The implications of an increased HIV-1 RNA concentration at viral set-point on disease progression and on transmission dynamics require further study.

This chapter is a shortened version of a recently published paper 'Viral load levels measured at set-point have risen over the last decade of the HIV epidemic in the Netherland'[111]. Suzanne Jurriaans, Margreet Bakker, Ard van Sighem, Daniela Bezemer, Christophe Fraser, Joep Lange, Jan Prins, Ben Berkhout, and Frank de Wolf are greatly acknowledged for their contribution.

Pregnant women

Mother-to-child transmission (MTCT) is the most important route of HIV transmission amongst children[112]. As a result of improved prevention in Western countries, MTCT has been reduced dramatically in these countries[113].

In January 2004, voluntary HIV-antibody testing, in which patients are given the opportunity to opt out, was introduced in the Netherlands[114,115]. Since then, HIV has been diagnosed in a substantial proportion of infected women who were previously unaware of their HIV infection.

Here we report on the trends in the number of pregnancies and demographics in HIV-infected women in the Netherlands between 1988 and 2009.

Total number of pregnancies

By June 2009, a total of 1,121 pregnancies amongst HIV-infected women was registered in the SHM database. Additional pregnancy-related data were available for 1,055 of the pregnancies. Only the pregnancies with available additional data were included in the analyses.

Out of the 3,146 women who are followed in the SHM database, 797 became pregnant, with a total number of 1,055 pregnancies. After being diagnosed with HIV, 186 women became pregnant for a second time. Data for only 18 pregnancies were collected in 2008 (Table 2.6). In total, 84 pregnancies were reported in 2008, but the data collection for 66 pregnancies is not yet complete, as the term date of these pregnancies was after December 31, 2008.

Demographics

The demographics of the HIV-infected women with a registered pregnancy are presented in Table 2.6. Age at first pregnancy did not change over time. Dutch women were significantly older when they became pregnant compared to non-Dutch women. Most women were infected with HIV through heterosexual contact. Region of origin was Sub-Saharan Africa for most women, and 15% of the women were born in the Netherlands. In 816 pregnancies a baby was delivered; 21% of pregnancies resulted in an abortion (induced or spontaneous).

Before the availability of combination antiretroviral therapy (cART), the proportion of induced abortion amongst HIV-infected women was much higher[116]. Awareness of the HIV infection in combination with the improvement of MTCT prevention has resulted in a reduced proportion of induced abortion[117]. The mode of delivery was available for 800 pregnancies;

466 babies were delivered vaginally, and 334 were delivered by caesarean delivery. Elective caesarean delivery is known to reduce the risk of MTCT in the event of a detectable maternal viral load. The benefit of an elective caesarean delivery has been questioned[118, 119] when an undetectable maternal viral load is achieved as a result of successful treatment with cART.

Incidence of pregnancy and geographic origin of the mothers

Overall, the incidence of pregnancy amongst women aged between 16 and 45 years was 43 pregnancies per 1000 PY (95% confidence interval [CI], 40-46). The incidences in the total group of women and in groups according to geographic origin are presented in Figure 2.6. In the total group, the incidence increased from 25 (95% CI, 15-39) in 1998 to 74 (95% CI, 61-87) in 2003 and then declined to 22 (95% CI, 17-29) in 2007. The incidence was higher amongst women originating from Sub-Saharan Africa, but it declined from 60 (95% CI, 31-104) in 1998 to 28 (95% CI, 19-40) in 2007. Amongst Dutch women, a small increase in the number of pregnancies was observed, from 18 (95% CI, 7-39) in 1998 to 45 (28-69) in 2003 and then decreased to 19 (9-34) in 2007.

Although most pregnancies occur amongst women originating from sub-Saharan Africa, the number of pregnancies in this group is declining. This decrease might be a result of the drop since 2003 in newly diagnosed heterosexually infected patients from Sub-Saharan countries. The women in the group from sub-Saharan countries who are currently in follow-up are ageing, with the occurrence of fewer pregnancies. These differences in the incidence of pregnancies between women of different geographic origins have been found previously, and incidence rates of pregnancy have been reported to be higher amongst women originating from Africa [120]. The decision to become pregnant while HIV-infected has been found to be socially and culturally related [116]. Higher incidence rates of pregnancy amongst women originating from Sub-Saharan Africa can be largely explained by the characteristics of the HIV epidemic in the Netherlands. A substantial proportion of the heterosexually infected individuals are women from sub-Saharan African countries in whom HIV is diagnosed for the first time as part of the prenatal screening program in the Netherlands.

HIV-infected children and adolescents

All HIV-infected children in the Netherlands are followed in one of the four specially designated paediatric HIV treatment centres. In this report we divided the HIV population aged below 18 years at time of HIV diagnosis into children and adolescents. The term 'children' refers to all individuals younger than 13 years of age at the time of HIV diagnosis, and 'adolescents' refers to individuals aged from 13 to 18 years at the time HIV was diagnosed. In addition to the routinely collected data for the children and adolescents, information on the region of origin of the parents was available. We described the demographic and clinical characteristics of the HIV-infected children and adolescents.

As of 1 June 2009, 208 children and 158 adolescents had been diagnosed with HIV (Table 2.7). The median age at diagnosis was 2.6 years (interquartile range [IQR], 0.7-6.3) for children and 17.1 years (16.1-17.6) for adolescents. Amongst the children, gender was equally distributed, whereas the majority of adolescents were girls. The higher proportion of girls in the group of adolescents might have resulted from HIV screening amongst pregnant women, in which the infection in women is detected earlier in its course. In total, 25 adolescents became pregnant for the first time before the age of 18 years. The median age at the start of the pregnancy was 17 years (IQR, 16-17). In 15 women, the HIV infection was diagnosed during the pregnancy. Although 22 out of 25 of these women became pregnant before the introduction of the national pregnancy screening[114,115], it is likely that these women were tested

for HIV because of their pregnancy. Twenty-three women originated from Sub-Saharan Africa, where the infection is highly endemic; the other women were from Latin America and Western Europe.

The main route of transmission was mother-to-child transmission (MTCT) for the children, and for adolescents it was transmission through heterosexual contact. 65% of the adolescents infected by heterosexual contact were girls born in Sub-Saharan Africa. Worldwide, 45% of the new HIV infections each year are amongst individuals aged 15 to 24 years[112]. In particular, young women are infected with HIV; of the young HIV-infected individuals in Sub-Saharan Africa, 76% are women[121]. The majority of HIV-infected adolescents living in the Netherlands are women originating from Sub-Saharan Africa, and this probably reflects the HIV epidemic in Sub-Saharan Africa.

However, the majority of children were born in the Netherlands; 167 out of the 208 were born before 1 January 2004 and thus before the national HIV screening amongst pregnant women was implemented[114, 115]. Of those born in the Netherlands, 50% had at least one parent who originated from Sub-Saharan Africa. Only two adolescents had parents who both originated from the Netherlands. Most children and adolescents were diagnosed with HIV after 2000.
A large proportion of the children and adolescents became lost to follow-up. Of the three children who died, one died at the age of 12 years, the two older children were aged more than 18 years at time of death. Although 8 adolescents died, 1 died before reaching the age of 18 years.

The rate of MTCT in the Netherlands has strongly declined over time (Figure 2.7). This decline is likely to be a result of the HIV screening amongst pregnant women in the Netherlands, which was introduced in January 2004. However, 3 children who were born with HIV in the Netherlands after January 2004 have been reported to the SHM. The mothers of the 2 children born in 2004 were not included in the national pregnancy screening because they became pregnant before 1 January 2004. The mother of the HIV-infected child born in 2005 had a negative result on the pregnancy screening test and was probably infected with HIV during her pregnancy. It is to be expected that the number of HIV-infected children infected by MTCT will stay close to zero as a result of the ongoing testing policy amongst pregnant women.

Elite controllers and long-term non-progressors

Median time from HIV-1 infection to death in untreated patients is estimated to be approximately 10-12 years[122-124]. However, there is considerable variation in survival time between patients. A small number of patients remain asymptomatic for many years and maintain high CD4 cell counts, low plasma HIV RNA levels without antiretroviral therapy, or both. Patients able to maintain high CD4 cell counts have been called 'long-term non-progressors' (LTNP), whilst those with low viral loads have been called 'HIV controllers' or 'elite controllers'. These patient groups may provide useful information on the underlying mechanisms of protection against disease progression and may contribute to the development of new vaccines and drugs. In this chapter we examine the prevalence and characteristics of HIV controllers and LTNP among patients with HIV-1 who were alive and in follow-up as of 1st June 2009.

In the literature, definitions of HIV controllers, elite controllers, and LTNP vary. Different cut-offs and lengths of follow-up have been used[125]. The definition used in this chapter is described in Figure 2.8 and follows mainly the definitions by Grabar et al[126]. Amongst the 15,602 adult patients with a known HIV-1 diagnosis, there were 11,795 patients in follow-up on June 1st

2009. Of these, 4,890 (41.5%) had been infected for at least 8 years, and at least 3 plasma viral load (pVL) measurements, obtained during the last 5 years of follow-up, were available for 4,729 (96.7%). Of those 4,729 patients, 1893 (40.0%) were asymptomatic; of the 1,893, 110 (5.8%) were antiretroviral therapy-naïve as of 1st June 2009. A group of 12 HIV controllers that included 8 elite controllers was selected (0.25% and 0.17% of the 4,729 patients, respectively), and there were 25 long-term non-progressors (LTNP) (0.53%) and 7 elite LTNP (0.15%). This confirms that the HIV controller and LTNP phenotypes are rare. Estimates of other studies are difficult to compare because of differences in definitions, denominators, or both. The prevalence of LTNP and elite LTNP in the study by Grabar et al. was 0.4% and 0.05%, respectively[126], which was similar to our prevalence.

Characteristics of these patients are shown in Table 2.8. Median age at HIV diagnosis in all groups ranged between 33.6 and 35.7 years. The percentage of patients infected through heterosexual contact was 24% amongst LTNP and 50% amongst HIV controllers. This compares to 26% in elite controllers continuously on cART.

Five patients were both HIV controllers and LTNP. The percentage of overlap was thus 42% amongst the 12 HIV controllers and 20% amongst the 25 LTNP. Only 2 patients were both elite controllers and elite LTNP. The percentage of overlap was thus 25% amongst the 8 elite controllers and 29% amongst the 7 elite LTNP. Viral load levels in most plasma samples were measured by assays with a lower detection limit of 50 copies/ml. Using a single copy assay, Dinoso et al. found no evidence that the level of viraemia was different between elite controllers (64% of samples were <1 copy/ml) and patients who had consistently <50 copies/ml for at least 6 months with cART (40% of samples were <1 copy/ml)[127].

By definition, the median nadir CD4 cell count was higher in LTNP (600 cells/mm^3) and elite LTNP (690 cells/mm^3) compared to HIV controllers (445 cells/mm^3), elite controllers (555 cells/mm^3), and elite controllers on cART (238 cells/mm^3). The median current CD4 cell count for elite controllers on cART was 690 cells/mm^3, and it was lower than in elite controllers not using cART, LTNP, and elite LTNP but higher than in HIV controllers (620 cells/mm^3). Another study has shown that, even amongst patients with plasma HIV RNA concentration <50 copies/ml, patients with a higher level of residual viraemia had a higher probability of absolute CD4 cell count decline[128]. Our finding that elite controllers not on cART have higher nadir and current CD4 cell counts compared to HIV controllers concurs with this result. The CD4/CD8 ratio was highest in the elite controller group, being 1.17 compared to approximately 0.80 in all other groups.

Patient selection in our study and in others is strict. The inclusion criterion that patients must be infected for at least 8 years excludes a number of patients more recently diagnosed. For basic science research that studies a few patients in-depth, it would be appropriate to use the most stringent case definition. On the other hand, in epidemiological studies, a less stringent case definition might be more appropriate. These studies usually require a large number of patients to have enough power to detect a significant association between a particular variable and HIV control or long-term non-progression. The disadvantage of having a less stringent definition of HIV control is that it could introduce some form of misclassification that might cause bias in the effect estimates, usually towards zero effect. Therefore, there is a trade-off between the power to detect an association and a precise definition of the phenotype HIV controller.

Will HIV controllers or long-term non-progressors not ever experience any adverse effects of HIV infection,

or are they just the tail of the distribution of patients with different rates of disease progression? Given that extremely sensitive viral load assays can detect low-level viraemia in most elite controllers[127,128] and given that in most patients, even after a prolonged period of viral suppression, viraemia returns, the latter seems more plausible[129].

Ageing of the population

As shown in Figure 2.2, the HIV-infected population in the Netherlands, as well as in other Western countries, is ageing. Two major causes underlying this ageing process can be identified. First, the life expectancy of HIV-infected patients has increased considerably with the advent of adequate antiretroviral treatment. As a result, HIV has changed from an inevitably fatal disease into a serious chronic infection. The other driving force behind the ageing of the population is the increasing age at which patients are diagnosed with HIV. Of the 12,258 patients in follow-up as of 1 June 2009, 3,469 (28.3%) were 50 years of age or older; of these, 3,075 (88.6%) were men and 394 (11.4%) women. The majority of the patients, 2,220 (64.0%), were infected via homosexual contact, whilst heterosexual contact accounted for 809 (23.3%) of the infections, including 494 (14.2%) men and 315 (9.1%) women. For 118 (3.4%) patients, the reported mode of transmission was injecting drug use, whilst for 263 (7.6%) patients the mode of transmission was unknown. In total, 59 (1.7%) patients were infected via contact with infected blood or blood products, including a group of haemophiliacs who were infected in the early 1980's.

Almost three-quarters of the elderly patients, 74.5% (2,576), originated from the Netherlands; homosexual men comprised 84.0% (1,859) of the patients. Of the heterosexually infected patients, 430 (53.2%) originated from the Netherlands, whilst 147 (18.2%) were of Sub-Saharan African origin, and 118 (14.6%) patients were born in Suriname or the Netherlands Antilles. Generally, older patients had been infected with HIV for years; 1,659 (47.8%) of them were diagnosed more than 10 years ago.

For 2,742 (79.0%) patients 50 years of age or older, the most likely country of infection was known. Of the 2,220 homosexual men, 1,677 (75.5%) were infected in the Netherlands, whilst for 409 (18.4%) patients the country of infection was unknown. Amongst the heterosexual patients originating from Sub-Saharan Africa, 75 (51.0%) were also infected in Sub-Saharan Africa, whilst 27 (18.4%) were infected in the Netherlands. The majority (275 patients, 64.0%) of the 430 Dutch heterosexual patients were infected in the Netherlands, 43 (10.0%) were infected in Sub-Saharan Africa, 61 (14.2%) in unknown countries, and 32 (7.4%), all of them men, in Southeast Asia, in particular Thailand.

Although more and more HIV-infected patients are being diagnosed earlier in their infection, as illustrated by the growing proportion of recent infections and increasing CD4 cell counts at diagnosis, there is still a large group of patients that present late in their infection. Of the patients diagnosed in 1996 or later, 38.7% of the homosexual men and 50.6% of the heterosexual men and women who were 50 years or older at diagnosis were diagnosed with CD4 cell counts below 200 cells/mm^3, compared with proportions of 25.5% and 40.8%, respectively, for patients younger than 50 years of age at diagnosis. Also, 24.1% of the older patients had AIDS-related symptoms at diagnosis, compared to 14.2% of the younger patients.

As of 2015, the group of patients above 50 years of age or more will have doubled in size to approximately 7,500 patients, which will be 41% of the total HIV-infected population in clinical care at that time[1]. Such a doubling in population size might be expected to put a substantial strain on HIV health care in the Netherlands. Due to the presence of non-HIV-related

age-related co-morbidities, treatment of HIV infection in older patients is likely to be different and more complicated than in younger patients. The total costs of HIV treatment are expected to soar from 110 million euro annually at present to 230 million in 2015. This may sound like an enormous sum of money, but it is only a fraction of the 74 billion euro that was spent on health care in 2007. In addition, well-treated HIV-infected patients can participate normally in social and economic life.

Table 2.1: Characteristics of the adult HIV-infected population in follow-up as of 1 June 2009.

	Men (N=9709, 79.2%)		Women (N=2549, 20.8%)		Total (N=12,258)	
	N	%	N	%	N	%
Transmission						
MSM *)	6953	71.6	-	-	6953	56.7
heterosexual	1610	16.6	2262	88.7	3872	31.6
IDU **)	242	2.5	93	3.6	335	2.7
blood (products)	102	1.1	67	2.6	169	1.4
vertical	9	0.1	8	0.3	17	0.1
other/unknown	793	8.2	119	4.7	912	7.4
Age category (years)						
18-24	167	1.7	131	5.1	298	2.4
25-34	1242	12.8	669	26.2	1911	15.6
35-44	3288	33.9	1005	39.4	4293	35.0
45-54	3224	33.2	534	20.9	3758	30.7
55-64	1408	14.5	152	6.0	1560	12.7
≥65	380	3.9	58	2.3	438	3.6
Region of origin						
the Netherlands	6482	66.8	709	27.8	7191	58.7
Sub-Saharan Africa	784	8.1	1123	44.1	1907	15.6
Western Europe	636	6.6	114	4.5	750	6.1
Latin America	675	7.0	224	8.8	899	7.3
Caribbean	324	3.3	137	5.4	461	3.8
Years aware of HIV infection						
<1	623	6.4	102	4.0	725	5.9
1-2	1590	16.4	359	14.1	1949	15.9
3-4	1443	14.9	394	15.5	1837	15.0
5-10	2516	25.9	898	35.2	3414	27.9
>10	3259	33.6	743	29.1	4002	32.6
Unknown	278	2.9	53	2.1	331	2.7

*) MSM: men having sex with men; **) IDU: injecting drug use

Table 2.2: Overview of the most frequently used cART regimens in the entire treated population as of 1 June 2009 and as of 1 June 2008 and in the population starting cART between 1 June 2008 and 31 May 2009 and between 1 June 2007 and 31 May 2008. Regimens including TDF and FTC are more frequently used with a combination of TDF+FTC+EFV being used in 22.3% of the treated population and in 55.4% of the population starting cART.

	1 June 2009 (N=9757)		1 June 2008 (N=9017)	
cART in the entire population	N	%	N	%
TDF+FTC+EFV	2174	22.3	1465	16.2
TDF+FTC+NVP	990	10.1	766	8.5
AZT+3TC+NVP	551	5.6	616	6.8
TDF+FTC+ATV/r	502	5.1	403	4.5
TDF+3TC+NVP	483	5.0	528	5.9
none	436	4.5	526	5.8
TDF+FTC+LOP/r	398	4.1	336	3.7
AZT+3TC+LOP/r	370	3.8	359	4.0
ABC+3TC+NVP	331	3.4	297	3.3
AZT+3TC+ABC	314	3.2	384	4.3
	2008-2009 (N=736)		**2007-2008 (N=1045)**	
first-line cART	N	%	N	%
TDF+FTC+EFV	408	55.4	505	48.3
TDF+FTC+NVP	99	13.5	114	10.9
AZT+3TC+LOP/r	43	5.8	61	5.8
TDF+FTC+LOP/r	33	4.5	84	8.0
TDF+FTC+EFV+LOP/r	30	4.1	21	2.0
TDF+FTC+ATV/r	29	3.9	50	4.8
ABC+3TC+NVP	12	1.6	15	1.4
ABC+3TC+EFV	9	1.2	56	5.4
AZT+3TC+SAQ/r	9	1.2	10	1.0
ABC+3TC+LOP/r	8	1.1	18	1.7

cART: combination antiretroviral therapy; AZT: zidovudine; 3TC: lamivudine; NVP: nevirapine; TDF: tenofovir; FTC: emtricitabine; EFV: efavirenz; ABC: abacavir; LOP/r: lopinavir (ritonavir-boosted); ATV/r: atazanavir (ritonavir-boosted); SAQ/r: saquinavir (ritonavir-boosted).

Table 2.3: Annual number of diagnoses since 1996 amongst adult HIV-1-infected patients stratified by gender and transmission risk group.

	MSM*	Heterosexual		Injecting drug use		Blood (products)		Other/unknown		Total
Year of diagnosis	**Men**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	**Men**	**Women**	
1996	371	85	78	35	13	3	3	41	5	634
1997	426	107	124	41	8	7	3	47	8	771
1998	321	101	111	20	3	6	6	29	9	606
1999	337	103	134	17	6	7	4	29	5	642
2000	352	154	185	14	3	3	3	37	8	759
2001	425	161	211	13	6	7	2	48	7	880
2002	454	156	249	14	2	11	7	61	5	959
2003	444	174	261	17	4	8	3	65	14	990
2004	554	182	248	9	3	4	3	76	10	1089
2005	605	187	245	13	3	3	3	66	11	1136
2006	604	152	178	7	5	4	5	56	6	1017
2007	716	137	188	6	3	2	6	50	6	1114
2008	710	132	142	3	0	4	2	42	6	1041
2009	97	31	18	1	0	0	0	8	2	157
Total	**6416**	**1862**	**2372**	**210**	**59**	**69**	**50**	**655**	**102**	**11795**

*) MSM: men having sex with men

Table 2.4: Mean (95% CI) differences in HIV-1 RNA concentration at viral set-point (log_{10} copies/ml) according to time of seroconversion. We used the HIV-1 RNA concentration measured in peripheral blood sampled earliest in the 9-27 months after seroconversion as the measurements at viral set-point. In addition, we selected results of the HIV-1 RNA measurements taken between 9 and 15 months (closest to 12), between 15 and 21 months (closest to 18), and between 21 and 27 months (closest to 24). Any measurements taken after the start of antiretroviral therapy were not used in any analysis.

Assays were classified according to the amplification technique: nucleic acid sequence-based amplification (NASBA), reverse transcriptase-polymerase chain reaction (RT-PCR), and branched DNA signal amplification (bDNA). Assays using the NASBA technique were NASBA HIV-1 RNA QT, NucliSens HIV-1 RNA QT, and NucliSens EasyQ (bioMérieux, Boxtel, The Netherlands). Assays using RT-PCR techniques were Amplicor HIV-1 Monitor, Cobas Amplicor, Cobas TaqMan HIV-1 (Roche Diagnostics, Pleasanton, CA, USA), LCx HIV RNA quantitative, and m2000rt HIV RNA (Abbott, Abbott Park, IL, USA). The only assay using the bDNA technique was Versant HIV-1 RNA version 3.0 (Siemens, Deerfield, IL, USA). Finally, HIV-1 RNA assays were also classified as standard (having a lower detection limit of 1000 or 400 copies/ml) and sensitive (having a lower detection limit ≤50 copies/ml).

Parametric survival regression models with a normal error distribution were used to model plasma HIV-1 RNA concentration at set-point. When below the limit of detection, the value was regarded as interval-censored between 1 copy/ml and the lower detection limit. Values above the upper detection limit were right-censored at the upper detection limit.

	Plasma HIV-1 RNA concentration	**First 9-27 months after seroconversion**[b]	**at 12 months**	**at 18 months**	**at 24 months**
	N	612	552	370	315
Unadjusted model	**Year of seroconversion**				
	2003-2007 (reference)	0.00	0.00	0.00	0.00
	1996-2002	-0.44 (-0.59, -0.29)	-0.45 (-0.61, -0.29)	-0.35 (-0.54, -0.15)	-0.39 (-0.62, -0.16)
		p<0.0001	p<0.0001	p=0.0005	p=0.0008
	1984-1995	-0.37 (-0.54, -0.20)	-0.37 (-0.54, -0.20)	-0.38 (-0.61, -0.15)	-0.32 (-0.54, -0.10)
		p<0.0001	p<0.0001	p=0.001	p=0.008
Adjusted model	**Year of seroconversion**				
	2003-2007 (reference)	0.00	0.00	0.00	0.00
	1996-2002	-0.41 (-0.67, -0.27)	-0.42 (-0.58, -0.26)	-0.33 (-0.53, -0.13)	-0.39 (-0.62, -0.16)
		p<0.0001	p<0.0001	p=0.001	p=0.0008
	1984-1995	-0.34 (-0.51, -0.17)	-0.34 (-0.51, -0.17)	-0.37 (-0.60, -0.13)	-0.32 (-0.54, -0.10)
		p<0.0001	p<0.0001	p=0.002	p=0.005
Adjusted model also including type of assay	**Year of seroconversion**				
	2003-2007 (reference)	0.00	0.00	0.00	0.00
	1996-2002	-0.44 (-0.60, -0.28)	-0.46 (-0.62, -0.29)	-0.34 (-0.54, -0.13)	-0.37 (-0.61, -0.13)
		p<0.0001	p<0.0001	p=0.001	p=0.003
	1984-1995	-0.55 (-0.82, -0.29)	-0.60 (-0.87, -0.32)	-0.40 (-0.76, -0.03)	-0.32 (-0.74, 0.11)
		p<0.0001	p<0.0001	p=0.03	p=0.14

[b] There were no significant differences in mean HIV-1 RNA concentration according to age at seroconversion (p=0.43), HIV transmission group (p=0.95), interval between seroconversion and viral set-point (p=0.96), or presence of a resistance mutation (p=0.92).

Table 2.5: Changes (95% CI) in CD4 cell count at viral set-point using different models modeled using linear regression models. CD4 cell counts were cube root-transformed to apply better to model assumptions. We used the CD4 cell count measured in peripheral blood sampled earliest in the 9-27 months after seroconversion as the measurements at viral set-point. In addition, we selected results of the CD4 cell count measurements taken between 9 and 15 months (closest to 12), between 15 and 21 months (closest to 18), and between 21 and 27 months (closest to 24). measurements taken between 9 and 15 months (closest to 12), between 15 and 21 months (closest to 18), and between 21 and 27 months (closest to 24).

CD4 cell count	first 9-27 months after seroconversion[b]	at 12 months	at 18 months	at 24 months
N	578	555	439	347
Median CD4 cell count (cells/mm^3)	530	530	490	480
Change in CD4 cell count at viral set-point	-0.028 (-0.041, -0.014)	-0.025 (-0.038, -0.011)	-0.027 (-0.041, -0.013)	-0.021 (-0.038, -0.004)
(cubic cells/mm^3/year)	p<0.0001	p=0.0004	p=0.0002	p=0.02
Difference in mean CD4 cell count				
(cube root cells/mm^3) **2003-2007** (reference)	0.00	0.00	0.00	0.00
1996-2002	0.31 (0.08, 0.54)	0.31 (0.07, 0.54)	0.50 (0.25, 0.76)	0.27 (-0.05, 0.59)
	p=0.008	p=0.01	p<0.0001	p=0.10
1984-1996	0.51 (0.26, 0.76)	0.45 (0.20, 0.70)	0.49 (0.24, 0.74)	0.35 (0.05-0.65)
	p<0.0001	p=0.0004	p=0.0001	p=0.02

[b] Adjusted for age at seroconversion, interval between seroconversion and viral set-point, and presence of a resistance mutation.

Table 2.6: Demographic characteristics of HIV-infected pregnant women, 1 January 1988 and 1 June 2009.

		Total women	pregnancies
Number(%)		797	1055
Known HIV infection before pregnancy(%)		397 (50%)	
Number of pregnancies after HIV diagnosis	1		797
	2		186
	3		49
	4		15
	5		5
	6		2
	7		1
Age at start of first pregnancy occurring in HIV infection	Years (Median (IQR*)	28 (24-33)	
Transmission route	- Heterosexual (%)	744 (93%)	
	- Other (%)	53 (7%)	
Region of origin	- Netherlands (%)	116 (15%)	
	- Sub Saharan Africa (%)	483 (61%)	
	- Latin America/ Caribbean (%)	113 (14%)	
	- Other (%)	85 (11%)	
Pregnancy outcome	- Partus (%)		816(77)
	- Abortion (%)		222 (21)
	- Unknown (%)		17 (2)
Mode of delivery pregnancy	- Vaginal delivery (%)		466 (44)
	- Caesarean delivery (%)		334 (32)
	- Unknown (%)		255 (24)
Number of pregnancies per calendar year:			
1988-1997			79 (7)
1998-1999			70 (7)
2000-2001			150 (14)
2002-2003			234 (22)
2004-2005			301 (29)
2006-2007			203 (19)
2008-2009			18** (2)

*) IQR: Interquartile range **) Data collection for calendar year 2008 not yet completed, data of 66 pregnancies not collected as the terme date after 31 December 2008.

Table 2.7: Demographic characteristics of HIV-1-infected children (age 0-12 years at time of HIV diagnosis) and adolescents (age 13-17 years at time of HIV diagnosis) ever in follow-up until 1 June 2009 in the SHM observational cohort.

Demographic Characteristics at diagnosis	Children N(%)	Adolescents N(%)
Total	208	158
Gender		
- boy	119 (57)	51 (32)
- girl	89 (43)	107 (68)
Route of transmission:		
- MTCT	173 (83)	3(2)
- Blood contact	22 (11)	14 (9)
- Unknown	12 (6)	10 (6)
- heterosexual contact	1(0.5)	112 (71)
- homosexual contact	0	13 (8)
Region of origin:		
- the Netherlands	111 (53)	35 (22)
- Western Europe	5 (2)	4 (3)
- Latin America/Caribbean	9 (4)	9 (6)
- Sub-Saharan Africa	73 (35)	102 (65)
- Other	10 (5)	8 (5)
Region of parents:		
- both the Netherlands	11 (5)	2 (1)
- one or both Sub-Saharan Africa	128 (61)	24 (15)
- one or both other region or unknown	69 (33)	132 (84)
Year at HIV diagnosis		
- <1998	70 (34)	34 (22)
- 1998-2000	24 (12)	13 (8)
- 2000-2003	49 (24)	73 (46)
- >2003	58 (28)	30 (19)
- missing	7 (3)	8 (5)
Age at diagnosis		
≤ 2 years of age	89 (43)	0
> 2 years of age	119 (57)	158 (100)
Lost to follow up	31 (15)	58 (37)
Deaths	3 (1)	8 (5)

Table 2.8: Characteristics of different groups of asymptomatic patients. The characteristics of a group of 696 patients who had started combination antiretroviral therapy (cART) before 1st June 2002, had been on continuous cART until 1st June 2009 (a gap of 14 days was allowed), and matched the definition of elite controllers (except that they were on therapy) is shown as a comparison group (elite controller on continuous cART).

LTNP: long-term non-progressors;

IDU: injecting drug users

	LTNP 500	Elite LTNP	HIV controller	Elite controller	Elite controller on continuous cART
Total	25	7	12	8	696
Gender					
Male	19	5	7	5	596
Female	6	2	5	3	100
Transmission risk group					
Homosexual	17	5	3	3	461
Heterosexual	6	2	6	3	182
IDU			1	1	19
Other	2		2	1	34
Region of origin					
W-Europe/N-America	4	2	2	2	78
The Netherlands	17	5	8	5	449
Sub-Saharan Africa	2		1	1	69
Southeast Asia					26
Caribbean/S-America	2		1		54
Other					20
Age at HIV diagnosis	33.6 (28.9-38.6)	35.5 (20.1-40.1)	35.4 (31.1-40.0)	35.7 (31.1-44.0)	34.9 (29.8-41.9)
Years since HIV diagnosis	11.3 9.9-13.9)	10.5 (9.1-11.3)	11.5 (9.3-13.2)	11.5 (9.7-12.6)	12.0 (10.1-14.9)
Age on 1st June 2009	46.8 (39.9-50.5)	46.8 (38.7-50.0)	47.8 (44.5-54.3)	47.8 (43.0-54.6)	48.1 (43.3-54.9)
Nadir CD4 (cells/mm^3)	600 (540-690)	690 (660-757)	445 (340-625)	555 (360-770)	238 (150-335)
Highest pVL (copies/ml)	2856 (1000-45600)	1135 (674-14000)	587 (410-1150)	587 (450-2400)	68100 (15500-1900000)
Current CD4 cell count	750 (640-1000)	757 (730-1110	620 (480-935)	775 (580-1045)	690 (510-910)
Current CD8 cell count	985 (860-1490)	940 (860-1510	860 (580-1040)	780 (470-910)	830 (590-1130)
Current CD4/CD8 ratio	0.80 (0.50-1.02)	0.80 (0.50-0.90	0.82 (0.33-1.26)	1.17 (0.54-1.29)	0.83 (0.60-1.14)

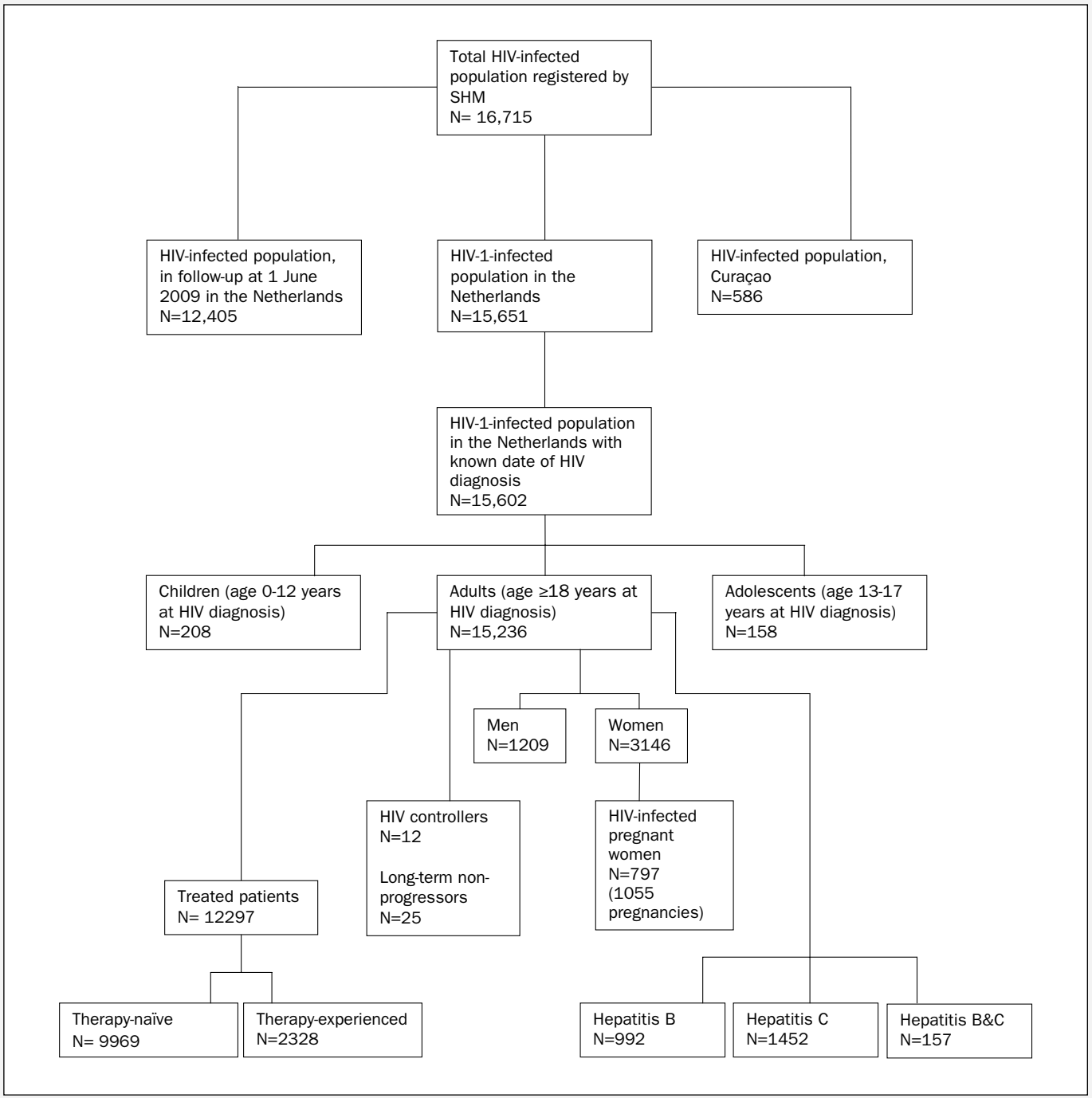


Figure 2.1: Overview of the HIV-infected population as registered by the Stichting HIV Monitoring (SHM).

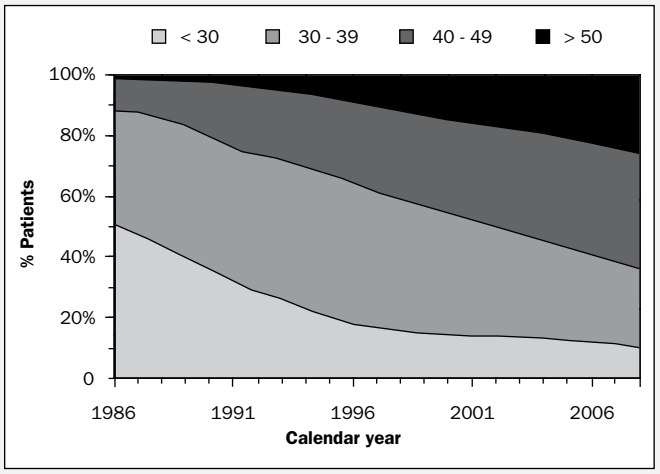


Figure 2.2: Proportion of patients in follow-up as of 1 June of each calendar year who were <30 years of age, 30 to 40 years, 40 to 50 years, or 50 years or older. In 1986, 50.3% of the patients in follow-up were younger than 30 years of age, whereas 0.9% were 50 years or older. As of 2009, these proportions had changed to 9.6% and 28.0%, respectively.

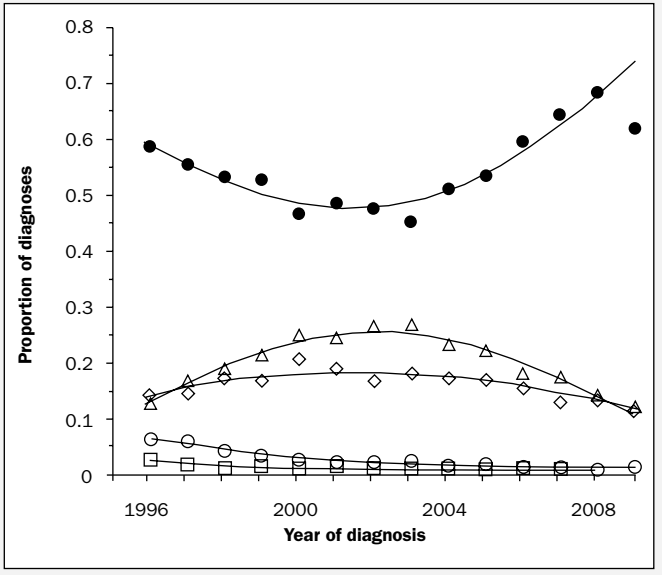


Figure 2.3: . The annual proportion of MSM (dots) in the annual tally decreased from 58.5% in 1996 to a nadir of 44.8% in 2003; thereafter, it increased to 68.2% in 2008. The proportion of heterosexual men (diamonds) increased from 13.4% in 1996 to 17.6% in 2003 and decreased thereafter to 12.7% in 2008. Heterosexual women (triangles) displayed a similar, although more pronounced, behaviour: 12.3% in 1996, 26.4% in 2003, and a decrease to 13.6% in 2008. The proportion of injecting drug users (circles: men; squares: women) decreased to almost 0% in 2008. Lines represent a Poisson regression model quadratic in time.

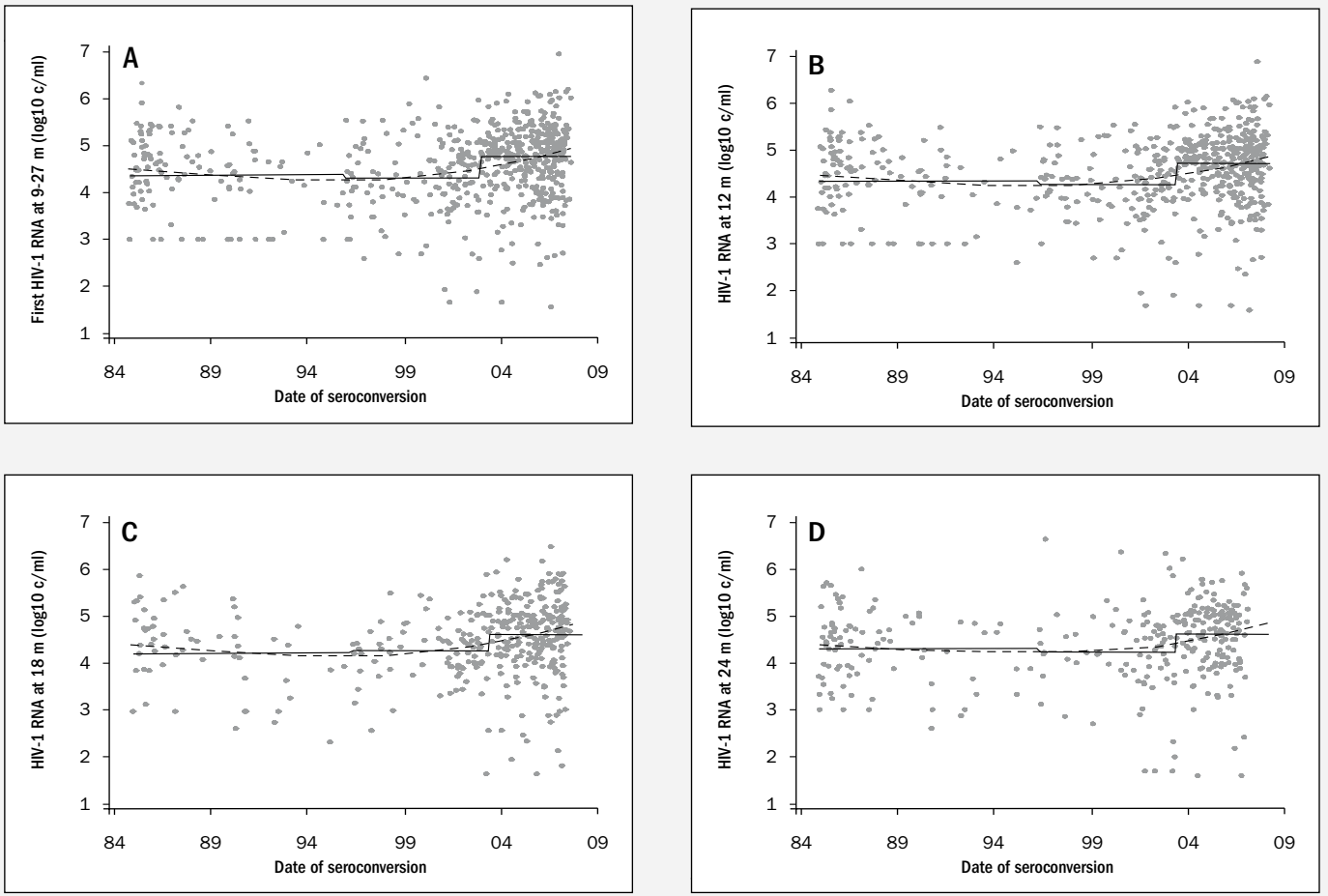


Figure 2.4: Mean (95% CI) differences in HIV-1 RNA concentration at viral set-point (log_{10} copies/ml) according to time of seroconversion. We used the HIV-1 RNA concentration measured in peripheral blood sampled earliest in the 9-27 months after seroconversion as the measurements at viral set-point. In addition, we selected results of the HIV-1 RNA measurements taken between 9 and 15 months (closest to 12), between 15 and 21 months (closest to 18), and between 21 and 27 months (closest to 24). Any measurements taken after the start of antiretroviral therapy were not used in any analysis.

Assays were classified according to the amplification technique: nucleic acid sequence-based amplification (NASBA), reverse transcriptase-polymerase chain reaction (RT-PCR), and branched DNA signal amplification (bDNA). Assays using the NASBA technique were NASBA HIV-1 RNA QT, NucliSens HIV-1 RNA QT, and NucliSens EasyQ (bioMérieux, Boxtel, The Netherlands). Assays using RT-PCR techniques were Amplicor HIV-1 Monitor, Cobas Amplicor, Cobas TaqMan HIV-1 (Roche Diagnostics, Pleasanton, CA, USA), LCx HIV RNA quantitative, and m2000rt HIV RNA (Abbott, Abbott Park, IL, USA). The only assay using the bDNA technique was Versant HIV-1 RNA version 3.0 (Siemens, Deerfield, IL, USA). Finally, HIV-1 RNA assays were also classified as standard (having a lower detection limit of 1000 or 400 copies/ml) and sensitive (having a lower detection limit ≤50 copies/ml).

Parametric survival regression models with a normal error distribution were used to model plasma HIV-1 RNA concentration at set-point. When below the limit of detection, the value was regarded as interval-censored between 1 copy/ml and the lower detection limit. Values above the upper detection limit were right-censored at the upper detection limit.

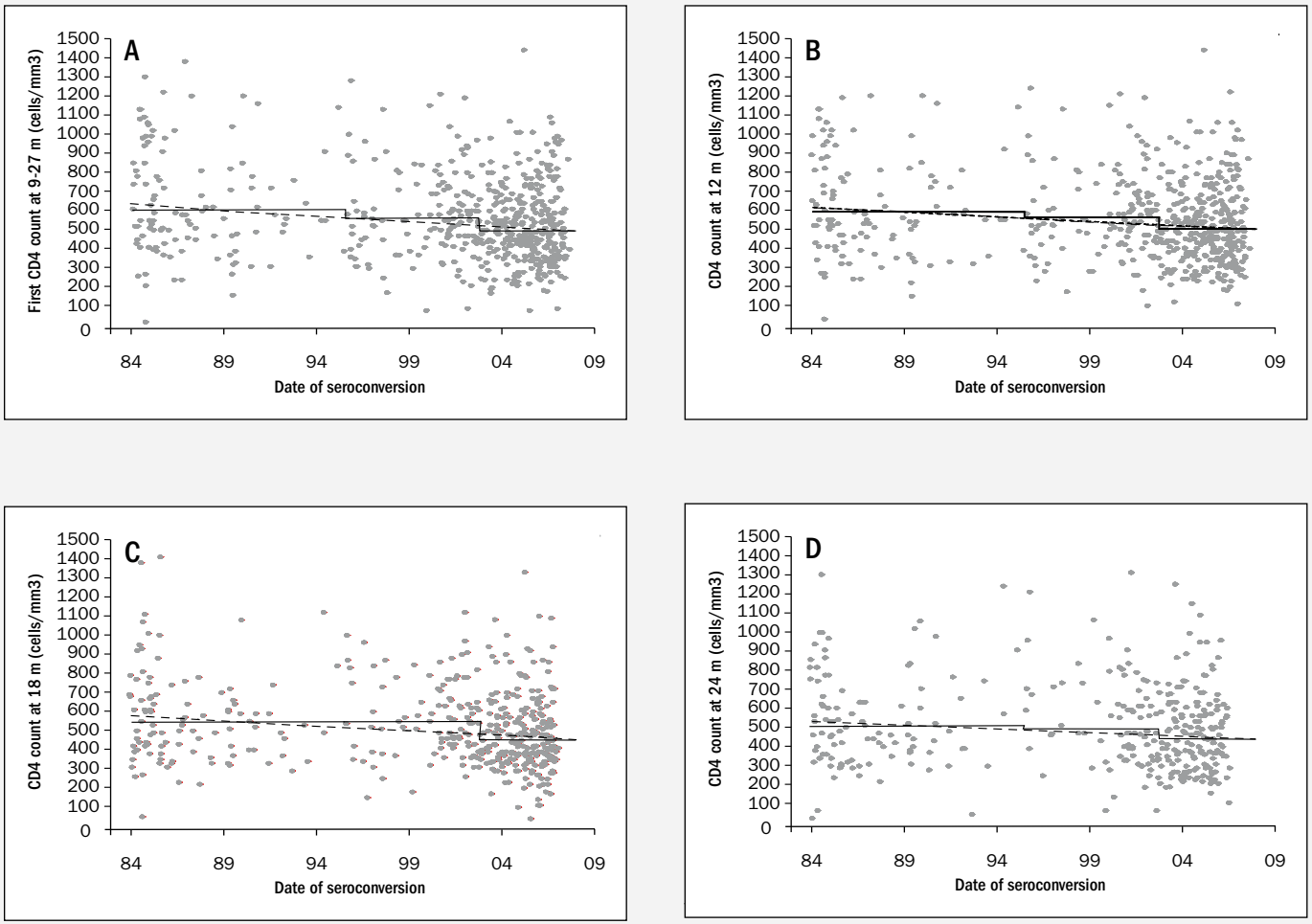


Figure 2.5: CD4 cell count at viral set-point and mean CD4 cell count at each time period. In men having sex with men (MSM) from western Europe or North America with a proven or likely subtype B infection: a) first CD4 cell count between 9 and 27 months after seroconversion (n=578), b) at 12 months (N=555), c) 18 months (N=439), and d) 24 months (N=347). The solid black line shows the mean CD4 cell count for patients with an estimated date of seroconversion from 1984 through 1995, 1996 through 2002, and 2003 through 2007 (as shown in Table 2.5). The dashed black lines were obtained using linear models assuming a constant decrease between 1984 and 2007. Potential confounders were the same as listed in the legend of Figure 2.4.

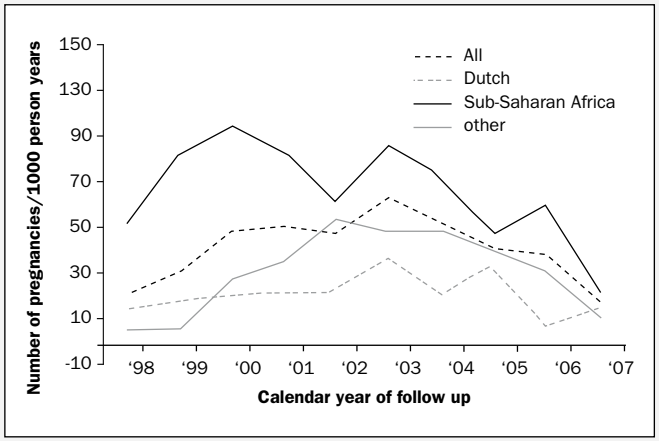


Figure 2.6: Incidence of pregnancies per 1000 person-years (PY) per calendar year of follow-up amongst HIV-infected women in the Netherlands, overall and according to region of origin. All women aged between 16 and 45 years were considered to be "at risk" for pregnancy. Person-years were calculated from the time of HIV diagnosis until the last visit, death, or point when the patient was lost to follow-up, reached the age of 45 years, or as of 1 January 2009.

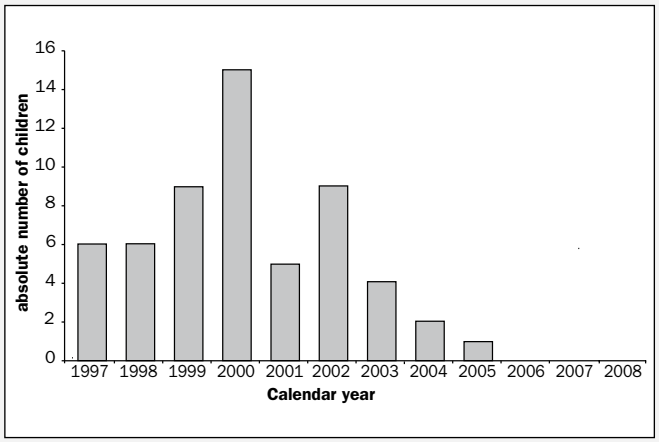


Figure 2.7: The number of children born with HIV in the Netherlands, according to year of birth. In the year 2000, 15 children were born with the infection; from that year on, vertical transmission of HIV decreased, reaching 0 in 2006, 2007, and 2008.

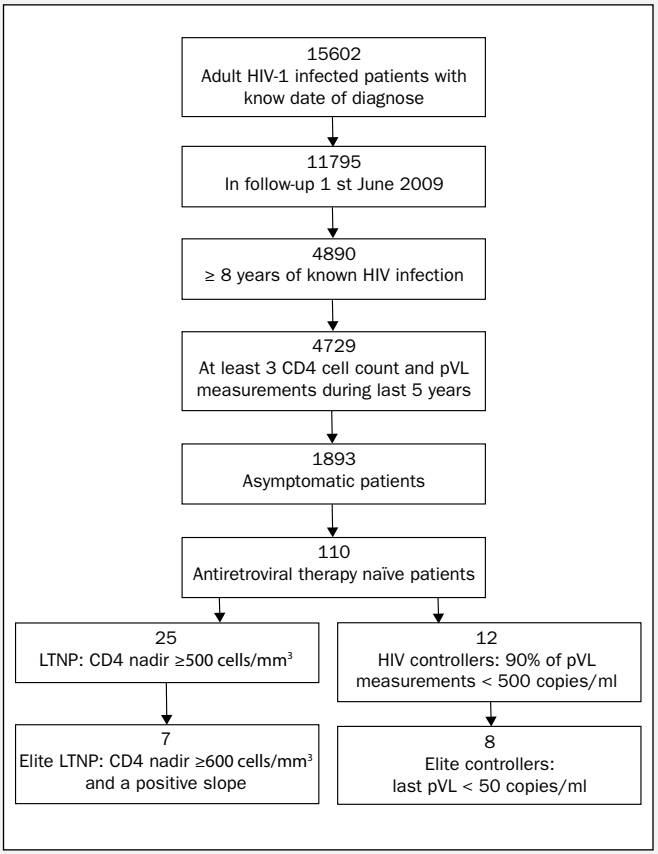


Figure 2.8: HIV controllers and LTNP are defined as untreated asymptomatic patients with at least 8 years of HIV-1 infection. At least 90% of plasma HIV RNA values of HIV controllers were 500 copies/ml or less. In addition, HIV controllers with a last HIV RNA value less than or equal to 50 copies/ml are 'elite controllers'. LTNP patients are those with a CD4 cell count nadir of at least 500 cells/mm^3. A subgroup of these with a CD4 cell count nadir of at least 600 cells/mm^3 and a positive CD4 cell count slope during the last 3 years of follow-up are 'elite LTNP'. An additional requirement for all these groups was that at least 3 HIV RNA and CD4 cell count measurements during the last 3 years of follow-up were available. In contrast to the definition of HIV controller used by Grabar et al., we use asymptomatic period of HIV infection of at least 8, rather than 10, years in order to have the same minimal length of follow-up in both the virological and immunologically defined groups.

3. Death, AIDS and serious non-AIDS events

Ard van Sighem, Luuk Gras

Provided combination antiretroviral therapy (cART) is started in a timely manner, the life expectancy of patients infected with HIV-1 increases significantly, although still not to the level of the age- and gender-matched general population[7]. As the HIV-1-infected population ages, non-AIDS diseases traditionally associated with older age in the uninfected general population are increasingly more common. In this chapter we describe trends in causes of death, AIDS and serious non-AIDS events.

Mortality and incidence of AIDS

From the group of 15,602 patients with an HIV-1 infection and a known date of diagnosis, 15,591 patients who were diagnosed before 1 June 2009 were selected. In this group, 1,419 cases of death were recorded from 1996 onwards during 105,329 person-years of follow-up (Table 3.1). This number corresponded to an average mortality rate of 1.35 (95% confidence interval [CI], 1.28-1.42) deaths per 100 person-years. The mortality decreased over time ($p<0.001$), from 1.92 (95% CI, 1.53-2.37) in 1997 to 0.91 (0.62-1.29) in 2009 (Figure 3.1). When patients who had an AIDS diagnosis within 6 weeks after an HIV diagnosis (N=2,304) were excluded, the overall mortality was reduced to 1.16 (95% CI, 1.10-1.24) per 100 person-years and also decreased over time ($p=0.01$). When the population was limited to the 12,118 patients diagnosed in or after 1996 (669 cases of death during 65,829 person-years of follow-up), the mortality was also lower, 1.02 (95% CI, 0.94-1.10) per 100 person-years, and did not change over time ($p=0.1$).

For the total group of 15,591 patients, 4,366 AIDS diagnoses were registered at or after HIV diagnosis. There were 2,573 new AIDS diagnoses recorded 6 weeks or longer after an HIV diagnosis, of which 2,109 (82.0%) were recorded in or after 1996. The total follow-up since 1996 until AIDS diagnosis was 89,795 person-years, yielding an average AIDS incidence of 2.34 (95% CI, 2.25-2.45). From 1996 onwards, there was a decline ($p<0.001$) in AIDS diagnoses from 9.0 (95% CI, 7.9-10.1) per 100 person-years in 1996 to 1.27 (1.06-1.51) in 2008 (Figure 3.1). After 2000, the AIDS incidence was 1.83 (95% CI, 1.73-1.93) per 100 person-years and declined over time ($p<0.001$). When only patients with an HIV diagnosis in or after 1996 were considered, the AIDS incidence after 2000 was 1.93 (95% CI, 1.81-2.05) per 100 person-years.

The population of patients starting cART in 1995 or later consisted of 2,384 patients with prior antiretroviral treatment (22,122 person-years of follow-up since 1996, 576 deaths) and 10,136 previously therapy-naïve patients (55,216 person-years of follow-up, 658 deaths). These patients treated with cART include both adults and children and therefore comprise a larger group than the 12,297 patients mentioned in the flowchart in chapter 2. Overall, the mortality rate declined from 4.5 (95% CI, 3.0-6.5) per 100 person-years in 1996 to 1.21 (1.00-1.46) in 2008 and 1.09 (0.74-1.56) in 2009. It should be noted, however, that this decline in mortality should be interpreted with caution. The decline is due in part to a survival effect in which patients who do not die contribute to the total number of person-years in each calendar year, whereas patients who die contribute only to the number of deaths in one year.

On average, the mortality rate after 2000 was 1.43 (95% CI, 1.34-1.53) per 100 person-years; in the therapy-naïve population it was 1.16 (1.07-1.26) and in the pre-treated population 2.31 (2.07-2.57). Between 1996 and 2009, the overall mortality in the therapy-naïve population was 1.19

(95% CI, 1.10-1.29) per 100 person-years and did not change over time (p=0.05). When patients with an AIDS diagnosis in the year prior to the start of cART were excluded, the mortality rate was 0.87 (95% CI, 0.79-0.97) per 100 person-years in the previously therapy-naïve population and 2.12 (1.91-2.34) in the pre-treated population, and both rates did not change over time (p=0.5).

In the total group who ever started cART, 1439 AIDS diagnoses were registered in 1996 or later during 70,807 person-years of follow-up after the start of cART. The incidence of new AIDS diagnoses decreased dramatically from 14.8 (95% CI, 11.9-18.2) in 1996 to 1.19 (0.97-1.45) per 100 person-years in 2008. In the therapy-naïve population (51,232 person-years of follow-up), the overall incidence of AIDS was 1.81 (95% CI, 1.69-1.93) per 100 person-years, which was lower than in the pre-treated population, for which the incidence was 2.62 (2.39-2.85). The AIDS incidence after 2000 was similar in the pre-treated and therapy-naïve populations, being 1.56 (1.35-1.79) and 1.59 (1.47-1.71) per 100 person-years, respectively (p=0.8).

Early diagnosis and prognosis

In the past 7 years, several prognostic models have been developed to estimate survival probabilities of HIV-infected patients[7,40-43]. Some of these models included patients at the start of cART, whereas other models took into account patients' initial response to treatment. So far, however, few prognostic models exist for patients who are not yet treated. Because current guidelines recommend treatment only when CD4 counts are less than 350 cells/mm^3, the number of patients who are not yet treated can be considerable. For example, 2,459 (20.1%) of the 12,258 adult patients being followed as of 1 June 2009 had not yet started antiretroviral therapy (see chapter 2).

In order to develop a prognostic model for patients who were untreated at the time of assessment of the prognosis, 4,174 patients were selected who were diagnosed between 1998 and 2007, were not yet treated at 24 weeks after diagnosis, and did not have AIDS at that time. Thus, a population was selected in which CD4 counts were relatively high, 480 (Interquartile range [IQR], 360-650) cells/mm^3. The hazard of death was modelled 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 that was averaged over the years 2000 to 2005. The model did not explicitly capture subsequent start of cART, but it assumed that cART would be started according to current guidelines, that is, as an 'intention-to-treat' approach.

The only covariates associated with progression to death were age at 24 weeks with hazard ratio (HR) 1.07 (95% CI, 1.03-1.10) per year older and being in CDC stage B (HR 4.8, 2.1-11.3). Further analysis showed that patients of older age were not further advanced in their HIV infection than patients of younger age since CD4 counts and CDC stage at 24 weeks were similar. Also, there were no differences in causes of death between older and younger patients. These findings are compatible with a model in which ageing is accelerated in HIV-infected patients[44]. Our analysis rendered further credibility to this supposition because it was found that probabilities of death within one year for HIV-infected patients were roughly the same as those for uninfected individuals a few years older.

The model was used to predict the expected age reached by HIV-infected patients and the number of remaining life years, given the patients' age at 24 weeks after diagnosis (Figure 3.2). The median number of remaining life years for individuals 25 years of age from the general population was 53.1 (IQR, 44.9-59.5) years for men and 58.1 (50.1-63.9) for women. For

HIV-infected patients who were 25 years of age at 24 weeks after diagnosis, the expected median number of remaining life years was 52.5 (IQR, 43.6-59.2) for men and 57.5 (48.5-63.5) for women. The number of life years lost, which was defined as the difference between the median age reached by an HIV-infected patient and the age reached by an age- and gender-matched non-infected individual, increased from 0.7 years at age 25 to 1.9 years at age 55 for HIV-infected men and from 0.7 to 2.2 years for women (Figure 3.2b). Hence, the life expectancy of HIV-infected individuals is, at most, a few years less than that of non-infected individuals. For patients with a CDC-B event at 24 weeks, however, the number of life years lost was greater: 3.4 years for men and 3.6 years for women 25 years of age and 8.9 and 11.6 years, respectively, for individuals 55 years of age.

Although life expectancies of HIV-infected individuals can almost equal those of non-infected individuals, this holds true only for patients who are still relatively early in their infection at (24 weeks after) diagnosis, i.e., they have high CD4 counts and are not yet eligible for treatment. About half of the patients with an HIV diagnosis between 1998 and 2007 were already treated by 24 weeks after the diagnosis, whilst one sixth of the patients already had AIDS. Hence, a substantial proportion of the patients were diagnosed with HIV late in their infection, which considerably worsens the prognosis compared to patients presenting early in the course of their infection[40-42]. Traditionally, the Netherlands has one of the lowest HIV-testing rates in the industrialised world[45]. This situation is changing, however, and amongst newly diagnosed HIV-positive men, the proportion of patients who ever had an HIV-negative test increased from 23% in 1996 to 62% in 2008. Nevertheless, in order to trace infections as early as possible, testing rates need to increase amongst those who are at high risk for HIV, thus enabling a maximum beneficial effect of cART on prognosis.

Cause of death

Out of the 15,602 patients with an HIV-1 infection and a known date of diagnosis, 11,724 started cART between July 1996 and December 2008 and had follow-up available after the start; these patients are further described in the remainder of this chapter. During 69,738 person-years of follow-up after initiation of cART, 1,103 patients died (1.58 deaths per 100 py of follow-up, 95% CI, 1.49-1.68). All patients were 16 years of age or older at the start of cART. In total, 141 deaths (12.8%) could not be classified because of insufficient clinical data. AIDS as the cause of death was recorded for 371 patients (39% of all known causes of death), and non-AIDS causes of death were recorded for 732 patients (61%).

Table 3.2 shows the cause of death for the 1,103 who died after starting cART, subdivided according to year of death[130]. The most frequently recorded cause of death (371 patients) was AIDS. AIDS-defining infection (147 patients) occurred slightly more frequently than AIDS-defining malignancy (130 patients), whilst 94 patients were recorded as having died because of AIDS, but without further classification. Non-AIDS-defining malignancy was the cause of death in 152 patients, cardiovascular complications in 99 patients, and non-AIDS-defining infection in 74 patients. The proportion of deaths due to AIDS showed a decreasing trend over time; it was 45% between 1996 and 2000, 33% between 2001 and 2004, and 28% between 2005 and 2009 ($p<0.0001$, test for trend). The proportion of deaths due to non-AIDS cancers increased from 7% between 1996 and 2000 to 18% between 2005 and 2009 ($p=0.0002$, test for trend). The proportion of deaths due to cardiovascular disease between 2001 and 2004 was similar to that between 2005 and 2009 and was higher than that between 1996 and 2000 (10.4% vs. 4.5%, $p=0.003$). Table 3.2 also shows the median last CD4 count prior to each specific cause of death. The median CD4 count prior to a death because of an AIDS-

defining infection was lower than that with an AIDS-defining malignancy, 50 cells/mm^3 (IQR, 20-120) and 100 (35-190), respectively (p=0.005, Wilcoxon test). The same trend was seen in non-AIDS-defining infections (median last CD4 count, 125 cells/mm^3 [IQR, 50-270]) and non-AIDS defining malignancies (median, 210 cells/mm^3 [95-400], p=0.001). The highest median CD4 counts prior to death were seen in patients who died by accident or violence (380 cells/mm^3 [IQR, 230-420]), and cardiovascular disease (320 cells/mm^3 [190-470]). Table 3.3 shows the incidence of the six most frequent causes of death (AIDS, non-AIDS malignancy, cardiovascular disease, non-AIDS infection, liver failure with hepatitis C virus [HCV] or hepatitis B virus [HBV] co-infection, and suicide), according to the latest CD4 count. The incidence of death due to AIDS was 155.8 / 1000 py (95% CI, 132.0-182.7) for patients with a latest CD4 count of less than 50 cells/mm^3, compared to 2.9 (2.1-3.9) for those with a count between 200 and 350 cells/mm^3 (p<0.0001). Also, the incidence of non-AIDS causes of death was higher with lower CD4 cell counts and was 71.8 / 1000 py (95% CI, 55.9-90.7) for patients with a latest CD4 count of less than 50 cells/mm^3 and 9.5 / 1000 py (7.9-11.2) for CD4 counts between 200 and 350 cells/mm^3. There was a clear association of a higher incidence of all five non-AIDS causes of death with a lower latest CD4 cell count. The association of a higher incidence of death with a lower CD4 cell count was weakest for death due to cardiovascular disease and suicide.

The Kaplan–Meier estimate of all-cause mortality 12 years after the start of cART was 12.4% in therapy-naïve patients and 25.2% in those who were pre-treated (p<0.0001). Figure 3.3 shows the cumulative incidence of competing causes of death[131,132] for the most frequent causes of death after starting cART in pre-treated and naïve patients. The cumulative incidence of (a) AIDS-defining infections and (b) cancers in pre-treated patients continued to rise with increasing time after the first start of cART, whereas in therapy-naïve patients the cumulative incidence of these causes of death levelled off after the first 3 years of starting cART. In naïve patients, the incidence of death because of AIDS per 1000 py was 7.46 (95% CI, 6.40-8.63) during the first 3 years after starting cART, 1.85 (1.29-2.57) between 3 and 7 years and further decreased to 0.86 (0.25-1.78) between 7 and 11 years. In contrast, the incidence of death due to non-AIDS malignancy increased with longer time after start of cART, 1.87 per 1000 py (95% CI, 1.37-2.51) during the first 3 years, 2.01 (1.42-2.76) between 3 and 7 years, and 2.34 (1.41-3.65) between 7 and 11 years. In pre-treated patients, the incidence of death due to AIDS also decreased with longer time after start of cART, but it remained high at 4.87 (95% CI, 3.12-7.26) per 1000 py between 7 and 11 years from the first start of cART. As treatment has turned HIV infection into a chronic disease, causes of death in the ageing HIV-infected population have come to resemble more closely those seen in the general population. This is reflected in the increasing incidence of death due to non-AIDS-defining malignancies and cardiovascular complications with longer time on cART, as well as the higher proportion of deaths due to malignancy and cardiovascular complications found in more recent years in our cohort of treated patients and in other cohorts[67,133,134].

Finally, we compared the incidence of death due to non-AIDS malignancy, cardiovascular disease (subdivided into myocardial infarction and stroke), and suicide in male and female patients to that of the age-standardized general population (Table 3.4). The incidence of death due to non-AIDS-defining cancer was 3.04 (95% CI, 2.22-4.07) for pre-treated male patients and 1.55 (0.50-3.63) per 1000 py for female patients. This compares to 1.31 and 0.60 per 1000 py for the male and female age-standardized general population. In men, the incidence of death due to cardiovascular disease, myocardial infarction, and suicide after starting cART was higher compared

to the age-standardized population, both in pre-treated and therapy-naïve patients. Other studies have also reported this result for myocardial infarction and certain non-AIDS-defining cancers, even after adjustment for other risk factors[46-50]. Although in pre-treated women the risk of death due to non-AIDS defining malignancies and suicide appeared to be increased compared to the age-standardized population, the 95% confidence intervals were wide because of the smaller number of person-years.

AIDS and serious non-AIDS events

Serious non-AIDS events in the ageing HIV-infected population are the same as the events associated with older age in uninfected subjects, such as non-AIDS-defining malignancies and cardiovascular, renal, and liver disease, but they are seen more often in infected individuals than in uninfected controls[46, 48-52]. Apart from traditional risk factors, older age, and antiretroviral therapy, increasing evidence has shown that HIV infection itself is associated with a higher incidence of these events[44]. The incidence of AIDS events after the first start of cART is shown in Figure 3.4, together with the first event out of the following 7 routinely recorded serious non-AIDS events: renal insufficiency (chronic and acute disease), liver events (cirrhosis, fibrosis or hepatocellular carcinoma), diabetes mellitus, myocardial infarction, cerebrovascular accident (CVA), osteoporosis and non-AIDS-defining malignancies (excluding basal and squamous cell carcinoma). Among the 11,724 patients who started cART between 1 July 1996 and 31 December 2008, 1,637 diagnoses of AIDS-defining diseases were recorded; from July 2002 onwards, 997 serious non-AIDS-defining events were recorded (data collection for all included serious non-AIDS events did not start until July 2002). The incidence of both AIDS and non-AIDS events was highest in the first year after the start of cART; for AIDS events it was 79.6/1000 PY (95% CI, 74.4-85.1) and for non-AIDS events it was 31.2 (26.7-36.2). Beginning 3 years after the start of cART and onwards, the incidence of serious non-AIDS events was higher than AIDS events, as shown in Figure 3.4.

Table 3.5 shows that the incidence of any AIDS event and almost all specific AIDS events was highest in 1996 (155.8/1000 PY for any AIDS event). As explained earlier in this chapter, this should be interpreted with caution. In 1996, the denominator consisted of only patients within the first year of starting cART, when the incidence of AIDS events was high due to immune reconstitution disease[135]. Overall, the most commonly diagnosed AIDS events was candidiasis (353 diagnoses, of which 338 were esophageal candidiasis), followed by Kaposi sarcoma (217 diagnoses). A recent study looked at the effect of specific AIDS events during cART on mortality[136]. Both Kaposi sarcoma and candidiasis were classified as a 'mild' AIDS disease. Compared to no AIDS event, esophageal candidiasis increased the probability of death 2.1-fold and Kaposi sarcoma 1.8-fold. Non-Hodgkin's lymphoma and progressive multifocal leucoencephalopathy were the two AIDS events that increased the probability of death most, more than 10-fold[136]. Whilst diagnoses of progressive multifocal encephalopathy were rare in our study (0.4/1000 PY in 2008), non-Hodgkin's lymphoma was one of the most common events, with an incidence of 1.7/1000 PY (95% CI, 0.9-2.8) in 2008. Whereas the incidence of any AIDS event per calendar year showed a decreasing trend, the incidence of the serious non-AIDS events was stable between 2002 and 2008 ($p=0.62$, test for trend). The incidence for any serious non-AIDS event was 22.0/1000 PY (95% CI, 14.0-24.7) in 2002 and 22.4 (19.0-26.1) in 2008. Non-AIDS malignancy was the most common serious non-AIDS event with a total of 322 diagnoses. The incidence showed an increasing trend over time ($p<0.0001$, test for trend) and was 5.9/1000 PY (95% CI, 4.3-7.9) in 2008. In contrast, the incidence of diabetes mellitus showed a decreasing trend over time ($p=0.0003$).

Table 3.6 shows an increasing incidence with older age for all non-AIDS events except liver events. The incidence of any of the serious non-AIDS events was 7.2/1000 PY (95% CI, 3.7 - 12.6) for male patients under 30 years of age, and it was 58.6 (48.9 - 69.7) for patients older than 60 years of age. The incidence of any serious non-AIDS event in female patients was lower than that in men but showed a similar strong increase with older age. In contrast, the incidence of AIDS events showed a stable (in female patients) or a decreasing trend (in male patients) with older age. The most common serious non-AIDS event above 60 years of age or more was non-AIDS malignancy for male patients (17.3/1000 PY) and diabetes mellitus for female patients 17.0/1000 PY. Liver events were the only serious non-AIDS event for which the trend did not increase with older age. The highest incidence of liver events was 5.1/1000 PY for male and 7.6/1000 PY for female patients aged between 40 and 50 years of age. The increasing number of older patients living with HIV-1 partly explains the increasing trend of serious non-AIDS events over time. Serious adverse events like cardiovascular disease, osteoporosis, malignancies, and renal disease are traditionally associated with older age in the general population. However, the higher number of older-aged patients living with HIV alone does not completely explain the increasing trend of certain adverse events with more recent calendar years. In comparison to HIV-negative individuals, HIV-infected patients have a higher rate of fatal and non-fatal non-AIDS events. This is also illustrated in Figure 3.5, which shows the incidence of non-AIDS malignancies for HIV-1-infected patients and the general population, according to age and gender[137]. The figure shows that the incidence of non-AIDS malignancies is higher in HIV-infected patients than in the general population across all age groups, except for women between 60 and 65 years of age. In this age group no non-AIDS malignancies were diagnosed, but because of the small number of person-years of follow-up, the confidence intervals are wide. The incidence among men is higher than among women. The higher incidence in HIV patients cannot be solely attributed to HIV infection. Traditional risk factors such as smoking and lifestyle may also play a role. The rate of smoking is probably higher in the HIV-infected population than in the general population. However, other studies that are adjusted for age and other risk factors including smoking still revealed a higher incidence of non-AIDS malignancies, renal disease, and myocardial infarction[46, 48-52] in HIV-1-infected patients compared to uninfected controls. This has led to the hypothesis that HIV is associated with an accelerated ageing process, further supported by a study showing an increased frailty amongst HIV-infected patients compared to uninfected individuals[53].

Finally, the incidence of AIDS and serious non-AIDS events is higher when latest CD4-cell counts are lower, as Table 3.7 shows. This relationship is stronger for AIDS events but is also clearly present for non-AIDS events. Among non-AIDS events, the association of a higher incidence with lower latest CD4 count was strongest for renal insufficiency and weakest for myocardial infarction. In a recent study, older age (≥60 years), lower latest CD4 cell counts (<100 cells/mm^3), and HCV co-infection, as well as higher latest plasma viral load levels (≥10,000 copies/ml), were independently associated with a higher incidence of non-AIDS events[138]. To reduce the incidence of serious non-AIDS events, it is therefore important to start cART in a timely manner to suppress plasma viral load to undetectable levels, to allow patients to spend as little time as possible at low CD4 cell counts, and to identify patients at risk for specific co-morbidities.

Table 3.1: Annual number of cases of death and AIDS amongst HIV-1-infected patients.

	AIDS			Death	
	Total	≥ 6 weeks after diagnosis	after start of cART	Total	after start of cART
≤1995	737	464	1	1	-
1996	358	285	91	43	29
1997	306	185	131	85	69
1998	248	134	114	84	75
1999	235	133	114	91	89
2000	245	113	87	81	78
2001	262	147	98	80	79
2002	299	155	119	122	84
2003	290	145	111	140	118
2004	279	168	114	143	127
2005	334	186	127	140	125
2006	274	163	115	114	101
2007	265	153	106	141	118
2008	199	127	100	124	112
2009	35	15	12	31	30
Total	**4366**	**2573**	**1440**	**1420**	**1234**

cART: combination antiretroviral therapy

Table 3.2: Cause of death according year of death. On the basis of clinical data at the time of death, the cause of death was classified according to the Coding of Death in HIV (CoDe) scheme.

	1996-2000		2001-2004		2005-2009		Total		Median last CD4
	N	%	N	%	N	%	N	%	count (IQR)
Total	266	100.0	365	100.0	472	100.0	1103	100.0	170 (50-350)
Death due to AIDS defining causes	119	44.7	120	32.9	132	28.0	371	33.6	60 (20-150)
Infection	45	16.9	53	14.5	49	10.4	147	13.3	50 (20-120)
Malignancy	40	15.0	40	11.0	50	10.6	130	11.8	100 (35-190)
AIDS, not specified	34	12.8	27	7.4	33	7.0	94	8.5	50 (10-130)
Non-AIDS-defining malignancy	20	7.5	46	12.6	86	18.2	152	13.8	210 (95-400)
Non-AIDS-defining infection	16	6.0	34	9.3	24	5.1	74	6.7	125 (60-270)
Liver failure / cirrhosis and HBV/HCV co-infection	10	3.8	16	4.4	35	7.4	61	5.5	120 (120-300)
Diabetes mellitus			1	0.3	3	0.6	4	0.4	270 (195-380)
Lactic acidosis	3	1.1	1	0.3	2	0.4	6	0.5	240 (70-310)
Cardiovascular complications	12	4.5	38	10.4	49	10.4	99	9.0	320 (190-470)
Myocardial infarction	8	3.0	17	4.7	19	4.0	44	4.0	270 (180-485)
Stroke	1	0.4	7	1.9	6	1.3	14	1.3	280 (210-530)
Other ischemic heart disease			1	0.3	3	0.6	4	0.4	280 (200-470)
Heart or vascular (other causes)	3	1.1	14	3.8	24	5.1	41	3.7	360 (200-430)
Lung related	2	0.8	8	2.1	17	3.6	27	2.5	190 (30-490)
Liver failure (without HBV/HCV)	3	1.1	1	0.3	2	0.4	6	0.5	110 (80-240)
Renal failure	2	0.8	3	0.8	1	0.2	6	0.5	205 (70-350)
Non-natural death	31	11.7	33	9.0	47	10.0	111	10.1	260 (100-460)
Accident or other violent death	5	1.9	6	1.6	7	1.5	18	1.6	380 (230-420)
Suicide	8	3.0	14	3.8	28	5.9	50	4.5	310 (210-600)
Euthanasia	18	6.8	13	3.6	12	2.5	43	3.9	110 (50-280)
Substance abuse	7	2.6	5	1.4	6	1.3	18	1.6	245 (90-490)
Other cause*	9	3.4	8	2.2	10	2.1	27	2.4	180 (90-385)
Unknown	32	12.1	51	14.0	58	12.3	141	12.8	260 (100-500)

* Other causes include pancreatitis, haematological, respiratory, urogenital, gastrointestinal tract, gynaecological, and central nervous system disorders.

HBV: hepatitis B virus; HCV: hepatitis C virus; IQR: interquartile range

Table 3.3: Incidence of the 6 most frequent causes of death according to latest CD4 count in 10,135 patients after first starting cART. Follow-up of each patient was split into periods of 3 months and for each period the latest CD4 cell count was selected. The reported 95% CI's are based on the Poisson distribution.

Cause of death	Latest CD4 count (cells/mm^3)	PY	Deaths	Incidence/ 1000 PY	(95% CI)
AIDS	<50	152	975	155.8	(132.0-182.7)
	50-200	134	7165	18.7	(15.7-22.1)
	200-350	41	14246	2.9	(2.1-3.9)
	350-500	18	16276	1.1	(0.7-1.7)
	≥500	16	29622	0.5	(0.3-0.9)
Any non-AIDS	<50	70	975	71.8	(55.9-90.7)
	50-200	189	7165	26.4	(22.8-30.4)
	200-350	135	14246	9.5	(7.9-11.2)
	350-500	96	16276	5.9	(4.8-7.2)
	≥500	99	29622	3.3	(2.7-4.1)
Non-AIDS	<50	18	975	18.4	(10.9-29.2)
malignancy	50-200	49	7165	6.8	(5.1-9.0)
	200-350	36	14246	2.5	(1.8-3.5)
	350-500	26	16276	1.6	(1.0-2.3)
	≥500	22	29622	0.7	(0.5-1.1)
Cardiovascular	<50	2	975	2.0	(0.2-7.4)
disease	50-200	24	7165	3.3	(2.1-5.0)
	200-350	28	14246	2.0	(1.3-2.8)
	350-500	23	16276	1.4	(0.9-2.1)
	≥500	22	29622	0.7	(0.5-1.1)
Liver disease	<50	6	975	6.1	(2.3-23.4)
and HCV and HBV	50-200	23	7165	3.2	(2.0-4.8)
co-infection	200-350	20	14246	1.4	(0.9-2.2)
	350-500	6	16276	0.4	(0.1-0.8)
	≥500	6	29622	0.2	(0.1-0.4)
Non-AIDS infection	<50	14	975	14.3	(7.8-28.1)
	50-200	34	7165	4.7	(3.3-6.6)
	200-350	10	14246	0.7	(0.3-1.3)
	350-500	9	16276	0.5	(0.3-1.0)
	≥500	7	29622	0.2	(0.1-0.5)
Suicide	<50	3	975	3.1	(0.6-9.0)
	50-200	10	7165	1.4	(0.7-2.6)
	200-350	13	14246	0.9	(0.5-1.6)
	350-500	6	16276	0.4	(0.1-0.8)
	≥500	18	29622	0.6	(0.4-1.0)

HBV: hepatitis B virus; HCV: hepatitis C virus; PY: person-years; CI: confidence interval.

Table 3.4: Incidence of various causes of death in HIV-1-infected patients after starting cART compared to the age-standardized general population. The reported 95% CI's are based on the Poisson distribution. Information on causes of death in the general population in the Netherlands was obtained from Statistics Netherlands[25]. Cause-specific incidence figures were standardized according to the age distribution in HIV-1-infected male and female patients as seen during the entire study period, subdivided into intervals of 3 months. *Reported figures for death due to non-AIDS defining cancer in the general Dutch population were derived as the incidence of all cancer-related death minus 50% of the incidence of death due to lymphoma or malignancy of the bone marrow minus the incidence of death due to cervical carcinoma.

		Incidence per 1000 PY (95% CI)			
Cause of death	**Gender**	**Pre-treated at start cART**	**Age standardized population**	**Naïve at start cART**	**Age standardized population**
Non-AIDS-defining cancer	Male	3.04 (2.22-4.07)	1.31*	2.40 (1.94-2.93)	1.18*
	Female	1.55 (0.50-3.63)	0.60*	0.51 (0.19-1.12)	0.61*
Cardiovascular disease	Male	2.63 (1.87-3.60)	0.90	1.42 (1.07-1.84)	0.82
	Female	0.31 (0.01-1.73)	0.21	0.17 (0.02-0.62)	0.23
CVA	Male	0.37 (0.11-0.79)	0.14	0.17 (0.07-0.36)	0.13
	Female	0.00 (0.00-1.14)	0.07	0.17 (0.02-0.62)	0.06
Myocardial infarction	Male	1.08 (0.62-1.76)	0.32	0.70 (0.46-1.01)	0.28
	Female	0.00 (0.00-1.15)	0.05	0.00 (0.00-0.32)	0.06
Suicide	Male	0.74 (0.37-1.33)	0.18	0.87 (0.61-1.21)	0.18
	Female	0.62 (0.08-2.25)	0.07	0.17 (0.02-0.62)	0.06

PY: person-years of follow-up; CI: confidence interval; cART: combination antiretroviral therapy; CVA: cerebrovascular accident.

Table 3.5: Incidence of specific AIDS events and serious non-AIDS events per 1000 person years of follow-up per calendar year. CVA: cerebrovascular accident.

* Included are events with less than 20 diagnoses: cryptosporidiosis infection (19 diagnoses), histoplasmosis (19 diagnoses), invasive cervical carcinoma (11 diagnoses), microsporidiosis (10 diagnoses), isosporiasis (4 diagnoses), leishmaniasis (4 diagnoses), salmonella septicaemia (2 diagnoses), extrapulmonary pneumocystis (1 diagnosis), and unspecified events (21 diagnoses).

Type-specific AIDS events (with use of the 1993 CDC classification) were combined into a single category. For example, cytomegalovirus retinitis and cytomegalovirus infection of other sites were combined into one category. Only the first diagnosed event of each type after start of cART was noted. Incidence figures for the serious non-AIDS events are shown only from the start of routine recording of the serious non-AIDS event in question. CDC-C events were collected beginning in 1996, whilst routine collection of diagnoses of non-AIDS malignancies, and diabetes mellitus started in 1998. Collection of data on myocardial infarction and CVA was started in 2000, and it was begun on renal insufficiency and osteoporosis in 2002.

		Incidence per 1000 person-years of follow-up												
	Total diagnoses	**1996**	**1997**	**1998**	**1999**	**2000**	**2001**	**2002**	**2003**	**2004**	**2005**	**2006**	**2007**	**2008**
Any AIDS event	1637	155.8	67.5	41.2	35.4	28.2	26.2	25.2	24.8	22.6	25.3	20.4	17.8	17.1
AIDS dementia complex / HIV encephalopathy	99	0.0	2.5	1.4	3.0	1.4	1.6	0.4	1.8	1.2	1.8	1.1	1.2	1.5
Cryptococcosis	45	0.0	0.5	0.7	1.1	0.9	0.8	1.4	0.5	0.9	0.4	0.3	0.7	0.3
Herpes simplex virus	102	11.1	3.0	2.7	2.2	1.2	1.2	0.7	1.4	1.3	1.5	2.0	1.3	0.4
Kaposi sarcoma	217	6.6	12.3	4.1	3.9	2.6	3.1	2.9	2.9	1.8	2.9	4.4	2.1	2.1
Disseminated mycobacterium disease	94	15.5	5.4	3.1	2.2	1.7	1.4	0.7	0.6	0.9	1.1	1.1	1.2	0.3
Other mycobacterium	57	6.6	1.5	1.4	2.2	2.1	1.0	0.9	0.3	0.4	0.5	0.1	0.6	0.6
Pneumocystis jiroveci (carinii) pneumonia	179	4.4	6.4	4.8	5.0	3.6	2.5	3.6	1.6	2.2	2.0	1.6	1.2	2.7
Recurrent pneumonia	177	6.6	2.5	2.7	2.2	2.4	3.9	2.3	3.1	2.8	2.6	1.4	3.0	2.3
Progressive multifocal leucoencephalopathy	49	4.4	1.5	0.3	0.8	1.7	0.8	0.9	0.3	0.4	0.4	0.8	0.8	0.4
Cerebral toxoplasmosis	103	13.3	3.0	3.1	2.5	1.9	2.3	0.7	2.3	1.6	1.6	0.8	0.8	0.0
HIV wasting syndrome	75	2.2	2.0	1.7	2.5	1.7	0.6	1.2	0.6	0.6	1.2	0.9	0.7	0.9
Candidiasis	353	31.0	12.9	7.6	6.7	5.0	6.6	4.7	5.2	3.4	4.9	5.1	3.5	3.6
Cytomegalovirus infection	170	46.6	8.9	2.4	3.1	3.3	2.3	2.0	2.3	2.7	1.6	1.8	1.3	1.0
Non-Hodgkin's lymphoma	172	15.5	6.9	5.8	1.9	1.9	1.2	2.1	2.9	1.9	3.7	2.0	1.5	1.7
Tuberculosis	185	6.6	3.4	3.8	2.5	2.4	2.5	3.9	3.2	2.7	3.1	2.4	1.9	1.9
Any other CDC-C events*	91	11.0	5.9	2.7	2.2	2.9	1.4	0.7	1.1	0.7	1.5	0.9	0.4	0.3
Any serious non-AIDS event	997							22.0	22.9	20.8	23.7	24.5	26.7	22.4
Renal insufficiency	244			9.3	8.1	6.2	4.1	4.0	5.9	3.7	7.2	3.9	3.5	4.0
Liver event	262			4.8	4.2	3.4	3.1	4.9	3.4	4.0	5.3	4.1	3.7	3.5
Diabetes mellitus	307			6.5	7.5	5.3	5.2	4.7	5.6	3.6	4.5	5.0	3.6	2.6
Myocardial infarction	162					4.1	2.1	4.3	3.1	3.0	2.6	2.5	2.5	2.6
Osteoperosis	82							1.0	1.8	1.5	1.5	1.8	1.9	1.9
CVA	106					2.3	1.6	1.6	2.4	1.6	2.7	1.6	1.7	1.3
Non-AIDS defining malignancy	322			3.2	3.0	1.9	1.4	5.7	3.9	5.6	5.3	6.4	6.4	5.9

Table 3.6: Incidence per 1000 person years (PY) of newly diagnosed routinely collected serious co-morbidities and any AIDS-defining event per age group for male and female patients after starting cART. The reported 95% CI's are based on the Poisson distribution.

		Male					Female				
	Age during follow-up (yrs)	Diagnoses	PY	Incidence /1000 PY	95% CI		Diagnoses	PY	Incidence /1000 PY	95% CI	
Any AIDS event	<30	99	2748	36.0	29.3	43.9	72	2912	24.7	19.3	31.1
	30-40	432	15131	28.6	25.9	31.4	171	5874	29.1	24.9	33.8
	40-50	453	19131	23.7	21.5	26.0	73	3375	21.6	17.0	27.2
	50-60	236	9387	25.1	22.0	28.6	18	856	21.0	12.5	33.2
	>=60	71	2969	23.9	18.7	30.2	12	396	30.3	15.7	52.9
Any serious non-AIDS event	<30	12	1659	7.2	3.7	12.6	20	2110	9.5	5.8	14.6
	30-40	121	9481	12.8	10.6	15.3	54	4482	12.0	9.1	15.7
	40-50	296	14158	20.9	18.6	23.4	71	2831	25.1	19.6	31.6
	50-60	236	6873	34.3	30.1	39.0	23	706	32.6	20.6	48.9
	>=60	128	2182	58.6	48.9	69.7	16	311	51.4	29.4	83.4
Renal insufficiency	<30	4	1672	2.4	0.7	6.1	7	2148	3.3	1.3	6.7
	30-40	35	9722	3.6	2.5	5.0	10	4649	2.2	1.0	4.0
	40-50	66	15243	4.3	3.3	5.5	19	3068	6.2	3.7	9.7
	50-60	57	7735	7.4	5.6	9.5	8	763	10.5	4.5	20.6
	>=60	33	2685	12.3	8.5	17.3	5	362	13.8	4.5	32.3
Liver events	<30	4	2751	1.5	0.4	3.7	6	2953	2.0	0.7	4.4
	30-40	50	15565	3.2	2.4	4.2	24	6257	3.8	2.5	5.7
	40-50	103	20178	5.1	4.2	6.2	28	3695	7.6	5.0	11.0
	50-60	37	10193	3.6	2.6	5.0	4	929	4.3	1.2	11.0
	>=60	9	3272	2.8	1.3	5.2	1	437	2.3	0.1	12.8
Diabetes mellitus	<30	2	2757	0.7	0.1	2.6	10	2927	3.4	1.6	6.3
	30-40	36	15592	2.3	1.6	3.2	27	6294	4.3	2.8	6.2
	40-50	83	20184	4.1	3.3	5.1	18	3687	4.9	2.9	7.7
	50-60	80	9927	8.1	6.4	10.0	5	922	5.4	1.8	12.7
	>=60	39	3092	12.6	9.0	17.2	7	411	17.0	6.8	35.1
Myocardial infarction	<30	0	2197	0.0	.	1.7	0	2601	0.0	0.0	1.4
	30-40	10	12707	0.8	0.4	1.4	3	5627	0.5	0.1	1.6
	40-50	53	18006	2.9	2.2	3.9	2	3527	0.6	0.1	2.0
	50-60	59	9038	6.5	5.0	8.4	0	886	0.0	0.0	4.2
	>=60	31	2931	10.6	7.2	15.0	4	403	9.9	2.7	25.4
Osteoperosis	<30	1	1684	0.6	0.0	3.3	2	2155	0.9	0.1	3.4
	30-40	3	9808	0.3	0.1	0.9	3	4700	0.6	0.1	1.9
	40-50	26	15390	1.7	1.1	2.5	8	3102	2.6	1.1	5.1
	50-60	20	7865	2.5	1.6	3.9	5	777	6.4	2.1	15.0
	>=60	9	2746	3.3	1.5	6.2	5	358	14.0	4.5	32.6

continued on next page

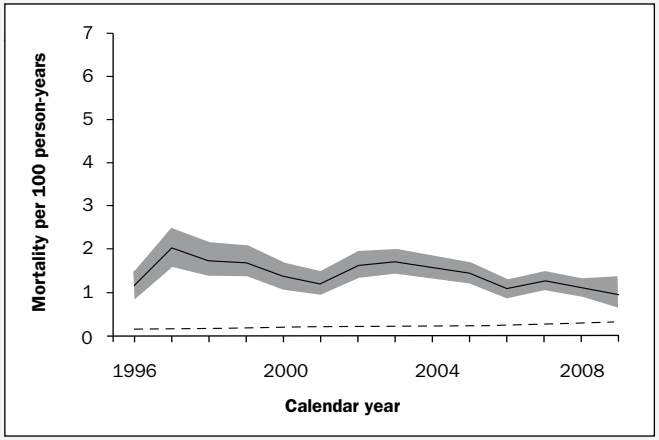
		Male					Female				
	Age during follow-up (yrs)	Diagnoses	PY	Incidence /1000 PY	95% CI		Diagnoses	PY	Incidence /1000 PY	95% CI	
CVA	<30	0	2197	0.0	0.0	1.7	1	2601	0.4	0.0	2.1
	30-40	11	12715	0.9	0.4	1.5	6	5602	1.1	0.4	2.3
	40-50	24	18161	1.3	0.8	2.0	4	3523	1.1	0.3	2.9
	50-60	33	9199	3.6	2.5	5.0	2	874	2.3	0.3	8.3
	>=60	22	3025	7.3	4.6	11.0	3	404	7.4	1.5	21.7
Non-AIDS malignancy	<30	4	2757	1.5	0.4	3.7	1	2955	0.3	0.0	1.9
	30-40	35	15632	2.2	1.6	3.1	11	6354	1.7	0.9	3.1
	40-50	99	20386	4.9	3.9	5.9	21	3763	5.6	3.5	8.5
	50-60	91	10204	8.9	7.2	10.9	6	923	6.5	2.4	14.1
	>=60	55	3185	17.3	13.0	22.5	3	437	6.9	1.4	20.1

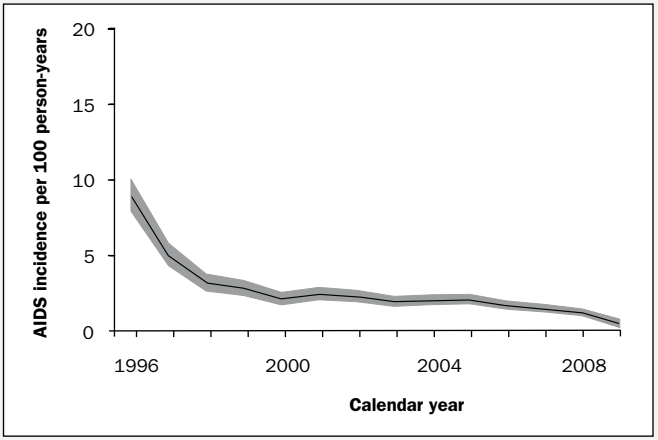
PY: person-years of follow-up; CI: confidence interval; CVA: cerebrovascular accident.

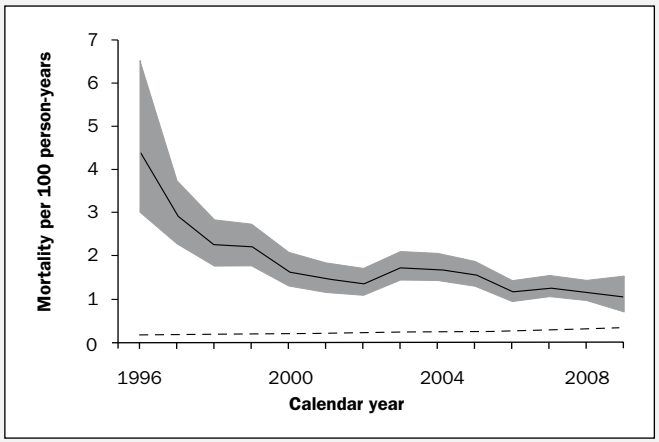
Table 3.7: Incidence per 1000 person years (PY) of newly diagnosed routinely collected serious co-morbidities and any AIDS-defining event per latest CD4 cell count after starting cART. Follow-up of each patient was split into periods of 3 months and for each period the latest CD4 cell count was selected. The reported 95% CI's are based on the Poisson distribution.

Cause of death	Latest CD4 count (cells/mm^3)	Diagnoses	PY	Incidence/ 1000 PY	(95% CI)	
Any AIDS event	<50	366	648	565.1	508.6	626.0
	50 - 200	528	5895	89.6	82.1	97.5
	200 - 350	295	12527	23.5	20.9	26.4
	350 - 500	184	14746	12.5	10.7	14.4
	≥500	196	27567	7.1	6.1	8.2
Any serious non-AIDS event	<50	49	448	109.3	80.9	144.5
	50 - 200	181	3730	48.5	41.7	56.1
	200 - 350	226	8813	25.6	22.4	29.2
	350 - 500	196	10937	17.9	15.5	20.6
	≥500	319	20282	15.7	14.0	17.6
Renal insufficiency	<50	33	471	70.1	48.2	98.4
	50 - 200	73	4075	17.9	14.0	22.5
	200 - 350	51	9448	5.4	4.0	7.1
	350 - 500	34	11661	2.9	2.0	4.1
	≥500	45	21815	2.1	1.5	2.8
Liver event	<50	10	860	11.6	5.6	21.4
	50 - 200	50	6409	7.8	5.8	10.3
	200 - 350	68	13327	5.1	4.0	6.5
	350 - 500	54	15546	3.5	2.6	4.5
	≥500	79	28788	2.7	2.2	3.4
Diabetes mellitus	<50	11	858	12.8	6.4	22.9
	50 - 200	41	6461	6.3	4.6	8.6
	200 - 350	62	13311	4.7	3.6	6.0
	350 - 500	67	15475	4.3	3.4	5.5
	≥500	120	28419	4.2	3.5	5.0
Myocardial infarction	<50	2	658	3.0	0.4	11.0
	50 - 200	18	5302	3.4	2.0	5.4
	200 - 350	38	11492	3.3	2.3	4.5
	350 - 500	32	13755	2.3	1.6	3.3
	≥500	71	25817	2.8	2.1	3.5
Osteoperosis	<50	3	495	6.1	1.3	17.7
	50 - 200	10	4170	2.4	1.1	4.4
	200 - 350	25	9564	2.6	1.7	3.9
	350 - 500	18	11766	1.5	0.9	2.4
	≥500	24	22008	1.1	0.7	1.6
CVA	<50	6	661	9.1	3.3	19.8
	50 - 200	19	5332	3.6	2.1	5.6
	200 - 350	31	11541	2.7	1.8	3.8
	350 - 500	20	13869	1.4	0.9	2.2
	≥500	29	25997	1.1	0.7	1.6
Non-AIDS malignancy	<50	11	834	13.2	6.6	23.6
	50 - 200	57	6263	9.1	6.9	11.8
	200 - 350	94	13055	7.2	5.8	8.8
	350 - 500	61	15329	4.0	3.0	5.1
	≥500	97	28524	3.4	2.8	4.1

PY: person-years of follow-up; CI: confidence interval; CVA: cerebrovascular accident







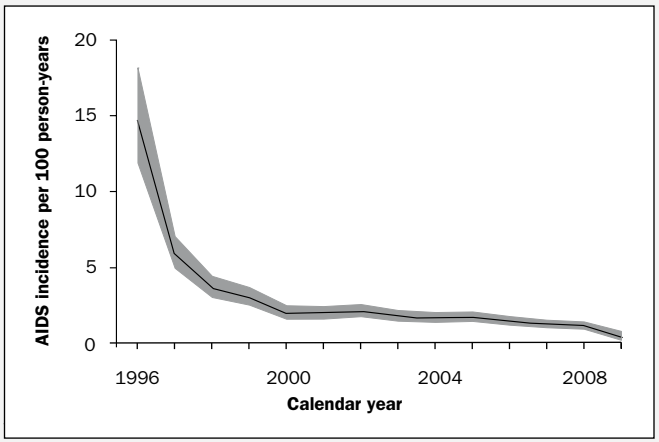


Figure 3.1: Mortality and incidence of AIDS in the HIV-1-infected population as a function of calendar year after diagnosis (upper plots) and after start of cART (lower plots). The black lines represent the incidence, whilst the grey areas are the 95% confidence intervals. The dotted line is the mortality rate for age- and gender-matched individuals from the general Dutch population.

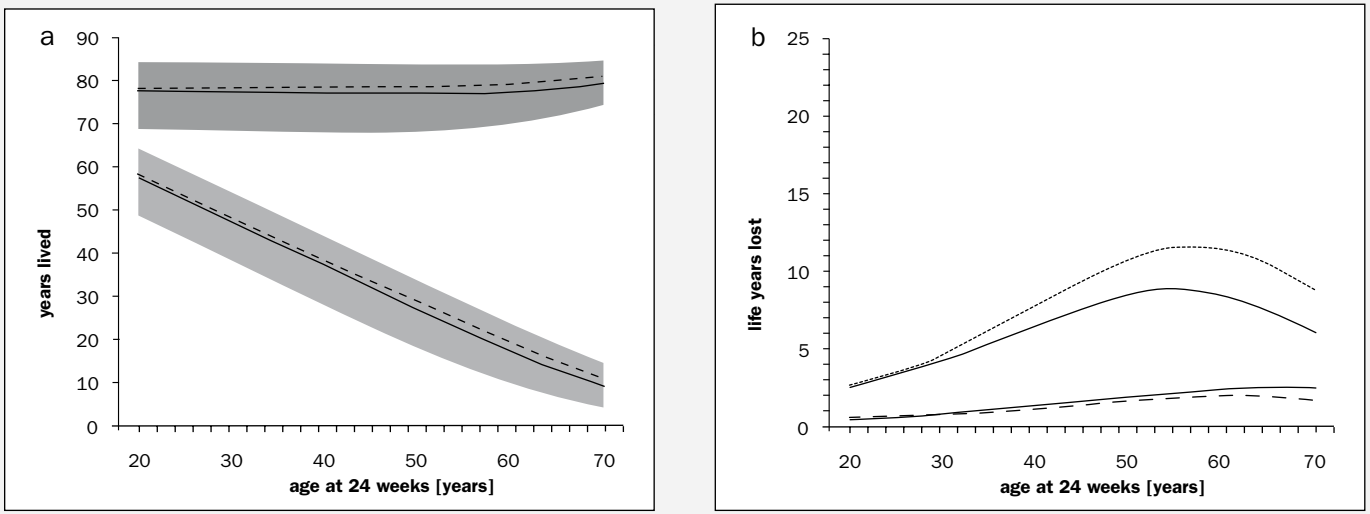


Figure 3.2: (a) Median age reached (upper lines, dark shading) and median number of years lived (lower lines, light shading) after 24 weeks after diagnosis for HIV-infected male individuals without a CDC-B event. Shaded areas represent the interquartile range and dashed lines represent the general population. (b) Number of life years lost for HIV-infected men (short dashes) and women (solid line) without a CDC-B event and for HIV-infected men (long dashes) and women (dotted line) with a CDC-B event at 24 weeks compared to age- and gender-matched non-infected individuals.

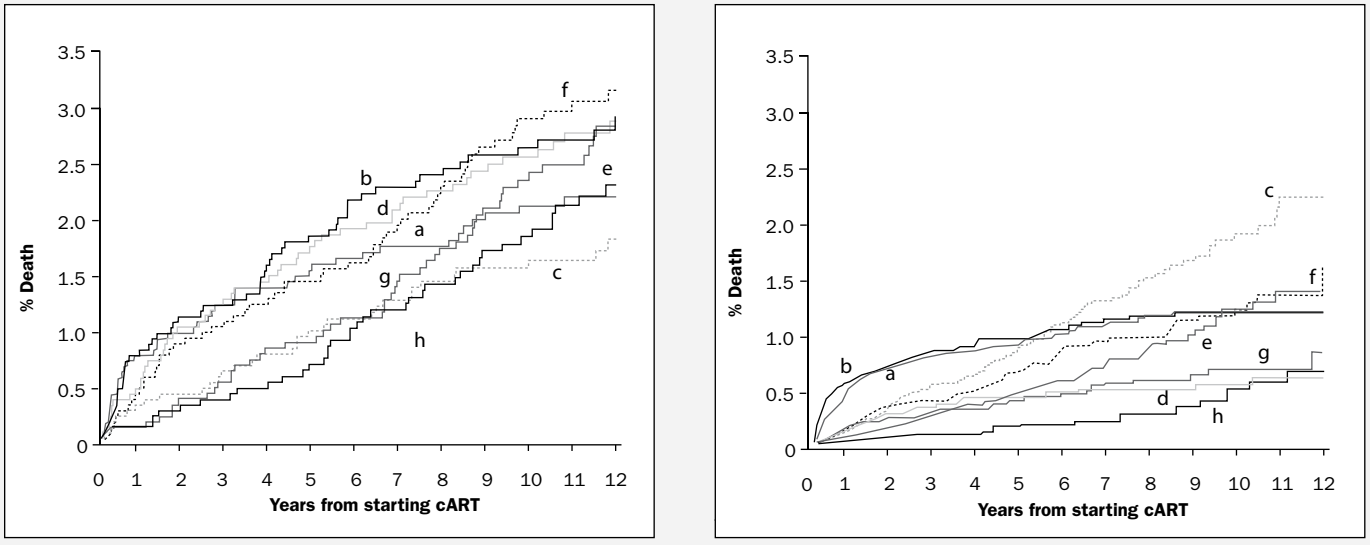


Figure 3.3: Cumulative incidence curves of death after starting combination antiretroviral therapy (cART) in 1,975 pre-treated patients (left) and 8,159 antiretroviral therapy-naïve patients (right) according the Causes of Death in HIV (CoDe) scheme.

a: death due to AIDS-defining infections, b: death due to AIDS-defining cancers, c: death due to non-AIDS-defining cancers, d: death due to non AIDS-defining infections, e: death due to cardiovascular complications, f: death due to suicide, euthanasia or violence, g: death due to AIDS (unspecified) and h: death due to liver failure in combination with hepatitis C virus (HCV) or hepatitis B virus (HBV) co-infection.

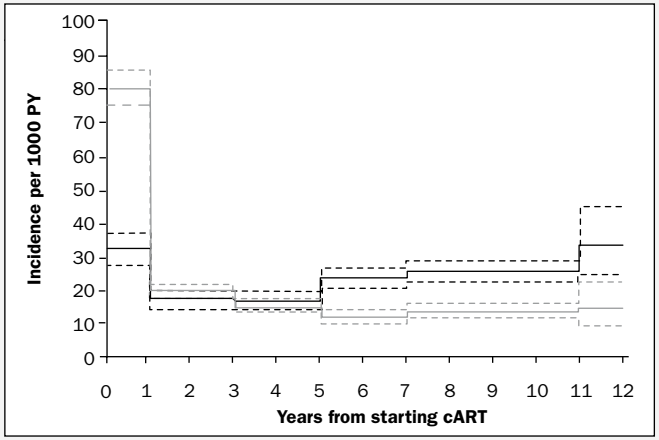


Figure 3.4: Incidence per 1000 person years of follow-up (95% confidence interval) of first AIDS diagnosis (grey line) and of first diagnosis of any serious non-AIDS event (black line) after starting cART. The reported 95% CI's are based on the Poisson distribution.
PY: person-years of follow-up; cART: combination antiretroviral therapy.

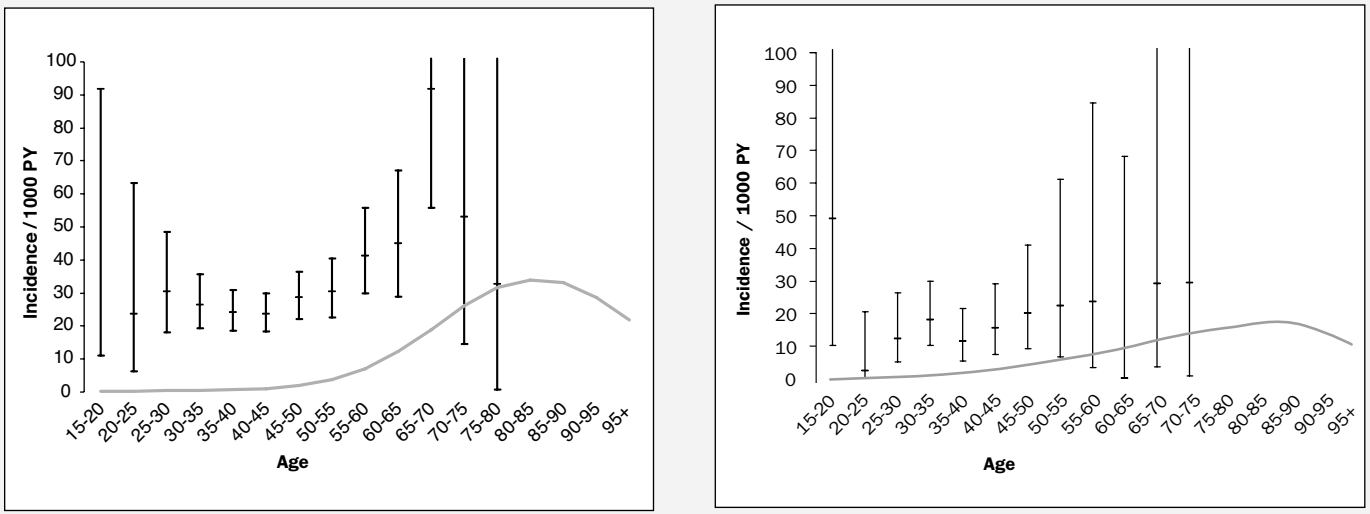


Figure 3.5: Incidence (95% CI – black bars) of non-AIDS malignancies after starting cART per age category during follow-up for male (left plot) and female (right plot) patients. The grey line shows the incidence of non-AIDS malignancies in the general population between 2002 and 2006. Age- and gender-specific incidence figures from the general population between 2002 and 2006 according to site were obtained from the website of the Association of Comprehensive Cancer Centres. The reported 95% CI's are based on the Poisson distribution.

PY: person-years of follow-up.

4. Response to cART

Luuk Gras, Colette Smit

cART in adults

During the first 6 months after the start of combination antiretroviral therapy (cART), plasma HIV RNA concentration levels in the majority of patients infected with HIV-1 decline below 50 copies/ml whilst CD4 cell counts rapidly increase. When cART is started in a timely manner and is continued without interruption for several years, CD4 cell counts have been shown to approach the normal levels seen in uninfected subjects[139]. When adherence to therapy is high, plasma HIV RNA can be maintained <50 copies/ml for long periods of time. Although the strategies for HIV management have improved (e.g., lower pill burden and easier dosing), continuous and lifelong cART is currently needed, because the combination of drugs from different classes does not eradicate HIV[140]. Patients may experience adverse events and clinical manifestations owing to the toxic effect of antiviral drugs on cells and cell metabolism[141]. Adverse events and toxicity may result in poorer patient adherence or even discontinuation of treatment, causing suboptimal drug levels and possibly treatment failure[142,143] and resistance[144].

In this chapter, we describe the effect of cART on viral load in plasma and change in CD4 count. Also, we show changes in the incidence of toxicity-driven therapy longitudinally in relation to calendar year of first starting cART.

Out of the 15,602 patients with an HIV-1 infection and a known date of diagnosis, 11,724 started cART between July 1996 and December 2008 and had follow-up available after the start. A further 456 females started cART during a pregnancy and were excluded from further analysis. These women are later described in this chapter. Out of the remaining 11,268 patients, 1,988 were pre-treated, and 9,280 were antiretroviral therapy-naïve at the first start of cART. Characteristics of these patients are shown in Table 4.1. Amongst the therapy-naïve patients, 5,099 started cART prior to 2004, 3,170 between 2004 and 2007, and 1,011 in 2008 (Table 4.1). A higher proportion of men having sex with men (MSM) ($p=0.0001$) and of patients originating from the Netherlands ($p<0.0001$) were found in the group of patients starting cART in 2008 compared to the group starting between 2004 and 2007. According to current guidelines[24,25], the initiation of cART is recommended when the CD4 count reaches a threshold of 350 cells/mm^3; this is reflected in the higher CD4 count at the start of cART in 2008 compared to that in previous years. The median CD4 count at the start of cART was 250 cells/mm^3 in 2008 compared to 200 cells/mm^3 between 2004 and 2007 ($p<0.0001$). Of patients starting cART in 2008, 29.7% did so with a CD4 count of less than 200 cells/mm^3, and 47.6% had between 200 and 350 cells/mm^3. Possibly because of the higher CD4 cell count at the start of cART, the percentage of patients with a CDC-C diagnosis prior to starting cART was lower than in patients starting in 2008 compared to the percentage in those starting between 2004 and 2007 ($p<0.0001$).

Virological response

The short-term (36 weeks) virological response after first starting cART is shown in Figure 4.1. The percentage of therapy-naïve patients with a plasma viral load less than 1000 copies/ml 36 weeks after starting cART increased from 80% in 1996 to 94% in 2008 (Chi-square test, $p<0.0001$). Since 2002, the percentage of patients with less than 50 copies/ml has remained nearly the same, with 81.5% in 2003 and 83.7% in 2008 ($p=0.60$, test for trend). Furthermore, the percentage of pre-

treated patients starting cART between 1996 and 1999 with a plasma viral load of <1000 copies was lower than amongst naïve patients (69% vs. 88%, p<0.0001). HIV RNA concentration at 36 weeks is an important marker, as it still has additional prognostic value after adjustment for viral load levels at 3 years after first start of cART[145].

The Kaplan-Meier estimate of the proportion of patients with viral suppression <50 copies/ml was 64.8% (95% confidence interval [CI], 63.4-66.3) within 6 months of starting cART and 78.7% (77.3-80.0) within 36 weeks. In unadjusted analyses, no significant differences in time to viral suppression were found between patients starting in different calendar years (results not shown). Table 4.2 shows that in adjusted analyses, however, patients starting in 2008 had a significantly longer time to viral suppression than patients starting in 2005 (Hazard ratio [HR] 0.86, p=0.01). In concordance with other studies[16], time to suppression was significantly longer in patients aged <30 years (HR compared to 30-40 years 0.78, 95% CI, 0.70-0.87; p<0.0001), in patients starting with CD4 counts ≥500 cells/mm^3 (HR compared to 200-350 0.79, 0.65-0.95; p=0.01) and patients starting on a protease inhibitor (PI)-based regimen (HR compared to non-nucleoside reverse transcriptase inhibitor [NNRTI]-based 0.83, 0.77-0.89; p<0.0001)
Figure 4.2 shows a stable percentage of patients with a plasma viral load <50 copies/ml of about 85% after week 36 from the start of cART. This percentage was 94% for those continuously on cART. The percentage of patients on cART with plasma viral load >500 copies/ml after 48 weeks fluctuated between 2% and 3%

Table 4.3 (left column) shows that patients <30 years of age had a lower probability of viral suppression <50 copies/ml after starting cART. Poor adherence might play a role as has been shown by other studies[17]. Patients who started with a PI-based regimen also had a lower probability of viral suppression (Odds ratio [OR] compared with NNRTI-based 0.61, 95% CI, 0.53-0.69; p<0.0001), as did patients who started with CD4 counts >350 cells/mm^3. Also, patients from Sub-Saharan Africa had a lower probability of <50 copies/ml compared to patients from the Netherlands and likewise, injecting drug users (IDU) and patients infected through heterosexual contact had a lower probability compared to men having sex with men (MSM).
When the analysis was restricted to those measurements obtained whilst patients were using cART, the probability of viral suppression was no longer significantly different between patients <30 years and patients 30 to 40 years of age (p=0.78). The results also suggested that if patients were able to stay on cART, virological efficacy was not significantly different between patients starting on PI-based and NNRTI-based initial regimens (p=0.92). However, in patients continuously on cART, the significantly lower probability of viral suppression remained in IDU and patients infected through heterosexual contact compared to that in MSM and in patients from Sub-Saharan Africa compared to that in patients from the Netherlands. Also, patients who started cART in 2003-2004 had a lower probability of viral suppression <50 copies/ml compared to those who started in 2005. From a public health point of view, keeping viral load at low levels is important, since there is evidence from other studies that patients with lower viral loads are less likely to transmit HIV infection to others[18,19]. Although, whether or not transmission occurs during therapy when plasma viral loads are below 50 copies/ml is currently debated[20-23].

Immunologic response

Out of 11,268 patients, a CD4 count at the start of cART was unavailable for 1,589 (14.2%), and they were excluded from further analyses. Overall, in antiretroviral therapy-naïve patients the median CD4 count after starting cART increased from 210 cells/mm^3 (Interquartile range [IQR], 100-300) to 350 (230-468)

after 24 weeks, 380 (260-530) at 48 weeks, 470 (330-650) at 144 weeks, 520 (370-710) at 240 weeks, and 600 (430-790) at 480 weeks. Pre-treated patients started cART at a median CD4 count of 210 cells/mm^3 (IQR, 110-350), but in comparison, counts in pre-treated patients were lower than in naïve patients thereafter: 345 CD4 cells/mm^3 (210-410) at 48 weeks; 420 (260-600) at 144 weeks; 460 (290-660) at 240 weeks; and 510 (330-720) at 480 weeks.

In therapy-naïve patients with continuous viral suppression <50 copies/ml, increases in CD4 count ranged between 480 cells/mm^3 for patients starting with <50 cells/mm^3 to 330 for patients starting between 350-500 cell/mm^3, as Figure 4.3 shows. Patients starting at CD4 counts ≥500 cells/mm^3 had a median increase of 220 cells/mm^3 at week 480 (Wilcoxon test comparing starting cART at <500 with ≥500 cells/mm^3, p=0.0001). In cases where cART was started when CD4 counts were still high, median CD4 counts after 480 weeks of virologically successful cART were 630 cells/mm^3 (IQR, 510-830) for patients starting between 200 and 350 cells/mm^3 and 750 (330-880) for starting between 350 and 500 cells/mm^3. The median CD4 cell count after 480 weeks of continuous cART in patients who started according to current guidelines are still lower than normal CD4 cell ranges. Normal CD4 levels in uninfected subjects were reported to be 1050, 840, and 800 cells/mm^3 for women, heterosexual men, and MSM, respectively[26], with a likely geographic variation in normal CD4 ranges[27]. Therefore, it might be beneficial to start at even higher CD4 cell counts, when CD4 cell counts drop below 500 cells/mm^3.
Median increases in CD4 count in pre-treated patients were lower than those in therapy-naïve patients in all baseline CD4 count strata, as Figure 4.3 shows. Other studies also have shown the importance of keeping HIV RNA levels at low levels. Levels higher than 1000 copies/ml are strongly associated with less restoration of CD4 cells in patients on uninterrupted cART[139, 146], with selection of resistant virus strains[147, 148], and with progression of disease[40, 149].

Toxicity-driven therapy changes

During the first 3 years after starting cART, patients were followed for a total of 26,433 person-years (PY); of that number, 25,747 person-years (97%) included cART (PYcART). The overall incidence of toxicity-driven regimen changes was 22.8 (95% CI, 22.3-23.4) per 100 PYcART. Patients could change the regimen more than once. During follow-up, 7,388 of the 11,268 patients (65.6%) did not change the regimen because of toxicity. The maximum number of changes because of toxicity in a single patient was 14.
The incidence of toxicity-driven regimen changes was higher in pre-treated patients (27.8, 95% CI, 26.3-29.3) per 100 PYcART compared to that in therapy-naïve patients (21.7, 21.1-22.4, difference p<0.0001); it was 21.8 (21.2-22.4) per 100 PYcART in men, and 27.5 (26.1-29.0) in women (p<0.0001). Overall, the incidence was highest (57.2 per 100 PYcART) during the first 3 months after starting cART; it declined to 25.7 per 100 PYcART between 3 and 6 months, 18.1 per 100 PYcART between 6 and 12 months, and 14.5 per 100 PYcART between 24 and 36 months (p<0.0001).

Table 4.4 shows that the incidence of toxicity-driven therapy changes was higher for naïve female patients aged <40 years and >50 years (26.5 and 35.4 per 100 PYcART, respectively) compared to 22.5 per 100 PYcART for female patients aged 40 to 50 years. In contrast, the incidence among therapy-naïve male patients did not seem to increase with age (linear trend, p=0.13). The risk for toxicity-driven therapy changes seemed increased only in patients with high weights at the start of cART (≥85 kg for men and ≥75 kg for women).

Figure 4.4 shows a strong trend of a decreasing adjusted relative risk for a toxicity-driven therapy change with later calendar year of starting cART. With the exception

of the year 2000, the risk was always lower compared to the previous year. In accordance with results from other studies[28-30], we found that female gender was associated with a higher risk of toxicity-driven therapy changes (HR compared to men, 1.56; 95% CI, 1.41-1.75; p<0.0001). This has been attributed to a lower body mass index[31] and a higher drug concentration in plasma in women[32], but in our study, differences in men and women remained after adjusting for weight. There was a significantly reduced risk for a toxicity-driven therapy change only for patients weighing ≥85 kg compared to those weighing <85 kg. The risk for a toxicity-driven therapy change did not differ significantly amongst patients weighing <85 kg. The risk for toxicity-driven therapy changes increased with older age at the start of cART (HR comparing patients ≥60 years of age with those 30-40 years, 1.39; 95% CI, 1.16-1.66; p=0.003). The risk also was increased in patients with an AIDS diagnosis at the start of cART (HR compared to patients with no AIDS diagnosis, 1.12; 95% CI, 1.03-1.22; p=0.006), a hepatitis C co-infection (HR compared to patients with no hepatitis C co-infection, 1.20; 95% CI, 1.04-1.40; p=0.02) and a plasma HIV RNA concentration more than 4 $\log_{10}$ copies/ml (HR compared to <4 $\log_{10}$ copies/ml, 1.14; 95% CI, 1.00-1.30, p=0.05). Finally, patients with a CD4 cell count at the start of cART ≥500 cells/mm^3 had a higher risk for toxicity-driven therapy changes compared to patients with lower CD4 cell counts (HR, 1.27; 95% CI, 1.10-1.48; p=0.001). This finding is in agreement with earlier reports on the loss of quality of life caused by treatment of HIV at an early stage of the infection[28,33]. However, other observers did not find that higher CD4 cell counts before highly active antiretroviral therapy (HAART) had an effect on the discontinuation of antiretroviral drugs because of toxicity[30,34].

In summary, cART has become virologically more effective over time, and the incidence of toxicity-driven therapy changes has decreased over time. Virological suppression in younger patients is less compared to that in older patients, most likely due to poorer adherence. Toxicity is a problem more common in older patients. When cART is started at a level of 350 to 500 CD4 cells/mm^3 and there has been 480 weeks of virologically successful cART, median CD4 counts approach normal levels, but they are still lower than levels seen in uninfected subjects.

cART in pregnant women

Without intervention, the risk of MTCT in HIV-infected pregnant women is 15% to 20%[150]. HIV-infected women with a detectable viral load at time of delivery have a high risk of vertical transmission of HIV. From 1998 onwards, HIV-infected pregnant women in the Netherlands have been treated with cART to reduce maternal levels of viral load. Treatment of HIV-infected women during their pregnancy and of the newborns during their first weeks of life, in combination with elective caesarean delivery when HIV RNA levels are detectable at time of delivery, reduces the risk of vertical HIV transmission to 2%[117]. Here we report on the clinical characteristics of HIV-infected pregnant women in the Netherlands and their immunologic and virologic responses to treatment.

A total of 1,055 pregnancies are registered in the SHM database, and cART was used in 676 women during pregnancy. Before 1998, when HIV-infected pregnant women were not treated, 75 pregnancies occurred, and 41 pregnancies resulted in an induced or spontaneous abortion. In this chapter we describe treatment responses in women who became pregnant after 1 January 1998 and who initiated cART before or during their pregnancy (n=676). Overall, 94% of the pregnant women were treated with cART during their pregnancy; 250 were already receiving treatment before they became pregnant, and 426 women initiated cART during pregnancy (Table 4.5). The proportion of women who were treated during their pregnancy increased

from 24% in 1998 to 100% in 2008 ($p<0.001$).

An overview of the most commonly used protease inhibitors (PI's) and non-nucleoside reverse transcriptase inhibitors (NNRT's) is shown in Table 4.6. The most commonly used cART regimens in pregnancy were ones that contained nevirapine and nelfinavir. Combinations including nevirapine and nelfinavir were well tolerated during pregnancy[151]. A nelfinavir-based regimen was the one most commonly used amongst pregnant women in the Netherlands. However, since 2003, the number of pregnancies in which HIV is treated with kaletra has increased. After the global re-call of nelfinavir after contamination with a genotoxic substance (www.who.int/hiv), kaletra became the most prescribed drug in HIV-infected pregnant women in the Netherlands. Kaletra was then used as an alternative to nelfinavir.

CD4 cell counts during pregnancy

The median CD4 cell counts at the beginning of pregnancy and at the time of delivery amongst women who were already on treatment and amongst those who initiated treatment during pregnancy are presented in Table 4.5. CD4 cell counts at the beginning and end of the pregnancy did not significantly differ between those two groups of women (Figure 4.5).

In the first 20 weeks of the pregnancy, CD4 cell counts decreased in both groups. This decrease was significantly stronger amongst women who initiated treatment during the pregnancy ($p<0.001$). Between weeks 20 and 28, CD4 cell counts started to increase amongst women who initiated treatment during pregnancy ($p<0.001$). After week 28, CD4 cell counts continued to increase in women who initiated treatment in their pregnancy, but the slope was less steep.

After week 20, CD4 cell counts slightly increased amongst women who were already on treatment, but this increase was not statistically significant and was less dramatic than the increase amongst women who started treatment in their pregnancy.

This decline in CD4 cell counts during the first 20 weeks of the pregnancy could be explained by hormonal changes, as reproductive hormones have an immunosuppressive function[152]. The increase in CD4 cell counts during the last trimester of the pregnancy have been shown to be pregnancy-related as well[153]. But because the increase in CD4 cell counts was much stronger amongst women who initiated treatment during their pregnancy, it is more likely to be a result of a successful response to treatment.

Viral load during pregnancy

HIV RNA levels at the beginning of pregnancy and at the time of delivery are shown in Table 4.5, stratified for women who were already on treatment and for women who initiated treatment during their pregnancy. HIV RNA levels were 1.40 (IQR, 1.40-2.84) $\log_{10}$ copies/ml for women who were already on treatment, whereas they were 3.87 (3.15-4.43) $\log_{10}$ copies/ml for women who initiated treatment during their pregnancy. At the time of delivery, the median HIV RNA levels significantly differed between both groups ($p=0.01$); 11% of the women who initiated treatment before pregnancy had a detectable load at time of delivery, whereas 28% of the women who initiated treatment during their pregnancy had a detectable load at the time of delivery. The risk of MTCT is very low amongst women who are effectively treated with cART[117], but a caesarean section is recommended in cases of a detectable viral load. In the Netherlands, 47% of the women with a detectable load indeed underwent a caesarean section.

Women who initiated cART before pregnancy had significantly lower HIV RNA plasma levels at the start of the pregnancy (Figure 4.6). In the first 20 weeks of the pregnancy, HIV RNA levels did not change significantly in either group. However, between weeks 20 and 28, a strong decline was seen amongst women who started treatment during their pregnancy ($p<0.001$), and this decline was steeper relative to women who initiated treatment before their pregnancy ($p<0.001$). After week

28, the decrease became more gradual, but it remained stronger amongst women who initiated cART during pregnancy ($p<0.001$).
The results of these analyses show a substantial decrease in HIV RNA levels amongst women who initiated cART before and during their pregnancy. The decline in HIV RNA levels amongst women who initiated treatment during their pregnancy was most marked between weeks 20 and 28. According to the current treatment guidelines, cART should be initiated during this time of the pregnancy[154]. A small decline was also seen amongst women who were already on treatment, and that probably reflects a change in regimen to a more effective combination or to a more preferable combination in pregnancy.

Although women who initiated treatment during their pregnancy had higher HIV RNA levels and somewhat lower CD4 cell counts, their immunologic and virologic responses to treatment did not differ from those of the women who were already on treatment. However, the proportion of women with detectable HIV RNA levels was higher amongst women who initiated cART during pregnancy than amongst those who started treatment before pregnancy. Therefore, measurement of HIV RNA levels at time of delivery, especially in women who initiated cART during their pregnancy, remains extremely important to reach a maximum level of prevention of MTCT.

Post partum: treatment after the pregnancy

The majority of pregnant women remained in care after their pregnancy. However, 150 out of 797 (19%) of the women did not visit one of the HIV treatment centres after 1 June 2008. Median time between parturition and date of last contact was 2.9 years (IQR: 1.4-4.5). Of the women who did not appear for care, 105 originated from Sub-Saharan Africa (25% of the total group of pregnant women from Sub-Saharan Africa), which means that 1 out of 4 HIV-infected women from Sub-Saharan Africa became lost to follow up after their pregnancy. Eleven percent of those lost to follow up were born in the Netherlands, and 20% were born in other countries.
After the women's first pregnancy, 74% remained on treatment; most of them did not change their regimen and remained on treatment with nelfinavir, nevirapine, or kaletra. However, 13 women stopped their treatment more than 30 days after their parturition date, and 25 women ended their treatment within 30 days after parturition.
Out of the 797 HIV-infected women who became pregnant, 14 died during follow up after the pregnancy. The median time between parturition and death was 3.3 years (IQR: 1.6-8.0). All women died between 2000 and 2008. Ten of these women remained on treatment after parturition, 2 ended their treatment more than 30 days after parturition, and 1 woman was on treatment at the time of death, but she became pregnant before the availability of cART. One woman was not treated for her HIV-infection; she was diagnosed with HIV during her pregnancy, which terminated in an abortion, and she died 4 months after being diagnosed with HIV.

cART in children and adolescents

Since 2004, HIV-infected children have been registered and monitored by the SHM. In this paragraph, clinical characteristics, immunologic and virologic response to treatment of HIV-infected children and adolescents are described. The term "children" refers to all individuals younger than 13 years of age at the time of HIV diagnosis, and "adolescents" refers to individuals aged from 13 to 18 years at the time HIV was diagnosed.

Clinical characteristics of the total population of HIV-infected children and adolescents in the Netherlands

Combination antiretroviral therapy (cART) was administered to 90% of the children and 76% of the adolescents (Tabel 4.7). The median CD4 cell counts at the start of cART were $702x10^6$ cells/L (Interquartile range [IQR], 193-1350) for children 2 years of age or

younger and the counts increased to 1430x10^6 cells/L (810-2094) at 24 weeks after the start of cART. Older children, aged 3 to 13 years, had lower CD4 cell counts at cART initiation (320x10^6 cells/L (IQR, 120-570)) and CD4 cell counts increased to 530x10^6 cells/L (312-790) at 24 weeks after the start of cART. Adolescents had lower CD4 cell counts, 251x10^6 cells/L (IQR, 150-400) at cART initiation and 400x10^6 cells/L (254-600) at 24 weeks. Amongst young children, HIV RNA levels decreased from 5.6 $\log_{10}$ copies/ml (IQR, 4.8-5.9) at baseline to 2.6 $\log_{10}$ copies/ml (2.1-2.9) 24 weeks after cART initiation. Older children and adolescents had somewhat lower HIV RNA levels.

Immune response

Young children had significantly higher CD4 cell counts at cART initiation compared to both older children and adolescents (Figure 4.7). In the first 12 weeks after cART initiation, a significant increase was observed amongst both younger and older children ($p<0.001$), and this increase was significantly more rapid compared to that in the adolescents (Figure 4.7). In all groups, CD4 cell counts continued to increase more than 12 weeks after cART initiation, but this increase was not significant for the older children and adolescents.

This age-related variation in the absolute number of CD4 cell counts was also observed in the non-HIV-infected population[155]. CD4 cell counts are known to decrease with increasing age, which explains the lower CD4 cell counts amongst the older children and the adolescents.

Virologic response

The older children and adolescents had significantly lower HIV RNA levels at the start of cART than did the young children ($p<0.001$) (Figure 4.8). In the first 12 weeks after cART initiation a strong decline in HIV RNA levels was seen in all groups ($p<0.001$), and more than 12 weeks after start of cART, the decrease in HIV RNA levels remained significant in all three groups. However, more than 24 weeks after cART initiation, HIV RNA levels did not decrease; they remained stable in children and adolescents.

With the improved formulation, children can be effectively treated with cART, and most of these children will reach the age of 18 years. Although young children have a comparable virologic response to treatment and an even better immunologic response compared to the adolescents as shown in our analysis, as well as in analyses by others[156,157], it remains to be seen if the prognosis for children treated with cART will compare favourably to the prognosis for those infected and treated later in life.

Table 4.1: Baseline characteristics of 11,268 patients starting cART between 1 July 1996 and 31 December 2008.

	Pre-treated		Naïve <2004		Naïve 2004-200		Naïve 2008	
	N	%	N	%	N	%	N	%
Total	1988	100	5099	100	3170	100	1011	100
Gender								
Male	1625	81.7	4081	80.0	2498	78.8	844	83.5
Transmission risk group								
MSM	1165	58.6	2713	53.2	1661	52.4	652	64.5
IDU	225	11.3	294	5.8	136	4.3	27	2.7
Heterosexual contact	456	22.9	1721	33.8	1105	34.9	267	26.4
Blood-blood contact	59	3.0	100	2.0	31	1.0	12	1.2
Other	83	4.2	271	5.3	237	7.5	53	5.2
Region of origin								
Netherlands	1258	63.3	2864	56.2	1707	53.8	655	64.8
W-Europe/N-America/Australia	252	12.7	439	8.6	220	6.9	62	6.1
Caribbean/Latin America	183	9.2	528	10.4	387	12.2	101	10.0
Sub-Saharan Africa	178	9.0	915	17.9	585	18.5	121	12.0
Other	117	5.9	353	6.9	271	8.5	72	7.1
Clinical stage CDC-C	742	37.3	1452	28.5	852	26.9	160	15.8
HBV								
negative	1614	81.2	4346	85.2	2802	88.4	904	89.4
positive	177	8.9	352	6.9	200	6.3	57	5.6
unknown	197	9.9	401	7.9	168	5.3	50	4.9
HCV								
negative	1332	67.0	3947	77.4	2606	82.2	852	84.3
positive	260	13.1	377	7.4	223	7.0	82	8.1
unknown	396	19.9	775	15.2	341	10.8	77	7.6
Initial regimen								
NNRTI-based	256	12.9	1511	29.6	2009	63.4	757	74.9
PI-based	1649	82.9	3223	63.2	1009	31.8	206	20.4
NRTI-based	39	2.0	223	4.4	10	0.3	2	0.2
Other	44	2.2	142	2,8	142	4.5	46	4.6
	Med	**IQR**	**Med**	**IQR**	**Med**	**IQR**	**Med**	**IQR**
Age at starting cART	38.6	33.3-45.5	37.4	31.8-44.4	39.9	33.4-46.7	40.5	33.9-47.5
CD4 cell count at starting cART (cells/mm^3)	230	120-380	220	100-370	200	110-280	250	170-320
HIV RNA at starting cART (log_{10} cps/ml)	4.38	3.34-5.00	5.00	4.53-5.43	5.00	4.61-5.40	4.98	4.45-5.37

MSM: men having sex with men; IDU: injecting drug use; W-Europe: western Europe; N-America: North America; HBV: hepatitis B virus; HCV: hepatitis C virus; med: median; IQR: interquartile range.

Table 4.2: Results from an adjusted Cox proportional hazard model of time from the start of cART to a first of 2 consecutive plasma HIV RNA concentration <50 copies/ml in 4,356 patients who were antiretroviral therapy naïve and started cART between 1 January 2003 and 31 December 2008. Variables with an overall p-value<0.20 were retained in the adjusted model.

	HR	95% CI	p
Calendar year of starting cART			
2003	0.94	(0.84 - 1.06)	0.31
2004	1.05	(0.94 - 1.18)	0.36
2005	1.00		
2006	1.03	(0.91 - 1.15)	0.67
2007	0.93	(0.84 - 1.04)	0.22
2008	0.86	(0.76 - 0.97)	0.01
Gender			
Male	1.00		
Female	1.10	(0.99 - 1.22)	0.07
Age at starting cART (years)			
<30	0.78	(0.70 - 0.87)	<0.0001
30-40	1.00		
40-50	1.06	(0.97 - 1.15)	0.18
≥50	1.07	0.96 - 1.18)	0.21
Transmission risk group			
MSM	1.00		
IDU	0.71	(0.58 - 0.85)	0.0004
Heterosexual contact	0.86	(0.78 - 0.95)	0.002
Other	0.86	(0.75 - 0.98)	0.03
Region of origin			
Netherlands	1.00		
Caribbean/Latin America	1.01	(0.90 - 1.13)	0.85
Other	1.10	(0.97 - 1.25)	0.15
Sub-Saharan Africa	1.04	(0.93 - 1.16)	0.47
W-Europe/N-America	0.84	(0.73 - 0.97)	0.01
CDC Clinical stage			
A-B	1.00		
C	1.06	(0.98 - 1.15)	0.16
CD4 count at the start of cART (cells/mm^3)			
<50	0.92	(0.81 - 1.05)	0.23
50-200	0.93	(0.86 - 1.01)	0.08
200-350	1.00		
350-500	0.93	(0.81 - 1.07)	0.31
≥500	0.79	(0.65 - 0.95)	0.01
Plasma HIV RNA concentration (log_{10} copies/ml)			
<4	1.69	(1.49 - 1.91)	<0.0001
4-5	1.00		
≥5	0.67	(0.62 - 0.73)	<0.0001
Initial regimen			
NNRTI-based	1.00		
PI-based	0.83	(0.77 - 0.89)	<0.0001
NRTI-based	0.63	((0.46 - 0.84)	0.002
Other	0.88	(0.75 - 1.04)	0.14

CI: confidence interval; cART: combination antiretroviral therapy; MSM: men having sex with men; IDU: injecting drug user; W-Europe: western Europe; N-America: North America; HBV: hepatitis B virus; HCV: hepatitis C virus; NNRTI: non-nucleoside reverse transcriptase inhibitor; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor.

Table 4.3: Adjusted estimates from a logistic model of the probability of viral suppression <50 copies/ml in 4,356 patients (left columns). Plasma viral load measurements obtained at 12, 36, 48 weeks and at every 24 weeks thereafter were included. The right columns shows results from a similar analysis with only those concentrations obtained from patients who had been continuously on cART. A longitudinal logistic model was used, adjusted for the number of weeks after starting cART and the variables listed in the table. A generalized estimating equations (GEE) model was used to adjust for repeated measurements per patient.

	All patients			Patients on continuous cART		
	OR	95% CI	p	OR	95% CI	p
Calendar year of starting cART						
2003	0.88	(0.72 - 1.07)	0.20	0.74	(0.59 - 0.92)	0.007
2004	0.98	(0.81 - 1.18)	0.81	0.63	(0.49 - 0.81)	0.0003
2005	1.00			1.00		
2006	1.08	(0.87 - 1.32)	0.49	0.98	(0.72 - 1.34)	0.92
2007	0.83	(0.68 - 1.01)	0.06	0.83	(0.70 - 0.97)	0.02
2008	0.82	(0.65 - 1.03)	0.08	0.90	(0.71 - 1.14)	0.36
Age at starting cART (years)						
<30	0.78	(0.65 - 0.93)	0.007	1.03	(0.82 - 1.30)	0.78
30-40	1.00			1.00		
40-50	1.12	(0.96 - 1.30)	0.14	1.10	(0.88 - 1.37)	0.40
≥50	1.19	(1.00 - 1.42)	0.05	1.07	(0.84 - 1.36)	0.57
Transmission risk group						
MSM	1.00			1.00		
IDU	0.85	(0.73 - 0.99)	0.04	0.71	(0.58 - 0.85)	0.0004
Heterosexual contact	0.70	(0.50 - 0.97)	0.03	0.86	(0.78 - 0.95)	0.002
Other	0.72	(0.57 - 0.89)	0.003	0.86	(0.75 - 0.98)	0.03
Region of origin						
Netherlands	1.00			1.00		
Caribbean/Latin America	0.86	(0.70 - 1.06)	0.17	0.94	(0.75 - 1.17)	0.57
Other	1.12	(0.88 - 1.41)	0.36	1.09	(0.85 - 1.40)	0.49
Sub-Saharan Africa	0.81	(0.67 - 0.99)	0.04	0.79	(0.64 - 0.98)	0.03
W-Europe/N-America/Australia	0.81	(0.64 - 1.04)	0.10	0.93	(0.72 - 1.21)	0.58
CDC Clinical stage						
A-B	1.00					
C	1.18	(1.01 - 1.37)	0.04			
CD4 count at the start of cART (cells/mm^3)						
<50	0.87	(0.69 - 1.10)	0.25	1.49	(1.05 - 2.12)	0.03
50-200	0.96	(0.83 - 1.11)	0.57	0.64	(0.50 - 0.81)	0.0002
200-350						
350-500	0.61	(0.47 - 0.77)	<0.0001	0.97	(0.58 - 1.62)	0.91
≥500	0.28	(0.21 - 0.37)	<0.0001	0.52	(0.44 - 0.62)	<0.0001
Plasma HIV RNA concentration (log_{10} copies/ml)						
<4	0.97	(0.75 - 1.25)	0.79	0.33	(0.18 - 0.60)	0.0003
4-5	1.00			1.00		
≥5	0.69	(0.60 - 0.79)	<0.0001	0.62	(0.54 - 0.71)	<0.0001
Initial regimen						
NNRTI-based	1.00			1.00		
PI-based	0.61	(0.53 - 0.69)	<0.0001	0.99	(0.83 - 1.18)	0.92
NRTI-based	0.55	(0.32 - 0.93)	0.03	1.00	(0.66 - 1.52)	0.99
Other	0.30	(0.24 - 0.38)	<0.0001	0.72	(0.56 - 0.93)	0.01

OR: odds ratio; CI: confidence interval; cART: combination antiretroviral therapy; MSM: men having sex with men; IDU: injecting drug user; W-Europe: western Europe; N-America: North America; NNRTI: non-nucleoside reverse transcriptase inhibitors; PI: protease inhibitors; NRTI: nucleoside reverse transcriptase inhibitors.

Table 4.4: Incidence of toxicity-driven therapy changes per 100 person-years on combination antiretroviral therapy (PYcART) (95% confidence intervals [CI]) during the first 3 years after starting cART for male and female patients who were antiretroviral therapy-naïve or pre-treated at the start of first initiation of cART. Reported 95% CI's are based on the Poisson distribution. The incidence of toxicity-related changes in the regimen during the first 3 years after the first start of cART was calculated as the total number of these changes divided by the person-years on cART. Thus, more than one toxicity-driven regimen per patient was allowed. Patient follow-up was censored at the date of death or at the last outpatient clinical visit, CD4 cell count, or HIV RNA measurement, whichever came first.

	Naïve				Pretreated			
	Male		Female		Male		Female	
Months after starting cART								
0-3	54.6	(51.5-57.9)	76.5	(69.0-84.5)	47.0	(40.9-53.9)	58.0	(43.8-75.4)
3-6	23.4	(21.2-25.9)	29.9	(24.8-35.7)	30.7	(25.2-36.9)	28.9	(18.1-43.8)
6-12	18.1	(16.6-19.6)	22.2	(18.9-25.8)	23.0	(19.6-26.8)	31.7	(23.3-42.2)
12-24	15.8	(14.7-16.9)	17.6	(15.4-20.0)	25.4	(22.8-28.3)	31.5	(25.3-38.9)
24-36	11.5	(10.5-12.5)	16.4	(14.1-19.0)	22.2	(19.6-25.0)	23.9	(18.3-30.8)
Age at the start of cART (years)								
<30	21.1	(19.0-23.4)	28.6	(25.4-32.1)	24.3	(18.4-31.5)	28.2	(20.9-37.3)
30-40	19.5	(18.5-20.7)	25.4	(23.1-27.8)	26.2	(23.7-28.8)	30.1	(25.3-35.5)
40-50	20.8	(19.7-22.1)	22.5	(19.5-25.8)	29.5	(26.9-32.4)	39.2	(30.7-49.4)
50-60	22.1	(20.3-24.1)	34.3	(27.7-42.1)	22.4	(18.8-26.5)		
≥60	20.7	(17.5-24.3)	37.6	(28.2-49.0)	29.2	(20.6-40.0)		
Weight at starting cART (kg)								
<55	20.9	(18.1-24.1)	27.7	(24.0-31.8)	27.9	(21.5-35.7)	39.0	(29.1-51.1)
55-65	22.0	(20.4-23.7)	27.8	(24.9-31.1)	27.5	(24.0-31.4)	34.0	(27.8-41.2)
65-75	20.9	(19.8-22.1)	27.3	(24.4-30.5)	28.5	(25.8-31.3)	30.0	(23.7-37.5)
75-85	20.5	(19.2-22.0)	23.1	(19.6-27.1)	23.7	(21.0-26.7)	21.4	(12.7-33.8)
≥85	17.7	(16.1-19.4)	24.1	(19.3-29.6)	26.5	(22.1-31.6)	29.3	(17.9-45.2)
≥60	20.7	(17.5-24.3)	37.6	(28.2-49.0)	29.2	(20.6-40.0)		

Table 4.5: Clinical characteristics of HIV-infected pregnant women, 1 January 1988-1 June 2009.

	Total
Start cART	
Before pregnancy (%)	250 (31%)
During pregnancy (%)	426 (52%)
No cART during pregnancy (%)	41^ (17%)
pregnancy before cART availability%	75
cART initiation before pregnancy:	
CD4 count at start of pregnancy	435 (310-620)
CD4 count at delivery	460 (300-610)
Undetectable load at delivery	
Yes	133 (53)
No	27 (11)
Unknown	90 (36)
HIV RNA level at start of pregnancy	1.40 (1.40-2.84)
HIV RNA level at delivery	1.40 (1.40-1.40)
cART initiation during pregnancy:	
CD4 count at start of pregnancy	440 (290-606)
CD4 count at delivery	470 (320-645)
Undetectable load at delivery	
Yes	269 (63)
No	121 (28)
Unknown	36 (8)
HIV RNA level at start of pregnancy	3.87 (3.15-4.43)
HIV RNA level at delivery	1.40 (1.40-2.28)

cART: combination antiretroviral therapy

^) 31 of these pregnancies were ended by abortion (induced or spontaneous)

Table 4.6: Overview of the most frequently used PI's and NNRT's in HIV-infected pregnant women in the Netherlands between 1 January 1998 and 1 January 2009.

	Total number of pregnancies with treatment	Known regime NVP	NFV	Kaletra	Other/ unknown
1998	9	2 (22)	0	0	7 (78)
1999	37	8 (22)	8 (22)	0	21 (57)
2000	56	6 (11)	21 (38)	0	29 (52)
2001	85	15 (18)	22 (26)	1 (1)	47 (55)
2002	94	14 (15)	16 (17)	4 (4)	60 (64)
2003	125	28 (22)	31 (25)	13 (10)	53 (42)
2004	143	35 (24)	45 (31)	12 (8)	51 (36)
2005	138	26 (19)	35 (25)	18 (13)	59 (43)
2006	107	14 (13)	22 (21)	13 (12)	58 (54)
2007	83	15 (18)	9 (11)	24 (29)	35 (42)
2008	18	3 (17)	1 (5)	3 (17)	11 (61)

PI's: Protease inhibitors

NNRTI's: non-nucleoside reverse transcriptase inhibitors

NVP: nevirapine

NFV: nelfinavir

Table 4.7 Clinical characteristics of HIV-1-infected children (age 0-12 years at time of HIV diagnosis) and adolescents (age 13-17 years at time of HIV diagnosis) ever in follow-up until 1 June 2009 in the SHM cohort.

Clinical characteristics at cART initiation	**Children**	**Adolescents**
cART use	188 (90%)	120 (76%)
Baseline CD4 cell counts ($x10^6$ cells/l) (median, IQR)		
≤ 2 years of age	702(193-1350)	-
> 2 years of age	320 (120-570)	251 (150-400)
Baseline HIV RNA (log_{10}/ml) (median, IQR)		
≤ 2 years of age	5.6 (4.8-5.9)	-
> 2 years of age	4.8 (4.3-5.4)	4.3 (3.5-5.1)
detectable HIV RNA levels at baseline		
≤ 2 years of age	72 (81%)	-
> 2 years of age	77 (65%)	84 (53%)
Clinical characteristics at 24 weeks after cART initiation		
CD4 cell counts at T1 ($x10^6$ cells/l) (median, IQR)		
≤ 2 years of age	1430 (810-2094)	-
> 2 years of age	530 (312-790)	400 (254-600)
HIV RNA at T1 (log_{10}/ml) (median, IQR)		
≤ 2 years of age	2.6 (2.1-2.9)	-
> 2 years of age	2.1 (1.7-2.6)	2.1 (1.7-3.2)
detectable HIV RNA levels at T1		
≤ 2 years of age	19 (21%)	-
> 2 years of age	14 (12%)	29 (18%)

Baseline: start of combination antiretroviral therapy (cART); T1, 24 weeks after start cART; IQR, interquartile range; MTCT, mother to child transmission.

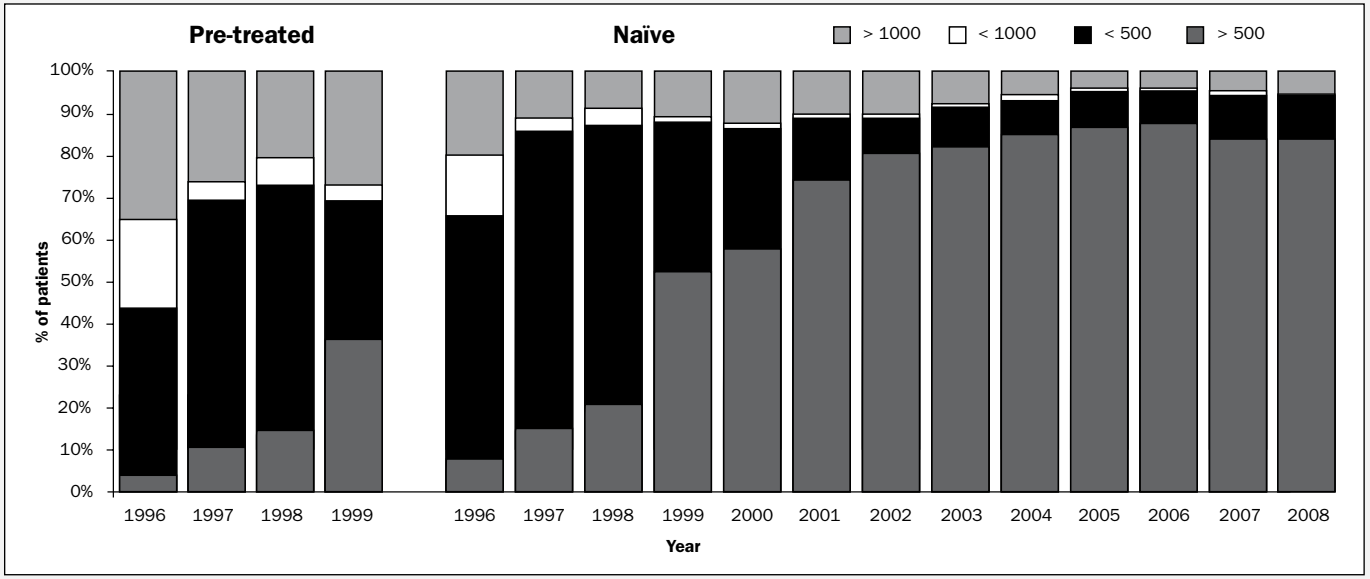


Figure 4.1: Plasma HIV-RNA (copies/ml) at week 36 for pre-treated and therapy-naïve patients at the start of combination antiretroviral therapy (cART) according to calendar year of starting cART. The figure includes a combination of assays for plasma viral load with a lower detection limit of 1000 copies/ml in earlier calendar years and those with limits of 400/500 and 50 copies/ml in later calendar years. From 2002 onwards, assays with a lower detection limit of 50 copies/ml were routinely used.

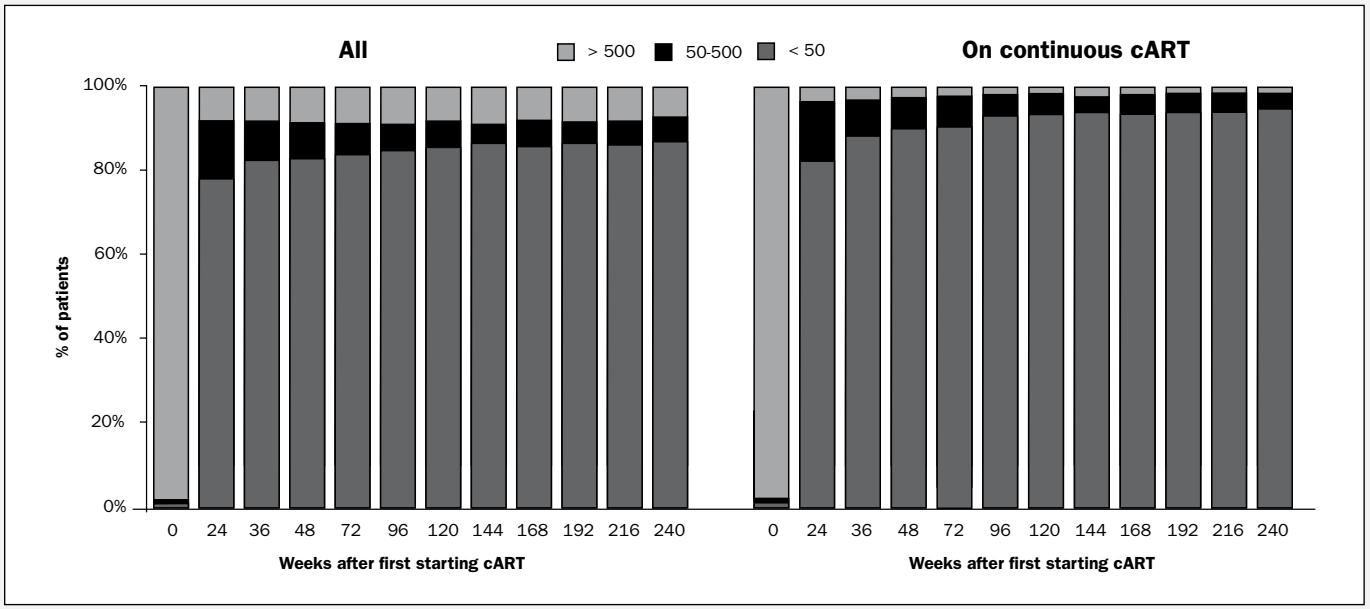


Figure 4.2: Plasma HIV RNA concentration (copies/ml) at weeks 24, 36, and 48 and at every 24 weeks of follow-up thereafter in 4,356 therapy-naïve patients starting combination antiretroviral therapy (cART) in or after 2000 and in a subgroup of patients continuously on cART. A therapy interruption of <2 weeks was allowed.

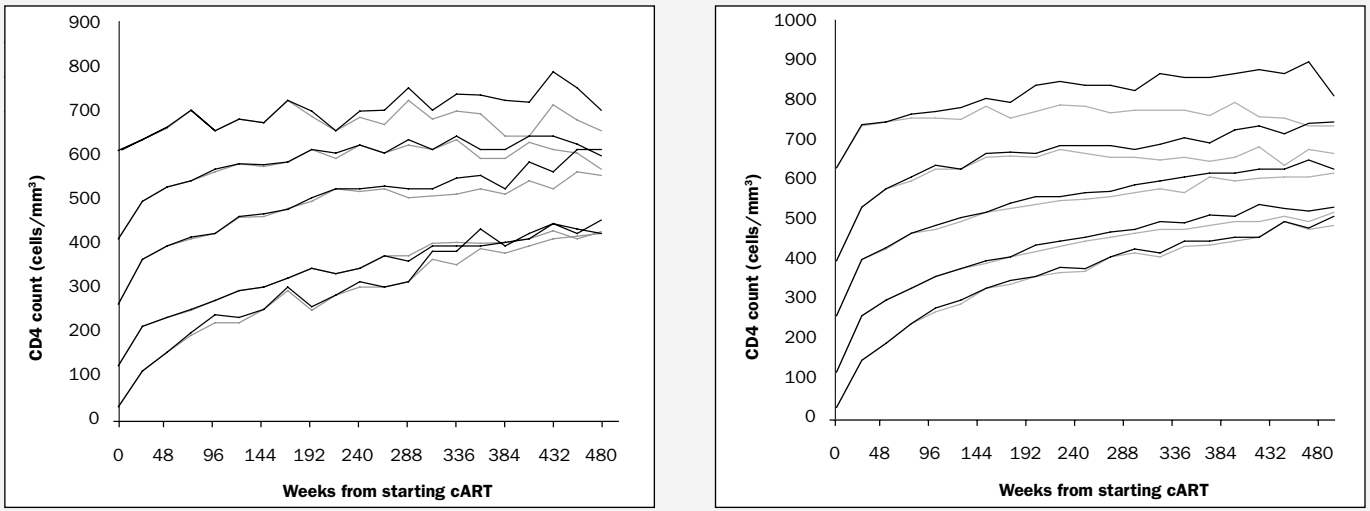


Figure 4.3: Median CD4 count according to CD4 count at start of combination antiretroviral therapy (cART) in pre-treated patients (left) and naïve patients (right) according to CD4 cell count at the start of cART (<50, 50-200, 200-350, 350-500 and ≥500 cells/mm^3). Grey lines show the median CD4 cell counts after starting cART for all patients and black lines shown the median CD4 counts for patients with an initial suppression to below 50 copies/ml within 9 months after starting cART and with plasma HIV RNA concentrations levels <50 copies/ml thereafter. In this last subgroup, CD4 cell counts were censored at the first of 2 consecutive measurements of HIV RNA >50 copies/ml after the initial suppression of <50 copies/ml.

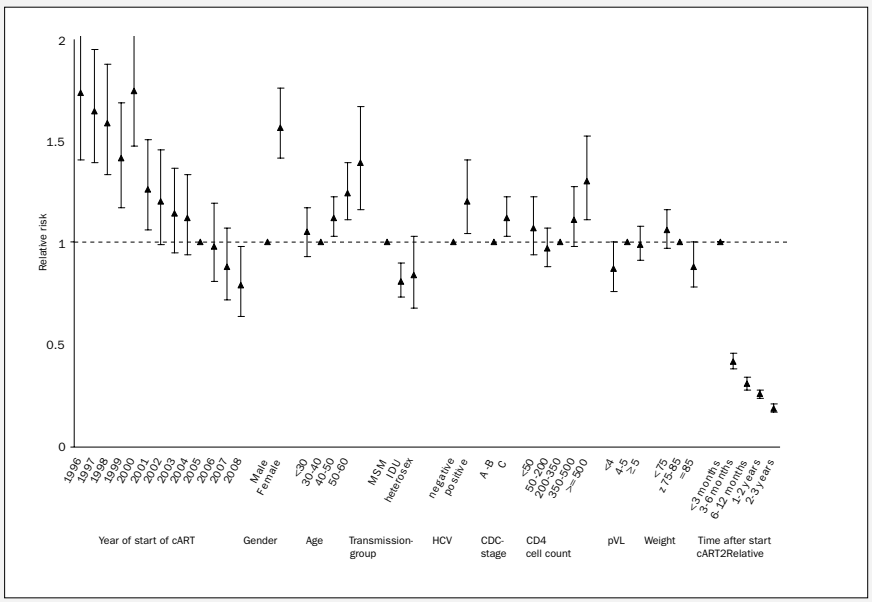
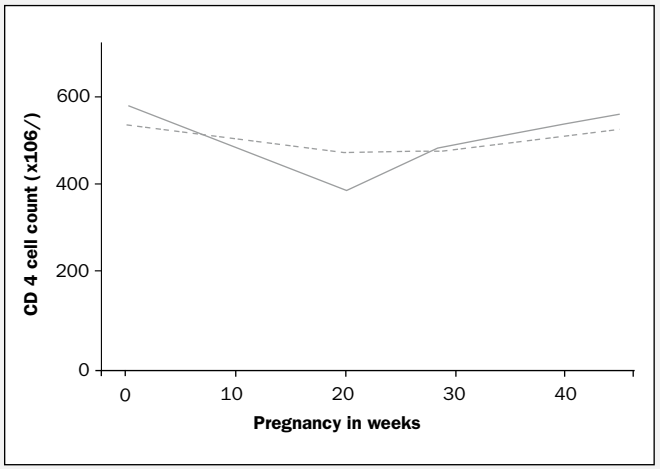


Figure 4.4: Relative risk estimates of toxicity-driven regimen changes during the 3 years after starting cART per 100 person-years of cART use in 9,280 therapy-naïve patients.



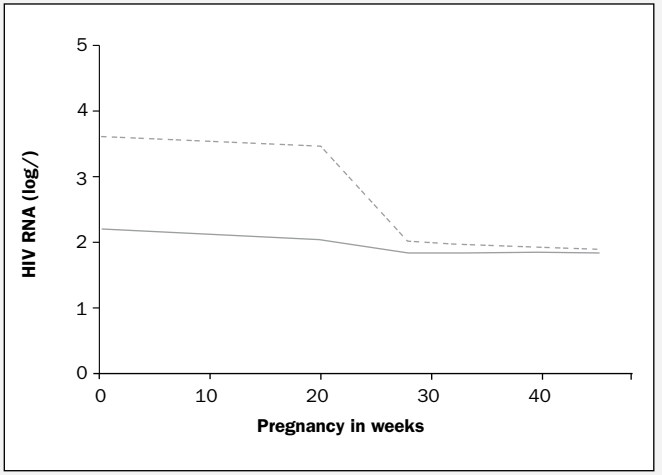
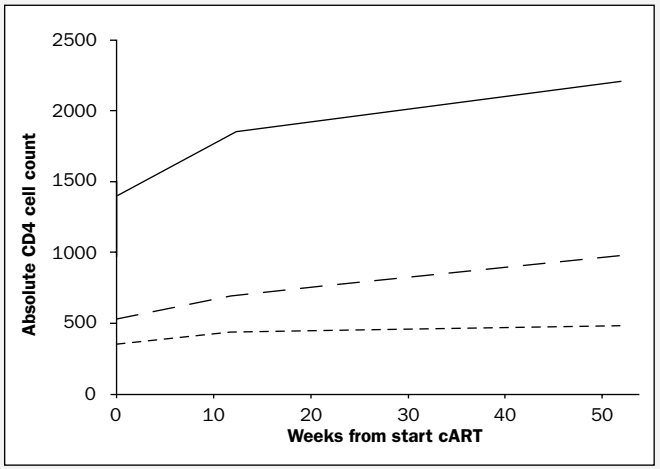


Figure 4.5 & 4.6: The immunologic and virologic trajectories during pregnancy amongst women who initiated cART before their pregnancy (solid line) and amongst women who initiated cART during their pregnancy (dashed line) were piecewise modeled, with a random intercept model. Time was described in weeks from the beginning of the pregnancy until delivery. When an HIV diagnosis was made during pregnancy, time was still included from the beginning of the pregnancy, but CD4 cell counts and HIV RNA levels were missing for the first weeks of the pregnancy. Since changes in CD4 cell counts and HIV RNA levels could occur during pregnancy, slopes were allowed to change at weeks 20 and 28 of the pregnancy.



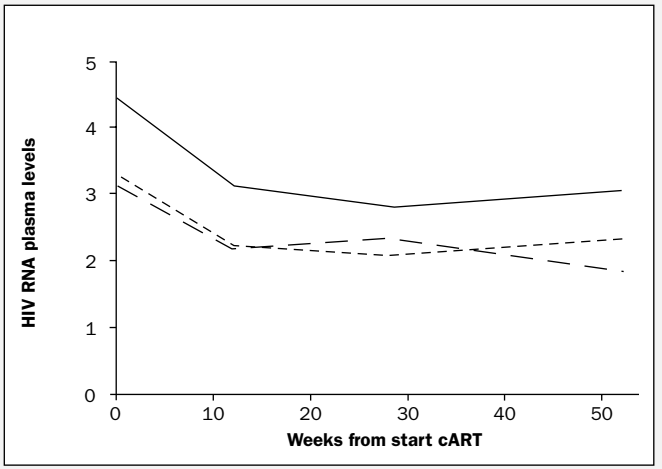


Figure 4.7 & 4.8: Absolute CD4 cell counts and HIV RNA levels amongst HIV-infected children in the Netherlands, since start of combination antiretroviral therapy (cART). (Solid line: young children, <=2 years, short dashes: older children, 3-12 years and long dashes; adolescents, 13-18 years.) Changes in CD4 cell and HIV RNA levels during treatment were modelled with a random intercept model, which allowed for a random intercept. The slope was allowed to change at 12 weeks after cART initiation. The immunologic and virologic responses were compared between young children (aged 2 years and below), the older children (aged 3 to 13 years) and the adolescents (aged 13 to 18 years).

5. Resistance

Ard van Sighem

When adherence to antiretroviral treatment is not optimal, suppression of HIV replication may be incomplete. This, in turn, may lead to selection of HIV virus strains that are resistant to one or more of the drugs used in the therapy regimen. The presence of resistant strains limits future therapy options and may lead to a worsened prognosis. In addition, resistant strains can be transmitted to uninfected patients. Monitoring the prevalence of resistance over time and the extent to which resistant strains are transmitted to uninfected individuals is one of the pillars of the monitoring program of the SHM.

Resistance during treatment

As drug-resistant virus strains are present only in patients with incomplete suppression of HIV, the prevalence of such strains in the treated population was studied in those patients who failed on antiretroviral treatment. Failure was defined as at least two consecutive viral-load measurements above 500 copies/ml after the start of treatment. A period of failure was considered to start at the midpoint of the interval between the last measurement below 500 copies/ml and the first one above that level. Analogously, the period of failure was considered to end at the midpoint of the interval between the last measurement above 500 copies/ml and the first one below that level. The annual proportion of patients failing whilst on treatment was calculated as the ratio of the number of patients failing to the number of patients being followed during the year.

The prevalence of resistance to antiretroviral drugs was determined by scanning genotypic sequences for specific major mutations at codons known to be associated with resistance to the three major classes of drugs: nucleoside reverse transcriptase inhibitors (NRTI's), non-nucleoside reverse transcriptase inhibitors (NNRTI's), and protease inhibitors (PI's)[158]. A genotypic resistance interpretation algorithm developed by Stanford University was used to infer a drug susceptibility score for each sequence according to a 5-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance[159].

The annual proportion of patients pre-treated with non-cART (combination antiretroviral therapy) regimens who failed on cART declined from 49% in 1997 to 11% in 2008. During the same period, the proportion of previously therapy-naïve patients who experienced failure remained between 6% and 8%. In the group of pre-treated patients, the fraction of failing patients from whom a sequence was obtained increased from 9% in 1997 to levels between 20% and 30% between 2000 and 2007. In the therapy-naïve group, the fraction of patients with a sequence was 35% in 2003, and it decreased to 19% in 2005 and thereafter.

In the total HIV-infected population, 3,211 sequences were obtained after the patients started cART. Of these sequences, 1,393 (43.4%) were obtained from pre-treated patients and 1,818 (56.6%) from previously therapy-naïve patients; 2,321 (72.3%) contained at least one resistance-associated mutation, and the rest, 890 (27.7%), contained none. Resistance was found in 1,227 (88.1%) sequences from pre-treated patients and in 1,094 (60.2%) sequences from therapy-naïve patients. In total, 2,610 (81.3%) sequences were obtained whilst the patients were on treatment, and 59 (1.8%) sequences were obtained within 2 weeks after discontinuation of treatment.

The levels and nature of drug resistance observed per calendar year were different between pre-treated and naïve patients (Figure 5.1). In the pre-treated group, the proportion of sequences with high-level resistance to zidovudine and stavudine was on average

50% (95% confidence interval [CI], 47-53) and 45% (43-48), respectively, and declined over calendar time. In recent years, the proportion of sequences with resistance to zidovudine, stavudine, didanosine, or abacavir was between 40% and 50%. Meanwhile, the proportion of sequences with resistance to lamivudine and emtricitabine was 63% (95% CI, 60-66) and did not change over time. High-level resistance to tenofovir was rare and varied between 0% and 5% between 1996 and 2008. However, when intermediate and high levels of resistance to tenofovir were combined, the overall level of resistance was 54% (95% CI, 51-57). Amongst patients who had started cART whilst being antiretroviral therapy-naïve, the prevalence of resistance to NRTI's was below 10%, except for resistance to lamivudine and emtricitabine, which declined over time to 41% (95% CI, 32-50) in 2008.

Resistance to NNRTI's increased after the introduction of nevirapine and efavirenz as part of the cART regimen in approximately 1998. Between 1999 and 2008, high-level resistance to nevirapine in the pre-treated population increased from 49% (95% CI, 37-60) to 64% (41-83). During the same period, the proportion of sequences resistant to efavirenz increased from 38% (95% CI, 27-49) to 45% (24-68). In the therapy-naïve population, resistance to nevirapine was found in 44% (95% CI, 35-54) of the sequences obtained in 2008, whilst resistance to efavirenz was found in 33% (25-42). In both pre-treated and therapy-naïve patients, the prevalence of resistance did not significantly change after 2002 ($p>0.04$). Predicted levels of resistance to the new NNRTI etravirine were less than 10%. When intermediate and high levels of resistance to etravirine were combined, the prevalence of resistance was 22% (95% CI, 20-24) amongst previously therapy-naïve patients and 32% (29-35) amongst pre-treated patients.

Resistance to PI's increased after their widespread introduction in approximately 1996. In the pre-treated population, the prevalence of resistance was highest for the older generation of PI's, including nelfinavir, saquinavir, and indinavir, and resistance to these PI's was found in more than 30% of sequences after 2002. In 2007, approximately 20% of the sequences were fully resistant to lopinavir, and less than 10% to tipranavir and darunavir. In the same year, intermediate or high levels of resistance to lopinavir were found in 77% of the sequences, to tipranavir in 57%, and to darunavir in 30%. In the naïve population, resistance to PI's was less than 10% in recent years.

As of 1 June 2009, a total of 12,258 HIV-1-infected adults were still being actively followed. In 1,380 (11.3%) of those patients, at least one sequence with resistance-associated mutations had been obtained, and 1,078 (78.1%, or 8.8% of the population in follow-up) had high-level resistance to at least one antiretroviral drug. These percentages most likely underestimate the true prevalence of resistance in the total population, since a resistance test was performed in only 20% to 30% of the patients failing on treatment. Besides, other cohorts have found higher prevalences. For example, in Switzerland, the prevalence of resistance in 2007 was estimated to be between 37% and 45%, whilst in British Columbia, Canada, resistance was found in 28% of the patient population[35,36].

The number of patients with high-level resistance to drugs from one class was 491 (35.6%). Resistance to drugs from two classes was found in 511 (37.0%) patients, whereas 168 (12.2%) were found to be resistant to drugs from all three classes. High-level resistance to at least one NRTI was found in 1,000 (72.5%) of the patients; of those patients, 883 (88.3%) were resistant to lamivudine and emtricitabine, and 454 (45.4%) to other NRTI's. High-level resistance to at least one PI was found in 317 (23.0%) patients and to at least one NNRTI in 700 (50.7%). Table 5.1 shows the inferred resistance level for each antiretroviral drug in the group of 1,380 patients.

Transmission of drug-resistant virus

Since 2003, treatment guidelines recommend obtaining a genotypic sequence at HIV diagnosis to assess whether patients are infected with a drug-resistant virus strain, since the presence of resistant virus will limit future therapy options. Before 2003, sequences at the time of diagnosis were not routinely obtained, and those sequences that are available were obtained mostly for dedicated studies or retrospectively when patients failed on antiretroviral treatment. In total, 2,238 patients diagnosed between 2003 and 2008 (2,740 patients when including diagnoses prior to 2003) had a genotypic sequence available within one year after diagnosis and before the start of antiretroviral treatment. During the same period, there were 6,387 HIV diagnoses. Hence, a sequence was obtained for 35.0% of the diagnosed patients.

Of the 2,238 patients, 671 (30.0%) were recently infected, i.e., they were diagnosed either during the acute phase of the infection or they had tested positive for HIV-1 less than 1.5 years after their last negative test. The other 1,567 (70.0%) patients with a known date of their first positive test for HIV constituted the group of newly diagnosed patients (Table 5.2). Of the 671 recently infected patients, 579 (86.3%) were men of Dutch origin who were infected by homosexual contact, whereas only 891 (56.9%) of the 1567 newly diagnosed patients shared the same characteristics. Heterosexually infected patients from Sub-Saharan Africa accounted for 244 (15.6%) of the newly diagnosed patients and for 11 (1.6%) of the recently infected patients. However, the improving access to antiretroviral treatment in Africa will most likely increase the prevalence of drug resistance in that region. This increased prevalence could subsequently lead to an increase in transmitted resistance not only in Sub-Saharan Africa but also in the migrant population in the Netherlands.

Amongst the 671 recently infected patients, resistance-associated mutations were found in 53 (7.9%, [95% CI, 6.0-10.2]). The annual percentage of patients with resistance-associated mutations did not change over time (Figure 5.2). In total, 651 patients were fully susceptible to all PI's, 631 to all NRTI's, and 651 to all NNRTI's. Five patients (0.7%) had intermediate or high-level resistance to at least one PI, 16 (2.4%) to at least one NRTI, and 8 (1.2%) to at least one NNRTI. Overall, 24 patients had intermediate or high-level resistance to at least one drug, corresponding to a prevalence of 3.6% (95% CI, 2.3-5.3), which was lower than the prevalence of major resistance-associated mutations. Apparently, the presence of resistance-associated mutations is not necessarily a sign of full resistance. Two patients had intermediate or high-level resistance to all three drug classes and one patient to two drug classes.

Resistance-associated mutations were found in 120 (7.7% [95% CI, 6.4-9.8]) of the 1,567 newly diagnosed patients (Figure 5.2). This proportion did not differ from that of patients with a recent infection ($p=0.8$). Amongst the 891 patients infected via homosexual contact, 84 (9.4%) had at least 1 mutation, compared to 29 (5.3%) of the 547 patients infected via heterosexual contact ($p=0.005$). Resistance was also more common amongst patients infected with a subtype B virus (9.2%), compared to those with a non-B subtype (3.8%) ($p<0.001$). On the basis of the prevalence of transmitted resistance in different transmission risk categories and the total number of diagnoses in each category from 2003 onwards, the prevalence of resistance in the total population diagnosed in or after 2003 was estimated to be 7.6%.

Intermediate or high-level resistance to PI's was found in 7 (0.4%) patients, to NRTI's in 34 (2.2%), and to NNRTI's in 38 (2.4%). These proportions for PI's and NRTI's did not differ from those observed in patients with a recent infection ($p>0.4$), but the proportion of patients with NNRTI resistance tended to be higher ($p=0.06$). Intermediate or high-level resistance to efavirenz was found in 26 (1.7%) newly diagnosed patients and in 8 (1.2%) recently infected patients ($p=0.4$),

whereas resistance to nevirapine was found in 38 (2.4%) newly diagnosed patients and in 8 (1.2%) of those recently infected (p=0.06). In total, 68 patients had intermediate or high-level resistance to at least one antiretroviral drug, corresponding to a prevalence of 4.3% (95% CI, 3.4-5.5), which was not significantly different from the prevalence amongst recently infected patients (p=0.4). Two patients had high-level resistance to drugs from all three classes. The prevalence of intermediate or high-level resistance to at least one drug in the total population diagnosed in or after 2003 was also estimated to be 4.3%.

The proportion of patients with evidence of transmitted drug resistance in the Netherlands was similar to proportions found in other European countries[37-39]. In the EuroSIDA study, the prevalence of transmitted drug resistance between 1996 and 2004 was 11.4%[38]. In Switzerland, the prevalence was 7.7% during the same period, and no changes over time were observed[37]. These relatively low levels of transmitted resistance may be the result of a limited reservoir of infectious patients in whom resistance developed during treatment. On the other hand, transmission of drug-resistant strains would also be low if HIV infections were predominantly transmitted by infected individuals who were untreated or not yet aware of their infection at the time of transmission. The latter scenario is likely for the group of homosexual men in the Netherlands[2].

Table 5.1: Number of patients in follow-up as of 1 June 2009 with evidence of resistance to specific antiretroviral drugs, according to the Stanford algorithm for scoring mutations.

	susceptible		potential low-level		low-level		intermediate		high-level	
	N	%	N	%	N	%	N	%	N	%
protease inhibitors[a]										
fAPV	971	70.7	53	3.9	108	7.9	144	10.5	98	7.1
IDV	953	69.4	54	3.9	66	4.8	129	9.4	172	12.5
NFV	884	64.3	21	1.5	37	2.7	117	8.5	315	22.9
SQV	977	71.1	47	3.4	32	2.3	137	10.0	181	13.2
LOP	968	70.5	86	6.3	90	6.6	171	12.4	59	4.3
ATV	925	67.3	32	2.3	118	8.6	165	12.0	134	9.8
TPV	1035	75.3	55	4.0	100	7.3	158	11.5	26	1.9
DRV	1079	78.5	71	5.2	150	10.9	70	5.1	4	0.3
nucleoside RT inhibitors[b]										
3TC/FTC	374	27.1	36	2.6	47	3.4	39	2.8	883	64.0
ABC	205	14.9	377	27.3	152	11.0	404	29.3	241	17.5
AZT	597	43.3	28	2.0	147	10.7	255	18.5	352	25.5
d4T	505	36.6	86	6.2	208	15.1	292	21.2	288	20.9
ddI	485	35.2	133	9.6	158	11.5	364	26.4	239	17.3
TDF	612	44.4	139	10.1	223	16.2	382	27.7	23	1.7
non-nucleoside RT inhibitors[b]										
EFV	631	45.8	33	2.4	117	8.5	105	7.6	493	35.8
NVP	608	44.1	52	3.8	8	0.6	12	0.9	699	50.7
ETR	661	47.9	164	11.9	181	13.1	334	24.2	39	2.8

fAPV: fos-amprenavir; IDV: indinavir; NFV: nelfinavir; SQV: saquinavir; LOP: lopinavir; ATV: atazanavir; TPV: tipranavir; DRV: darunavir; RT: reverse transcriptase; 3TC: lamivudine; FTC: emtricitabine; ABC: abacavir; AZT: zidovudine; d4T: stavudine; ddI: didanosine; TDF: tenofovir; EFV: efavirenz; NVP: nevirapine; ETR: etravirine;

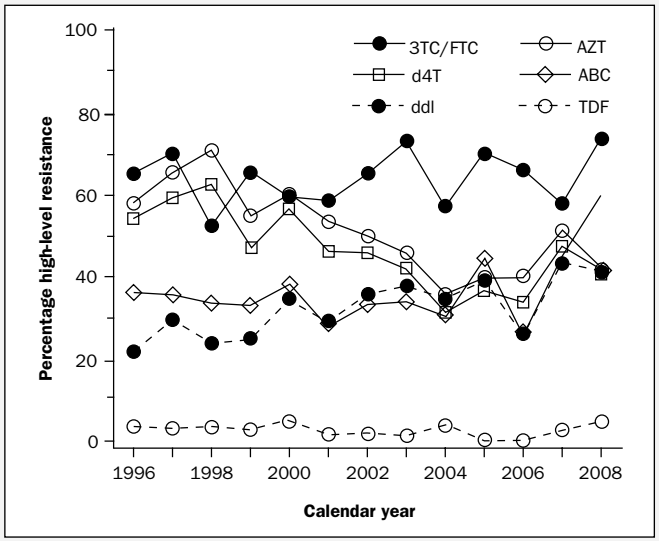
[a]protease not available for 6 patients;

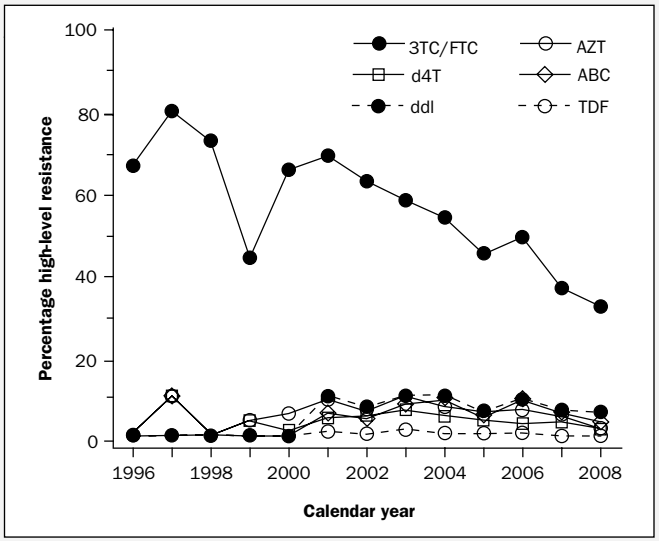
[b]RT not available for 1 patient

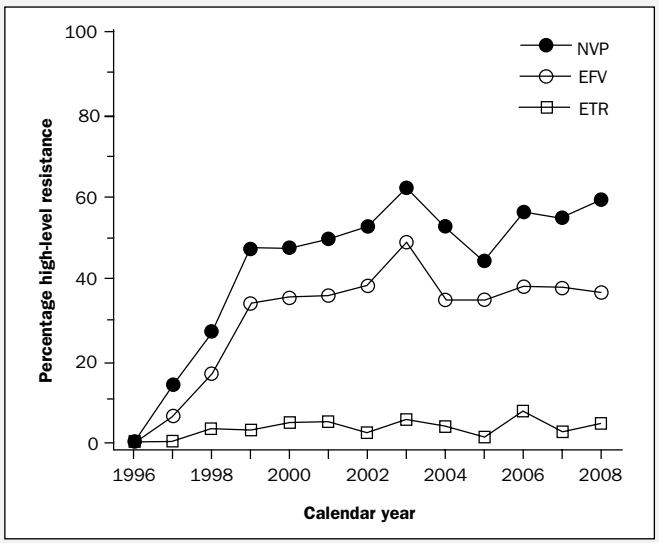
Table 5.2: Characteristics of 671 recently infected and 1567 newly diagnosed patients with a pre-treatment genotypic sequence within one year after diagnosis.

	new diagnoses, N=1567		**recent infections, N=671**	
	N	**%**	**N**	**%**
male gender	1232	78.6	636	94.8
region of origin				
the Netherlands	841	53.7	507	75.6
Sub-Saharan Africa	291	18.6	25	3.7
transmission category				
MSM	891	56.9	579	86.3
heterosexual contact	547	34.9	69	10.3
injecting drug use	11	0.7	0	0
other/unknown	118	7.5	23	3.4
non-B subtype	442	28.2	82	12.2
≥1 RAMs				
any drug	120	7.7	53	7.9
PI's	17	1.1	17	2.5
NRTI's	81	5.2	33	4.9
NNRTI's	38	2.4	8	1.2
intermediate/high-level resistance				
any drug	68	4.3	24	3.6
PI's	7	0.4	5	0.7
NRTI's	34	2.2	16	2.4
NNRTI's	38	2.4	8	1.2
	median	**IQR**	**median**	**IQR**
CD4 (cells/mm^3)	300	130-480	480	342-650
RNA (log_{10} copies/ml)	4.8	4.2–5.2	4.9	4.3–5.4
age (years)	38.3	31.3-45.7	36.9	30.2-43.5

MSM: men having sex with men; RAMs: resistance-associated mutations; PI: protease inhibitor; NRTI: nucleoside reverse transcriptase inhibitor; NNRTI: non-nucleoside reverse transcriptase inhibitor







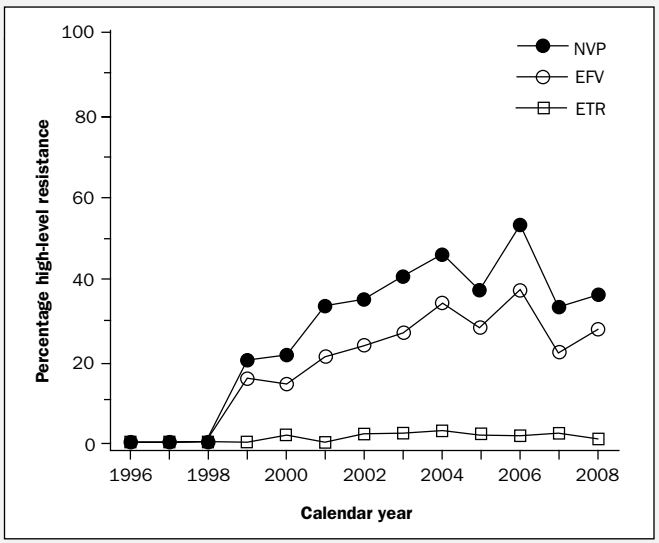


Figure 5.1: Annual percentage of sequences with high-level resistance, according to the Stanford algorithm for scoring mutations, in patients pre-treated with non-cART combinations (left) and previously therapy-naïve patients (right). cART: combination antiretroviral therapy; 3TC/FTC: lamivudine/emtricitabine; d4T: stavudine; ddI: didanosine; AZT: zidovudine; ABC: abacavir; TDF: tenofovir; NVP: nevirapine; EFV: efavirenz; ETR: etravirine; NFV: nelfinavir; IVD: indinavir; fAPV: fos-amprenavir; TPV: tipranavir; SQV: saquinavir; ATV: atazanavir; LOP: lopinavir; DRV: darunavir.

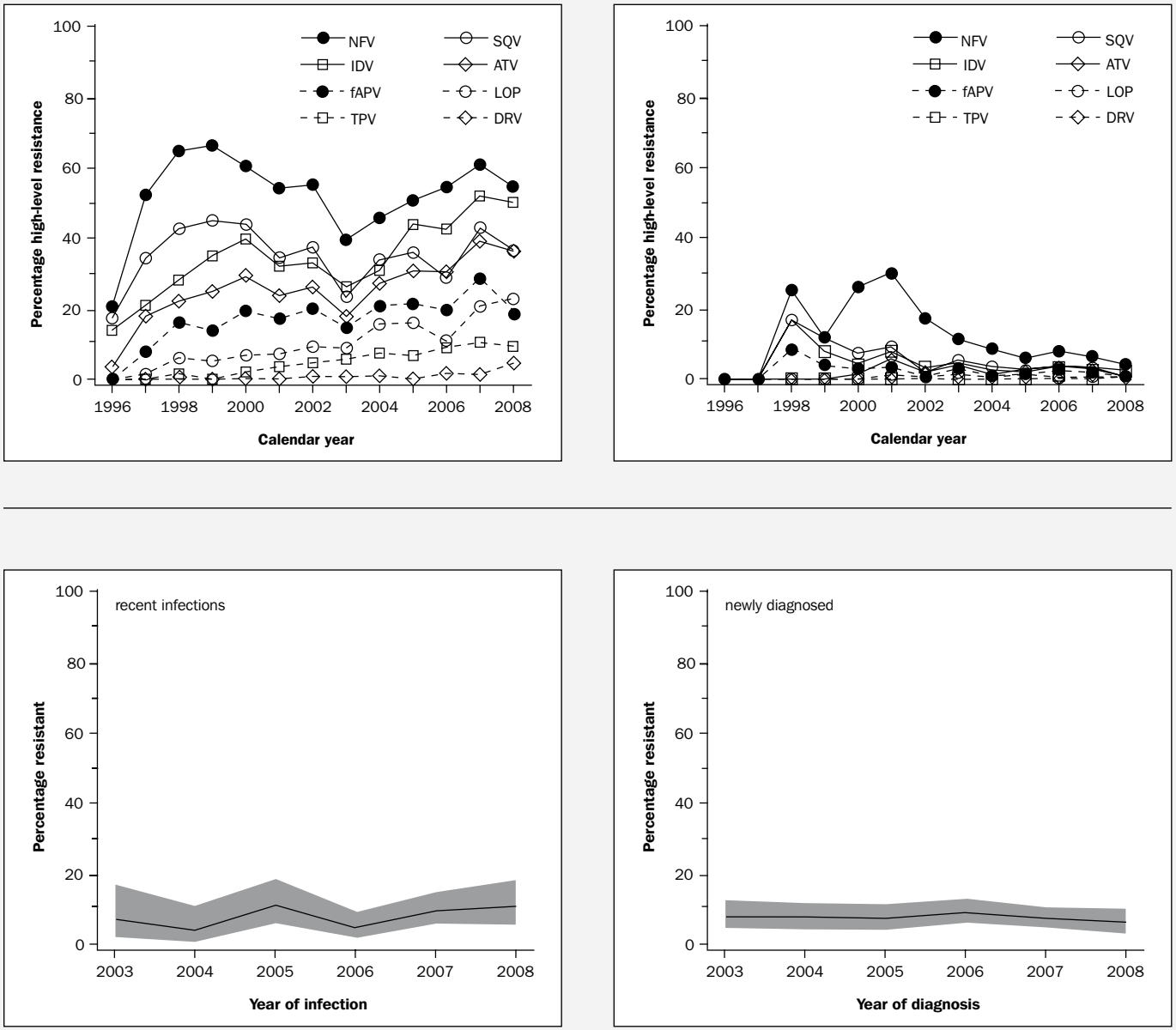


Figure 5.2: Percentage of transmissions of drug-resistant virus as a function of calendar time amongst recently HIV-infected and newly diagnosed patients. The solid black line represents the percentage, whilst the grey areas are the 95% confidence intervals (CI). Amongst the 671 recently infected patients, resistance-associated mutations were found in 7.9% (95% CI, 6.0-10.2; 53 patients) and this percentage did not change over time (p=0.2). Resistance-associated mutations were found in 120 (7.7% [95% CI, 6.4-9.8]) of the 1567 newly diagnosed patients.

6. Hepatitis B and C co-infection

Colette Smit, Camiel Welling

Since 2001, the number of HIV-infected homosexual men co-infected with hepatitis C has continued to grow, whilst the impact of hepatitis C co-infection on all-cause mortality has declined, probably as a result of improved immune status by effective HIV treatment.

Prevalence and demographics

As a result of shared routes of transmission, hepatitis B (HBV) and hepatitis C (HCV) are highly prevalent amongst HIV-infected patients. In Western countries, approximately 10% of the HIV-infected patients are co-infected with HBV, whilst the prevalence of HCV ranges from 7% to as high as 82% in patients with a reported history of injecting drug use[160,161].

Definition of HBV and HCV

HBV was defined by a positive result on a hepatitis B surface antigen (HBsAg) test (EIA, Axsym) or by a positive HBV DNA test result. HCV co-infection was defined by a positive result on a qualitative or quantitative RNA test result. We assumed that patients with a positive HCV antibody test (EIA, Axsym) but without an available HCV RNA test were also co-infected with HCV. However, patients with a positive HCV antibody test and a negative result on an HCV RNA test were classified as HCV-negative, since a HCV co-infection could not be confirmed.

Prevalence

In total, out of the 15,236 HIV-infected patients aged 18 years or older at time of HIV diagnosis, 13,056 were tested for both HBV and HCV. In addition, 1,140 were tested for HBV only and 340 for HCV only. Of the 14,160 patients tested for HBV, 1,149 were infected with HBV, and of the 13,396 patients tested for HCV, 1,609 were co-infected with HCV. Co-infection with both HBV and HCV was found in 157 of the 13,056 patients tested for both viruses.

As of 1 June 2009, 91% of the patients had been screened for HBV and/or HCV (Table 6.1). In total, 13,056 patients had a test result for both HBV and HCV. Although not all patients currently have been screened for HBV and HCV, the proportion of patients screened for both co-infections has increased from 64% in 2006 to 95% in 2009. Overall, the prevalence for HBV, HCV, and HBV+HCV was 8, 12, and 1%, respectively.

Demographics

Most patients co-infected with HBV and/or HCV were male and infected with HIV via homosexual contact (Table 6.2). Only 1% of the patients infected by injecting drug use were co-infected with HBV only, but 76% of these patients were co-infected with HCV. Nine percent of the injecting drug users were co-infected with both HBV and HCV.
The median age at time of HIV diagnosis was 36 years (interquartile range [IQR], 29-43). Most HBV and HCV co-infected patients were born in the Netherlands; 20% (272/1,362) of the patients born in a European country other than the Netherlands were co-infected with HCV, whilst only 4% of the patients originating from Sub-Saharan Africa were co-infected with HCV. The prevalence of HBV co-infection is much higher in patients originating from Sub-Saharan Africa, 9% (227/2,445). Almost half (46%) of the patients co-infected with HBV and/or HCV received their HIV diagnosis before 1996.

Risk factors for HCV diagnosis

In recent years, an increase in HCV co-infection among HIV-infected homosexual men has been reported[12], probably as a result of increased sexual transmission of HCV. Coexisting sexually transmitted infections and rough sexual techniques are noted as potential risk factors for this sexual HCV transmission.

Risk factors for HCV co-infection were studied in the present cohort by use of logistic regression analyses, with special attention given to changes over calendar time in the transmission of HCV in the specific risk groups for HCV co-infection.

In the univariate analyses, women had a significantly higher risk for HCV coinfection compared to men (Table 6.3). Compared to Dutch patients, patients who were born in Europe, excluding the Netherlands, were 2.3 (95% confidence interval [CI], 1.96-2.70) times more likely to be co-infected with HCV. The unadjusted odds ratio (OR) for patients with a history of injecting drug use was 231 (CI; 160-334). Odds for HCV co-infection was significantly lower among patients infected with HIV through heterosexual contact, compared to those infected by homosexual contact. The calendar year of HIV diagnosis, combination antiretroviral therapy (cART) use, AIDS event, alcohol abuse, and drug abuse were also associated with HCV co-infection in the univariate analyses.
In the multivariate model, being born in an European country other than the Netherlands, younger age at HIV diagnosis, an early calendar year of HIV diagnosis, having an history of injecting drug use or being infected with HIV through blood contact and drug abuse remained significantly associated with HCV co-infection. When injecting drug users were excluded from the multivariate analyses, the results did not change.

Changes over time in HCV co-infection among HIV risk groups

Although patients with a history of injecting drug use and patients with HIV transmission through blood contact are important risk groups for HCV co-infection, 37% (539/1452) of the patients co-infected with HCV were homosexual men. When this was stratified to calendar year of HCV diagnosis, a shift in HIV risk group was observed (Figure 6.1).

Up to calendar year 2000, the majority of newly diagnosed patients co-infected with HCV were injecting drug users, accounting for at least 60% of the new diagnoses. From 2004 onwards, a significant decrease among injecting drug users has been seen ($p<0.001$), whereas from 2001, the number of new HCV diagnoses among homosexual men has begun to increase significantly ($P<0.008$). From 2006 onwards, the number of new HCV diagnoses has been significantly higher in homosexual men than among injecting drug users. Because of the major drop in new HCV diagnoses among injecting drug users in the most recent years, homosexual men contributed the most to the number of new HCV diagnoses. The drop in new HCV diagnoses among injecting drug users could be explained by the saturation, that is, the high HCV prevalence and the minimal influx of new injecting drug users. The increase in new HCV diagnoses among homosexual men may reflect the improved testing policy in this HIV risk group, due to the publication of reports about the increased risk for HCV co-infection in homosexual men[12, 162]. It has been suggested that HIV might be a cofactor for sexual transmission of HCV[163], and specific sexual techniques and sexually transmitted infections (STI's) also might be associated with sexual transmission of HCV. Drug use among homosexual men may also be a risk factor for HCV transmission[12,164]

HCV genotype distribution

In 687 co-infected patients HCV was genotyped. Genotype 1 (N=418) was found in 61% of the patients (Table 6.4). Genotype 3 and 4 accounted for 19% (N=127) and 16% (N=109) of all available genotypes, respectively. Other genotypes or combined infections were not frequently found. On the basis of the transmission route of HIV, 43% of the patients with genotype 1 were infected with HIV through homosexual contact and 32.5% by injecting drugs. Genotype 3 was most prevalent amongst patients who were injecting drug users (57%), and genotype 4 amongst those who were homosexual men (66%). When stratified to year

of HCV diagnosis, a yearly increase was observed in the prevalence of genotypes 1 and 4, whereas the prevalence of genotype 3 has decreased from 2003 onwards. This shift in HCV genotypes reflects the increase in HCV diagnoses among homosexual men and the coincident decrease among patients with a history of injecting drug use.

The risk of progression to liver disease and death

Irrespective of co-infection with HIV, chronic HBV and HCV infection is associated with liver fibrosis, cirrhosis, hepatic failure, and cancer[165]. HIV is known to accelerate clinical progression of HBV- and HCV-related liver disease, and in HIV-infected patients these diseases are important causes of death[10, 68] (Chapter 3 of this report).

In total, 408 cases of liver disease were reported in the SHM database; 405 patients were diagnosed with fibrosis and 198 with cirrhosis; hepatocellular carcinoma occurred in 3 patients. A large proportion of the patients diagnosed with cirrhosis were first diagnosed with fibrosis (n=207). The prevalence of liver disease was 0.1% in the patients infected only with HIV, whereas 10% of the patients co-infected with HBV were diagnosed with liver disease. The occurrence of liver disease was even higher amongst the patients co-infected with HCV (12%), and 17% of the triple-infected patients progressed to liver disease. The probability of progression to a liver event was not the same for the different patient groups. Time to a liver event was faster among patients who were co-infected with HBV and/or HCV compared to those without a hepatitis co-infection (p-value log-rank test: <0.0001). The risk of the development of a liver event was significantly higher among patients with a HBV co-infection as well as among those with an HCV co-infection and those with triple infection (Table 6.5). Also, after adjustment for differences in sex, age, risk group, region of origin, and baseline CD4 cell counts and HIV RNA levels, the risk of liver disease was almost two times higher for patients with an HBV and/or HCV co-infection compared to patients who were infected solely with HIV.

In the total population, an increase in the number of HCV diagnoses over time was seen, whilst the number of patients with a liver event and the number of deaths have remained stable over time (Figure 6.2). When the patients were categorized according to their route of HIV transmission (homosexual contact or injecting drug use), a steep increase in the number of new HCV diagnoses was seen amongst homosexual men, whilst the number of liver events and all-cause deaths in this group was very low. Among injecting drug users the number of new HCV diagnoses decreased. This number has been much lower in recent years as compared to the number of new HCV diagnoses in homosexual men, whereas the number of new liver events and deaths has been found to be higher amongst injecting drug users than amongst homosexual men.

In total, 9% (1,411) of the HIV-infected patients died during follow-up. The proportion of deaths among patients who were not screened for HBV and HCV was much higher; 26% of the patients in this group died. This large proportion of deaths may have caused the lack of screening, since some patients died before there was an opportunity to screen for co-infection. The proportion of deaths during follow-up was 10% in the patients co-infected with HBV, 16% in the patients co-infected with HCV, and 23% in the triple-infected patients.

For the total population, the probability of dying was not the same for all patients (Figure 6.3.A) in the first 5 years after cART initiation (p<0.0001). Five years after cART initiation, the all-cause mortality was 6% (95% CI, 6-7%) among the patients infected with HIV only and 6% (4-8%) for the HBV co-infected patients. The mortality rate was 12% (CI, 10-14%) amongst the HCV co-infected patients. A comparable mortality rate was observed in the group of triple-infected patients, with 11% (CI, 6-18%) during a period of 5 years after the start

of cART. However, 12 years after cART initiation, the mortality rate among patients infected with only HIV was 13% (CI, 12-14%), whereas it was 20% (16-24%) for the patients co-infected with HBV and 24% (21-27%) amongst the patients co-infected with HCV. The highest mortality rate was in the group of triple-infected patients, with 28% (CI, 20-39%) during a period of 12 years after the start of cART.
The significant differences in the probability of dying disappeared when patients infected with HIV through injecting drug use were excluded (Figure 6.3.B). These results were confirmed by the hazards ratios for progression to death (Table 6.5). HCV co-infection and triple infection were associated with a faster progression to death in the unadjusted analyses. However, after adjustment for differences in sex, age, risk group, ethnicity, and baseline CD4 cell counts and HIV RNA levels, patients with a HCV co-infection were no longer at increased risk of dying. This suggests that a history of injecting drug use is a more important risk factor for death than HCV co-infection.

Treatment and treatment effects

Since life expectancy improved after the introduction of cART, a substantial proportion of those patients co-infected with HBV or HCV are at risk for progression to liver-related diseases. Therefore, treatment of HBV and HCV co-infection in patients with HIV has become more important.

Current guidelines recommend the use of tenofovir and emtricitabine or tenofovir and lamivudine as the nucleoside reverse transcriptase inhibitor (NRTI) backbones in cART combinations for HBV-HIV co-infected patients[166,167]. Long-term use of a combination that includes these NRTI backbones improves the control of HBV by delaying or preventing liver complications[168].
Most of the HBV-HIV co-infected patients (65%) in care at one of the Netherlands HIV treatment centres received an NRTI backbone to help control the HBV infection. Of the treated patients, 387 received a combination of tenofovir and lamivudine; 77 patients were treated with tenofovir and emtricitabine, whilst 178 patients received lamivudine without tenofovir. In total, 369 (57%) of the patients initiated their HBV-suppressing combination antiretroviral therapies (ARV) between 2003 and 2006.

The low death rate found in the SHM cohort among HBV-HIV co-infected patients probably reflects the positive effects of tenofovir and emtricitabine or tenofovir and lamivudine on the HBV disease progression, since 65% of the patients co-infected with HBV in our cohort were treated during follow up. However, we do not have clinical data available to evaluate the effectiveness of HBV treatment by showing a decrease in HBV DNA levels.

From 1998 onwards, the standard treatment for HCV has been a combination of interferon (IFN) and ribavirine (RBV), but more recently, pegylated interferon (PEG-IFN) has been used. Between 1 January 1996 and 1 June 2009, 362 (25%) of HCV-HIV co-infected patients received HCV treatment. The majority of the treated patients received a combination of (PEG)-IFN and RBV, whilst 29 patients were treated with (PEG)-IFN only and 20 patients were treated with only RBV. Twenty percent of the triple-infected patients received HCV treatment, which was in most cases a combination of (PEG)-IFN and RBV.
The proportion of patients receiving HCV treatment varied between HCV genotypes. Patients with HCV genotype 2 were less likely to receive HCV treatment, 31% versus 44% among the other HCV genotypes ($p<0.001$).
Overall, the median duration of HCV treatment was 26 weeks (Interquartile range [IQR], 17-48). Although, the median time of treatment varied between genotypes and was longest for genotype 4 (41 weeks (24-47), these differences in the duration of treatment between

genotypes did not differ significantly (P=0.28). HCV RNA levels were available for 153 (42%) of the 362 patients who were receiving HCV treatment. At the time of initiation of HCV treatment, 92% of the patients had a detectable HCV RNA load. After HCV treatment, 99 (43%) out of 228 patients had an undetectable HCV RNA load. The HCV treatment response did not differ between HCV genotypes (p=0.08).

Recently, in the Netherlands, most of the new HCV diagnoses in HIV-infected patients have been among homosexual men. Homosexual men are now the largest group of HCV-HIV co-infected patients in the Dutch population of HIV-infected patients. Several studies have reported an increased death risk in the HCV co-infected population[9,10]. However, the impact of HCV co-infection on the risk of dying remains controversial, as other observers did not find an increased risk of dying. Earlier, we reported higher mortality rates by HCV co-infection[1], but we are no longer seeing the increased risk of death in HCV co-infected patients in the SHM cohort. Recently, much attention has been given to the increase in new HCV infections among homosexual men; we assume the increase in new HCV diagnoses to be the result of a more active screening policy for co-infections among HIV-infected patients. Most of the newly discovered HCV infections have been found among homosexual men who are well treated for their HIV infection, and the HCV infections have been detected early in their course. This may result in a greater chance of spontaneous clearance of HCV compared to that in the injecting drug users, because the chance of HCV clearance is greater among HIV-infected patients with relatively high CD4 cell counts. Treatment of HIV is likely to contribute to a higher level of CD4 cell counts that can result in the spontaneous clearance of HCV[11]. In addition, the number of patients treated for their HCV co-infection increased, which might also result in a lower risk of dying. Most HCV infections among homosexual men are recently acquired infections[12] in which progression to liver fibrosis has not yet occurred. Among newly diagnosed patients with HCV-HIV co-infection, if HCV treatment is initiated very shortly after the discovery of the HCV infection, then successful treatment rates from 71 to 80% can be achieved[13,14]. The success of HCV treatment is determined by genotype, since genotypes 1 and 4 are hard to treat[15]. However, in the group of homosexual men, in which liver-related disease and mortality is low, most are infected with genotype 4. In our analyses, the number of treated HCV co-infected patients was too small to determine the effect of HCV genotypes on treatment success.

Successful treatment of HCV infection, in combination with the increased number of recently diagnosed HCV infections, has resulted in a decreased impact of HCV on the all-cause mortality in the Dutch population of HIV-infected patients. Larger observational studies are needed to further evaluate the impact of HCV treatment on the decrease of all-cause and liver-related mortality and the impact of the different HCV genotypes on population level. SHM is coordinating such a study within a large international cohort collaboration, COHERE (Collaboration of Observational HIV Epidemiological Research Europe).

Table 6.1: Overview of the screening for hepatitis B (HBV) and hepatitis C (HCV) co-infection in the Dutch population of HIV-infected patients.

	Total	Tested	Positive test result	Missing
HBV	15236	14160	1149	1076
HCV	15236	13396	1609	1840
HBV&HCV	15236	13056	157*	2023

* Positive test result for both HBV and HCV

Table 6.2: Demographic characteristics of HIV-infected patients with hepatitis B and/or C co-infection.

	Total	No screening	HIV only	HBV	HCV	HBV &HCV
	N	**N**	**N**	**N**	**N**	**N**
Total	15236	736	11899	992	1452	157
Gender						
Male	12090	566	9406	849	1134	135
Female	3146	170	2493	143	318	22
Transmission						
MSM	8552	349	6992	616	539	57
heterosexual	4861	266	4075	299	205	16
IDU	664	37	51	6	507	63
blood (products)	192	4	136	6	44	2
other/unknown	966	80	645	65	157	19
Age category (years)						
18-24	1632	74	1245	113	175	26
25-34	5664	273	4322	398	600	71
35-44	4928	221	3848	327	490	42
45-54	2140	105	1756	110	153	16
55-64	718	49	595	42	30	2
≥65	153	14	133	2	4	0
Region of origin						
the Netherlands	8688	409	6795	494	884	106
sub-Saharan Africa	2445	146	1963	227	96	13
Europe, excl Nl	1362	74	911	87	272	18
Latin America	1118	33	940	71	70	4
Caribbean	570	24	485	33	22	6
Other	565	36	416	39	67	7
Calendar year of HIV diagnosis						
<=1996	4043	249	2728	324	661	81
1997-1999	2033	82	1586	140	199	26
2000-2001	1643	72	1313	107	144	7
2002-2005	4186	179	3433	254	293	27
2006-2009	3331	154	2839	167	155	16
Liver events	408 (3)	4 (0.5)	85 (0.1)	97(10)	180(12)	26(17)
Deaths	1411(9%)	188(26%)	855(7%)	98(10%)	234 (16%)	36(23%)
cART use	**12297**	**524**	**9531**	**847**	**1263**	**132**

MSM: men who have sex with men
IDU: injecting drug users
cART: combination antiretroviral therapy

Table 6.3: Risk factors for hepatitis co-infection among the Dutch population of HIV-infected patients.

		Univariate Odds Ratio	95% CI	Multivariate Odds Ratio	95% CI
Gender	Male	1			
	Female	1.15	1.01 – 1.31		
Region of origin	The Netherlands	1		1	
	Rest of Europe, including Russia	2.30	1.96 – 2.70	1.76	1.42 – 2.18
	Africa and the Middle East	0.47	0.39 – 0.56	0.61	0.48 – 0.78
	Latin America and the Caribbean	0.45	0.37 – 0.56	0.48	0.37 – 0.63
	Asia	0.71	0.51 – 0.99	0.95	0.64 – 1.41
	Other or Unknown	1.18	0.84 – 1.66	1.15	0.76 – 1.74
Median age	at HIV diagnosis	0.98	0.97 – 0.98	0.99	0.982 – 0.997
	at 01-01-2009	1.01	1.01– 1.02	not included	not included
	(N=11529) at time of death	0.97	0.96 – 0.98	not included	not included
Calendar year of	< 1993	5.67	4.72 – 6.82	2.33	1.82 – 2.97
HIV diagnosis	1993 – 1996	3.00	2.47 – 3.64	1.53	1.20 – 1.96
	1997 – 2000	1.97	1.63 – 2.39	1.43	1.14 – 1.80
	2001 – 2004	1.46	1.21 – 1.76	1.38	1.12 – 1.71
	2005 – 2008	1		1	
ART use					
	No	1			
	Yes	1.69	1.44 – 1.99		
AIDS events	No	1		1	
	Yes	1.36	1.22 – 1.52	0.81	0.70 – 0.95
Transmission	Homosexual	1		1	
HIV infection	Heterosexual	0.69	0.58 – 0.82	0.89	0.73 – 1.08
	Injecting drug use	230.99	159.89 – 333.72	86.89	59.00 – 127.97
	Blood contact	4.45	3.14 – 6.31	5.16	3.58 – 7.45
	Other or Unknown	3.17	2.62 – 3.84	2.95	2.37 – 3.67
Substance abuse	No abuse	1		1	
	Alcohol abuse	1.40	1.02 – 1.92	1.19	0.82 – 1.70
	Drug abuse	20.48	17.22 – 24.35	5.44	4.23 – 6.99
	Combined Alcohol and Drug Abuse	23.62	17.76 – 31.42	5.21	3.48 – 7.80

CI: confidence interval

ART: antiretroviral therapy

Table 6.4: Distribution of Hepatitis C subtypes amongst 687 patients with HIV co-infection.

Genotype	Subtype	No.	% amongst genotype	% of total
1	A	219	52.4	
	B	59	14.1	
	A/B	13	3.1	
	other or unknown	127	30.4	
	TOTAL	**418**		**60.8**
2	A	3	12.5	
	B	10	41.7	
	other or unknown	11	45.8	
	TOTAL	**24**		**3.5**
3	A	92	72.4	
	B	2	1.6	
	other or unknown	33	26.0	
	TOTAL	**127**		**18.5**
4	A	4	3.7	
	C	10	9.2	
	D	16	14.7	
	C/D	16	14.7	
	other or unknown	63	57.8	
	TOTAL	**109**		**15.9**
				0.1
5	A	1	100	
	A	1	50	
6	unknown	1	50	
	TOTAL	**2**		**0.3**
Double infection	1 + 3	3	50	
	1 + 4	3	50	
	TOTAL	**6**		**0.9**

Table 6.5: Risk of an AIDS-defining event and death amongst HIV-infected patients with and without hepatitis co-infection. To evaluate the association between co-infection and progression to liver disease and death, the impact of HBV and/or HCV co-infection on the time to a liver event and to death was estimated by a Cox proportional hazard model. Follow-up time was from the date of cART initiation to that of last contact or most recent clinical visit, date of diagnoses with a liver event or death, or 1 June, 2009. Models were adjusted for age at time of HIV diagnosis, sex, risk group, ethnicity, baseline CD4 cell counts and HIV RNA levels.

	Liver event		Death	
	Crude HR^ (95% CI[#])	Adjusted HR (95% CI)*	Crude HR^ (95% CI[#])	Adjusted HR (95% CI)*
HIV	1	1	1	1
HIV/HBV	1.64 (1.21-2.23)	1.96 (1.37-2.79)	1.19 (0.95-1.48)	1.25 (0.94-1.66)
HIV/HCV	1..81 (1.37-2.41)	1.81 (1.24-2.62)	1.86 (1.59-2.16)	1.14 (0.87-1.50)
HIV/HBV/HCV	1.48 (0.93-2.37)	1.56 (0.92-2.63	2.14 (1.45-3.13)	1.47 (0.88-2.47)

HR: Hazard ratio; CI: 95% confidence interval

*adjusted for age, sex, region of origin, transmission group, baseline CD4 cell counts and HIV RNA levels.

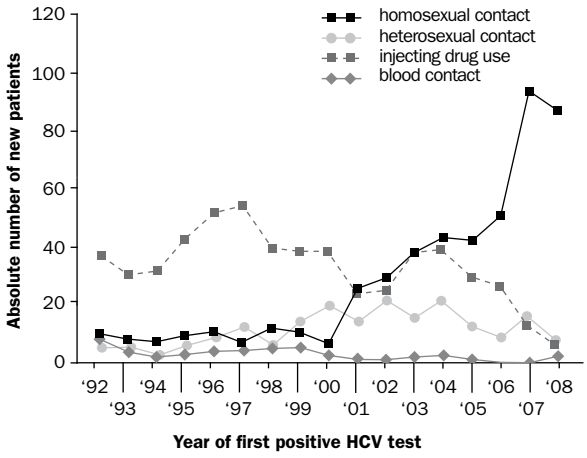
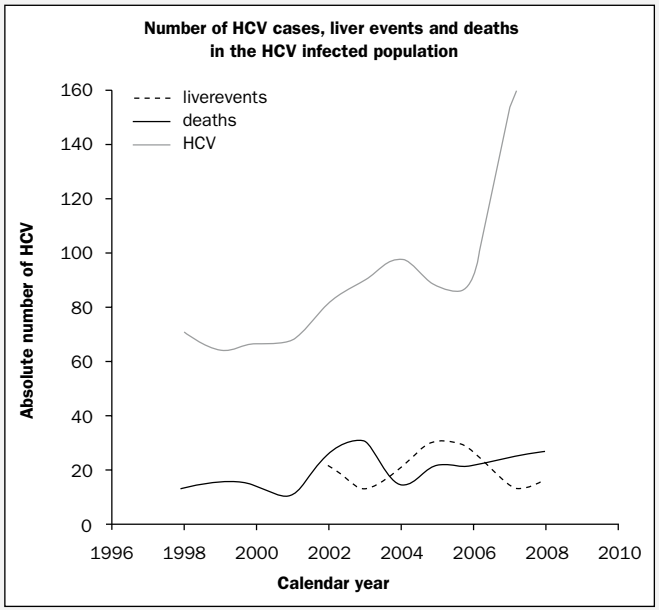
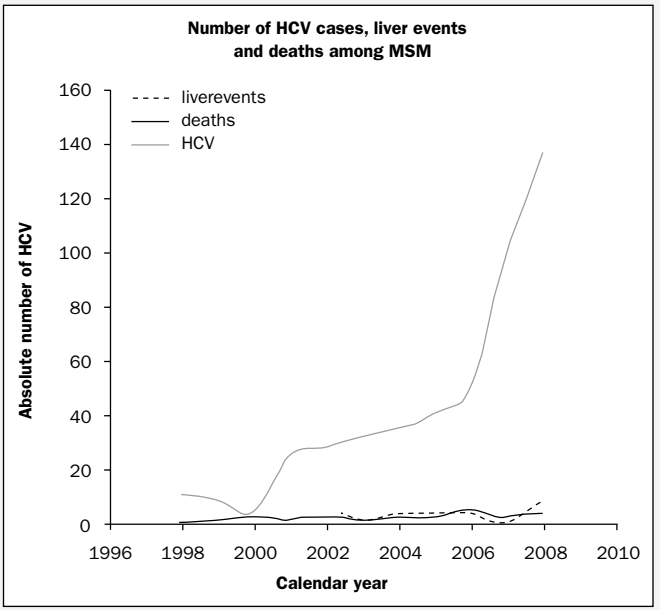


Figure 6.1: Distribution of HIV transmission route amongst HIV-infected patients with HCV co-infection, in absolute numbers per year of first positive HCV test result.





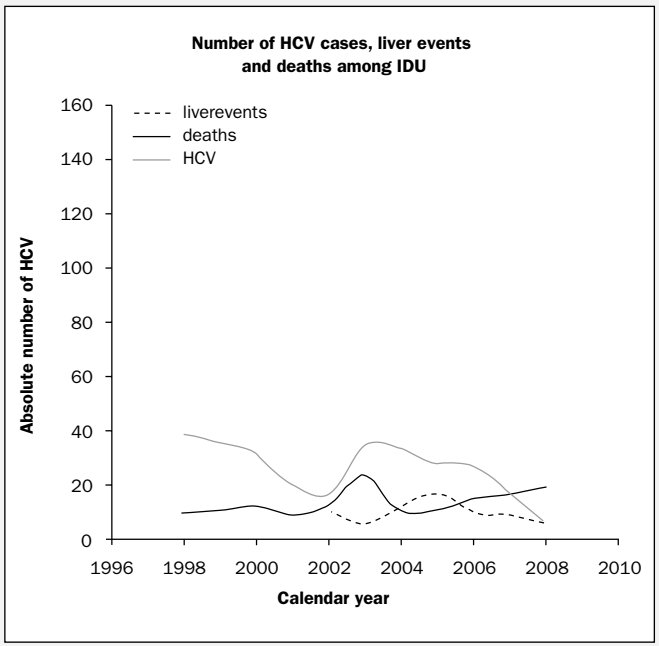


Figure 6.2: The number of HCV diagnoses and the number liver events and deaths in the HCV co-infected population per calendar year, for the total population and separate for MSM and injecting drug users.

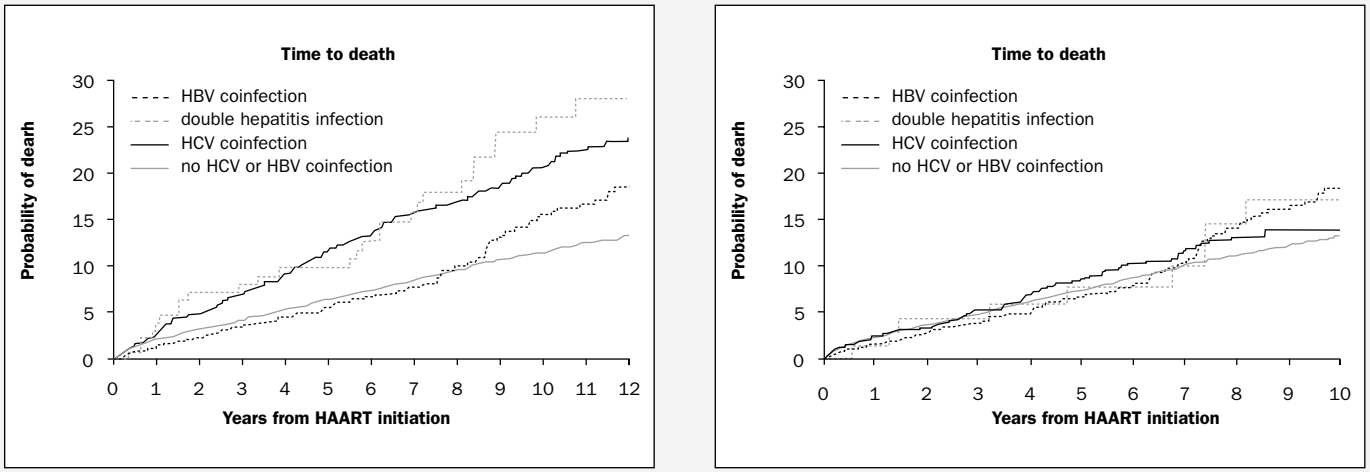


Figure 6.3: All-cause mortality among patients infected with HIV only, HBV co-infected patients, HCV co-infected patients, and patients with a triple infection. A: probability of dying in the total population. B: probability of dying, excluding patients who were infected with HIV through injecting drug use. Kaplan-Meier estimates of the probability of dying were plotted for the total group of patients and for the total population, excluding patients infected by injecting drug use, because almost all patients in that group are co-infected by HCV.

special reports

7. The Amsterdam Cohort Studies – Annual report 2008

Ineke Stolte, Hanneke Schuitemaker

The Amsterdam Cohort Study (ACS) on Human Immunodeficiency Virus (HIV) infection and AIDS among homosexual men (HM) was initiated in 1984, followed shortly by the Amsterdam Cohort Study among drug users (DU) in 1985. The ACS, a collaboration of the Public Health Service Amsterdam (PHSA), the Academic Medical Centre of the University of Amsterdam, Sanquin Blood Supply Foundation, the University Medical Centre Utrecht (UMCU), and the Jan van Goyen Clinic, are part of the Netherlands HIV Monitoring Foundation and are financially supported by the Centre for Infectious Disease control of the Netherlands National Institute for Public Health and the Environment.

As of 31 December 2008, 2,383 homosexual men and 1,647 (injecting) drug users were included in the ACS. It should be noted that the number of drug users is lower than noted in the previous report because 18 drug users who were enrolled in the ACS in 2007 when they started HCV treatment did not meet the inclusion criteria for enrolment in the ACS, and therefore they have been excluded in the 2008 report. Every 3 to 6 months, participants complete a standardised questionnaire designed to obtain information regarding medical history, sexual and/or drug use behaviour, underlying cognitions, health care use, depression, psychological disorders, and demographics. In addition, they undergo a medical examination (HIV-positive participants and, in the past, HIV-negative drug users as well), and blood is drawn for diagnostic tests and storage.

Of the 2,383 HM, 585 were HIV-positive at study entry, and 208 seroconverted during follow-up. For the 1,647 DU, 322 were HIV-positive at study entry, and 96 seroconverted during follow-up. By 31 December 2008, 335 HM and 411 DU had died, several other participants were requested to leave the study or left at their own request. About 90% of participants who visited the ACS during a given calendar year returned for a follow-up visit the next year. In total, the PHSA was visited 47,524 times by HM and 25,131 times by DU.

ACS Open*

Over the past 25 years large amounts of social-scientific, demographic, clinical, and biomedical data have been obtained from the participants of the ACS by the different participating research groups. In 2005, the ACS Open project group, composed of data managers and scientists from all participating research groups, started to combine the data sets and build an easily accessible multidisciplinary database comprising all longitudinally obtained epidemiological, social-scientific, and biomedical information and containing data about the availability of stored samples in the repositories. In 2009/2010, these data sets will be available for scientists in the participating research groups and their collaborators.
The ACS data are very suitable for use by universities and research institutes to teach epidemiological, biomedical, and social scientific students how to analyze longitudinal data sets. The concurrence of epidemiological and biomedical data also enables researchers from various disciplines to practice statistical techniques like survival, multilevel, and repeated measurement analysis. For this purpose, a data set that includes social-scientific, demographic, clinical, and biomedical information obtained from the participants of the ACS over the past 25 years of follow-up is available at www.amsterdamcohortstudies.org.

**) This project 'The opening up of the Amsterdam Cohort Studies (ACS Open)' has been funded by MaGW and ZonMw (grant number 91104002).*

The cohorts in 2008

Homosexual men

In 2008, 532 HM were followed at the PHSA of Amsterdam. Twenty-eight of them were newly recruited in 2008. From 2005, recruitment was open for HM of all ages with at least one sexual partner in the preceding 6 months. Of the HM followed in 2008, 481 men were HIV-negative, and 51 men were HIV-positive. The HIV-positive men, of whom 38 were HIV seroconverters, were followed according to the 'HIV Onderzoek onder Positieven' (HOP) protocol, which was initiated in October 2003 for HM who seroconverted or were HIV-positive at study entry into the cohort of young HM after 1999.

Another 12 HIV-positive men were included in the HOP in 2008, of whom 6 were exclusively followed in an HIV treatment centre outside the PHSA. By the end of 2008, 34 HIV-positive men were still in active follow-up in an HIV treatment centre outside the PHSA. From June 2006 onwards, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants have also been invited to participate in the ACS. By the end of 2008, 12 HIV discordant and 2 HIV-positive concordant couples were included in this partner study, of which 7 couples were still in active follow up.

In 2008, 208 HIV-positive HM who were recruited as part of the ACS before 1999 were seen at the Jan van Goyen Clinic or at one of the 22 other HIV treatment centres in the Netherlands. Sixty-eight of them were HIV seroconverters. Plasma and cells from 57 of the 125 HIV-positive HM in active follow-up at the Jan van Goyen clinic in 2008 were stored. Of these, 35 were HIV seroconverters, and the remaining 22 were defined as 1) slow or non progressor or matched fast progressor in 1996; 2) were HIV-positive for more than 10 years and had a CD4 count greater than 400 cells/μl after 10 years of follow-up after an HIV-positive result without effective therapy.

Drug users

In 2008, 390 drug users were followed at the PHSA of Amsterdam. Fifty-five were young drug users aged 30 years or less; were recruited after 2000; and had used cocaine, heroin, or amphetamines at least 3 times a week in the 2 months preceding enrolment. Of the 390 DU followed in 2008, 35 were HIV-positive, and 19 seroconverted for HIV during follow-up in the ACS. In 2005, within the DU cohort, a feasibility study was started to evaluate the possibility of hepatitis C virus (HCV) testing and treatment combined with methadone programs. As part of this project (the Dutch-C study), in 2008 15 HCV mono-infected DU had initiated HCV therapy, resulting in a total group of 50 DU treated for HCV.

Primo-cohort

In addition to the cohorts mentioned above, the ACS is now also including patients who present with primary HIV-1 infection at the PHSA or at the outpatient clinic of the AMC. A portion of these patients are enrolled in the so-called primo-SHM study, a randomized study on the effect of early quadruple antiviral therapy as compared to no therapy. By the end of 2008, 172 patients were already included as patients with primary infection. In 2008, 23 new patients with acute HIV-1 infection were enrolled in the study, of which 16 participated in the randomised controlled trial. Blood is collected from all of these patients for storage of plasma and peripheral blood mononuclear cells (PBMC), and sampling is more frequent early after entry into the study. Follow-up of individuals who are randomized to the no-treatment arm is discontinued 1 year after they have to start HAART because of a CD4+ T cell decline <350 cells/μl. Similarly, follow-up of individuals who have to reinitiate HAART because of a CD4 decline (<350 cells/μl blood) after scheduled interruption of the first HAART regimen initiated during the primary infection phase is discontinued 1 year after therapy re-initiation.

HIV incidence

Eight homosexual men and no drug user had a first HIV-positive test in 2008 after a previous HIV-negative test. HIV incidence in 2008 was 2.01 per 100 person-years among HM, and remained relatively stable since 1996. Among DU, the HIV incidence was less than 1 per 100 person-years. Figures 7.1 and 7.2 show the yearly observed HIV incidence rates for homosexual men and drug users from the start of the ACS through 2008.

Transmission of therapy resistant HIV strains

Surveillance of transmission of drug-resistant HIV-1 strains was performed for 7 HM seroconverters, and 5 of the 6 seropositive HM at entry. In most individuals, only naturally occurring sequence variation was found, but in one of the seroconverters, sequences harboring resistance-associated mutations were found. A 41L mutation and a so-called 215-revertant (215L) were found.

HAART uptake

All 234 (208 who were recruited before 1999 and 26 after 1999) HIV-positive HM visiting the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands in 2008 received any form of antiretroviral therapy. Of 192 HM for whom viral load results were available, 189 (98%) had a viral load of less than 50 copies/ml (assays: bDNA, M2000rt).

Of the 50 HIV-positive DU who visited the PHSA of Amsterdam in 2008 and for whom treatment data were available, 41 (79%) received any combination of antiretroviral therapy. Of these, 38 (93%) had an undetectable viral load (less than or equal to 150 copies/ml [assay: m2000rt]) at their latest visit. Of 9 HIV-positive DU not receiving HAART, 3 (33%) had an undetectable viral load.

Adherence was investigated amongst 102 HIV-positive DU who attended the ACS and reported HAART use between January 1999 and February 2009. Full adherence (defined as taking more than 95% of medication in the past 6 months) was reported in 88% of visits. (Lambers et al., submitted).

Risk behaviour HM

Of the 405 HIV-negative HM who filled in a questionnaire at least once up until July 2008, 56% reported unprotected anal intercourse (UAI) in the past 6 months. Trends in UAI among HIV-negative HM participating in the ACS have slowly increased since 1996 (see Figure 7.3).

Risk behaviour in DU

In the cohort of HIV-negative DU, reports of both injecting and borrowing needles significantly declined over the period 1985-2008 (Lindenburg et al, AIDS 2006 and update in 2009). Reports of sexual high risk behaviour and sexually transmitted infections at follow-up visits decreased before 1996, but remained relatively stable after 1996 (see Figure 7.4).

HCV in drug users

Non-injecting drug users

Amongst self-declared never-injecting drug users, the HCV antibody prevalence at ACS entry was 6.3%. HCV strains that circulate among never-injectors phylogenetically cluster with those circulating among their injecting counterparts. Although this is all suggestive for under-reporting of past injecting behaviour, household or sexual transmission of HCV from injectors to non-injectors cannot be ruled out. This stresses the need for HCV-testing among DU who report never injecting (Van den Berg, 2009).

Clinical course

DU co-infected with HCV and HIV remain at increased risk of dying from hepatitis/liver-related causes in the era of HAART, compared to HCV-mono-infected DU, suggesting that HIV continues to accelerate progression of HCV disease (Smit, 2008).

The rate of spontaneous viral clearance amongst DU from the ACS was 33% following acute infection; it was higher in women, DU without HIV, and those without an active hepatitis B infection. Multiple HCV infections were observed in 10 of 24 HCV-seroconverters with spontaneous viral clearance (11 re-infections; 3 super-infections) and in 13 of 35 HCV-seroconverters without viral clearance (20 super-infections). The incidence of HCV re-infection was at least similar to that of initial HCV infection. Although partial immunity cannot be excluded, this will further complicate vaccine development. Harm reduction will remain dependent on precautionary measures preventing the further spread of HCV and on the treatment of those chronically infected (Van de Laar, 2009).

Steering committee: the Politburo

In the year of 2008, the "Politburo" met several times. Forty proposals for use of data and/or samples (serum/PBMC) were submitted to the politburo: 21 from AMC-Experimental Immunology, 8 from the AMC-Medical Microbiology, 1 from AMC-Internal Medicine, 2 from the PHSA, 5 from the UMCU, and 3 from researchers not affiliated with the ACS. All requests were approved, some after revision. One request was withdrawn after approval.

Publications in 2008 that include ACS data

Bezemer, D., F. de Wolf, M. C. Boerlijst, A. van Sighem, T. D. Hollingsworth, M. Prins, R. B. Geskus, L. Gras, R. A. Coutinho, and C. Fraser. 2008.
A resurgent HIV-1 epidemic among men who have sex with men in the era of potent antiretroviral therapy.
Aids 22:1071-7.

Bezemer, D., A. van Sighem, F. de Wolf, M. Cornelissen, A. C. van der Kuyl, S. Jurriaans, L. van der Hoek, M. Prins, R. A. Coutinho, and V. V. Lukashov. 2008.
Combination antiretroviral therapy failure and HIV super-infection.
Aids 22:309-11.

Bhaskaran, K., C. Mussini, A. Antinori, A. S. Walker, M. Dorrucci, C. Sabin, A. Phillips, and K. Porter. 2008.
Changes in the incidence and predictors of human immunodeficiency virus-associated dementia in the era of highly active antiretroviral therapy.
Ann Neurol 63:213-21.

Buchholz, A., A. Krol, F. Rist, P. T. Nieuwkerk, and G. M. Schippers. 2008.
An assessment of factorial structure and health-related quality of life in problem drug users using the Short Form 36 Health Survey.
Qual Life Res 17:1021-9.

Bunnik, E. M., L. Pisas, A. C. van Nuenen, and H. Schuitemaker. 2008.
Autologous neutralizing humoral immunity and evolution of the viral envelope in the course of subtype B human immunodeficiency virus type 1 infection.
J Virol 82:7932-41.

Dunn, D., P. Woodburn, T. Duong, J. Peto, A. Phillips, D. Gibb, and K. Porter. 2008.
Current CD4 cell count and the short-term risk of AIDS and death before the availability of effective antiretroviral therapy in HIV-infected children and adults.
J Infect Dis 197:398-404.

Guiguet, M., K. Porter, A. Phillips, D. Costagliola, and A. Babiker. 2008.
Clinical Progression Rates by CD4 Cell Category Before and After the Initiation of Combination Antiretroviral Therapy (cART).
Open AIDS J 2:3-9.

Jarrin, I., R. Geskus, K. Bhaskaran, M. Prins, S. Perez-Hoyos, R. Muga, I. Hernandez-Aguado, L. Meyer, K. Porter, and J. del Amo. 2008.
Gender differences in HIV progression to AIDS and death in industrialized countries: slower disease progression following HIV seroconversion in women.
Am J Epidemiol 168:532-40.

Jurriaans, S., K. Kozaczynska, F. Zorgdrager, R. Steingrover, J. M. Prins, A. C. van der Kuyl, and M. Cornelissen. 2008.
A sudden rise in viral load is infrequently associated with HIV-1 superinfection.
J Acquir Immune Defic Syndr 47:69-73.

Miedema, F. 2008.
A brief history of HIV vaccine research: stepping back to the drawing board?
Aids 22:1699-703.

Navis, M., D. E. Matas, A. Rachinger, F. A. Koning, P. van Swieten, N. A. Kootstra, and H. Schuitemaker. 2008.
Molecular evolution of human immunodeficiency virus type 1 upon transmission between human leukocyte antigen disparate donor-recipient pairs.
PLoS One 3:e2422.

Navis, M., I. M. Schellens, P. van Swieten, J. A. Borghans, F. Miedema, N. A. Kootstra, D. van Baarle, and H. Schuitemaker. 2008.
A nonprogressive clinical course in HIV-infected individuals expressing human leukocyte antigen B57/5801 is associated with preserved CD8+ T lymphocyte responsiveness to the HW9 epitope in Nef.
J Infect Dis 197:871-9.

Pantazis, N., G. Touloumi, P. Vanhems, J. Gill, H. C. Bucher, and K. Porter. 2008.
The effect of antiretroviral treatment of different durations in primary HIV infection.
Aids 22:2441-50.

Pasternak, A. O., K. W. Adema, M. Bakker, S. Jurriaans, B. Berkhout, M. Cornelissen, and V. V. Lukashov. 2008.
Highly sensitive methods based on seminested real-time reverse transcription-PCR for quantitation of human immunodeficiency virus type 1 unspliced and multiply spliced RNA and proviral DNA.
J Clin Microbiol 46:2206-11.

Piriou, E., K. van Dort, S. Otto, M. H. van Oers, and D. van Baarle. 2008.
Tight regulation of the Epstein-Barr virus setpoint: interindividual differences in Epstein-Barr virus DNA load are conserved after HIV infection.
Clin Infect Dis 46:313-6.

Rits, M. A., K. A. van Dort, and N. A. Kootstra. 2008.
Polymorphisms in the regulatory region of the Cyclophilin A gene influence the susceptibility for HIV-1 infection.
PLoS One 3:e3975.

Schellens, I. M., J. A. Borghans, C. A. Jansen, I. M. De Cuyper, R. B. Geskus, D. van Baarle, and F. Miedema. 2008.
Abundance of early functional HIV-specific CD8+ T cells does not predict AIDS-free survival time.
PLoS One 3:e2745.

Schellens, I. M., C. Kesmir, F. Miedema, D. van Baarle, and J. A. Borghans. 2008.
An unanticipated lack of consensus cytotoxic T lymphocyte epitopes in HIV-1 databases: the contribution of prediction programs.
Aids 22:33-7.

Smit, C., C. van den Berg, R. Geskus, B. Berkhout, R. Coutinho, and M. Prins. 2008.
Risk of hepatitis-related mortality increased among hepatitis C virus/HIV-coinfected drug users compared with drug users infected only with hepatitis C virus: a 20-year prospective study.
J Acquir Immune Defic Syndr 47:221-5.

Steingrover, R., K. Pogany, E. Fernandez Garcia, S. Jurriaans, K. Brinkman, H. Schuitemaker, F. Miedema, J. M. Lange, and J. M. Prins. 2008.
HIV-1 viral rebound dynamics after a single treatment interruption depends on time of initiation of highly active antiretroviral therapy.
Aids 22:1583-8.

Tesselaar, K., and F. Miedema. 2008.
Growth hormone resurrects adult human thymus during HIV-1 infection.
J Clin Invest 118:844-7.

Touloumi, G., N. Pantazis, H. A. Stirnadel, A. S. Walker, F. Boufassa, P. Vanhems, and K. Porter. 2008.
Rates and determinants of virologic and immunological response to HAART resumption after treatment interruption in HIV-1 clinical practice.
J Acquir Immune Defic Syndr 49:492-8.

Van de Laar, T. J. W., A. T. Urbanus, S. M. Bruisten, H. J. C. de Vries, H. F. J. Thiesbrummel, R. A. Coutinho, and M. Prins. 2008.
Reply to Richardson et al.
The Journal of Infectious Diseases 197:1214-1215.

Van Manen, D., M. A. Rits, C. Beugeling, K. van Dort, H. Schuitemaker, and N. A. Kootstra. 2008.
The effect of Trim5 polymorphisms on the clinical course of HIV-1 infection.
PLoS Pathog 4:e18.

Van Montfort, T., A. A. Thomas, G. Pollakis, and W. A. Paxton. 2008.
Dendritic cells preferentially transfer CXCR4-using human immunodeficiency virus type 1 variants to CD4+ T lymphocytes in trans.
J Virol 82:7886-96.

Vrisekoop, N., I. den Braber, A. B. de Boer, A. F. Ruiter, M. T. Ackermans, S. N. van der Crabben, E. H. Schrijver, G. Spierenburg, H. P. Sauerwein, M. D. Hazenberg, R. J. de Boer, F. Miedema, J. A. Borghans, and K. Tesselaar. 2008.
Sparse production but preferential incorporation of recently produced naïve T cells in the human peripheral pool.
Proc Natl Acad Sci U S A 105:6115-20.

Vrisekoop, N., R. van Gent, A. B. de Boer, S. A. Otto, J. C. Borleffs, R. Steingrover, J. M. Prins, T. W. Kuijpers, T. F. Wolfs, S. P. Geelen, I. Vulto, P. Lansdorp, K. Tesselaar, J. A. Borghans, and F. Miedema. 2008.
Restoration of the CD4 T cell compartment after long-term highly active antiretroviral therapy without phenotypical signs of accelerated immunological aging.
J Immunol 181:1573-81.

Theses in 2008 that include ACS data

Buchholz A.
Health-related Quality of Life and Psychosocial Functioning in Problem Drug Users.
Co-promotor: Prof dr. GM Schippers
Promotor: Prof dr F Rist

Van de Laar T.J.
Molecular Epidemiology of hepatitis C virus.
Co-promotor: Dr SM Bruisten, Dr M Prins
Promotor: Prof dr RA Coutinho

Witteveen E.
Knowledge gained through experience in young problem drug users. Reflections on interventions and change.
Co-promotor: Dr EJC van Ameijden
Promotor: Prof dr GM Schippers

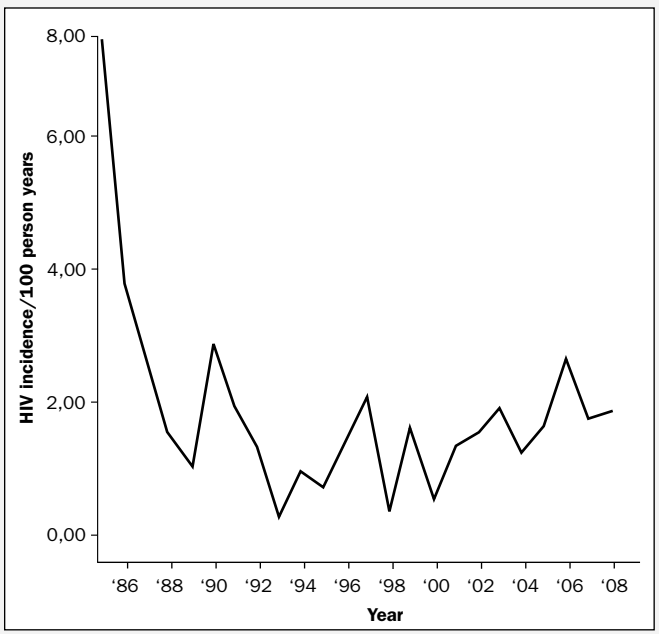


Figure 7.1: Yearly HIV incidence per calendar year in the ACS among homosexual men, 1984-2008.

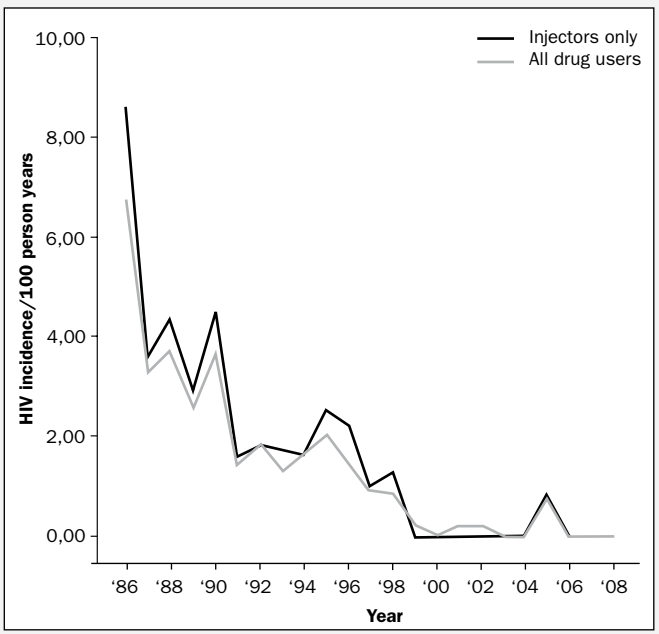


Figure 7.2: Yearly HIV incidence per calendar year in the ACS among drug users, 1986-2008.

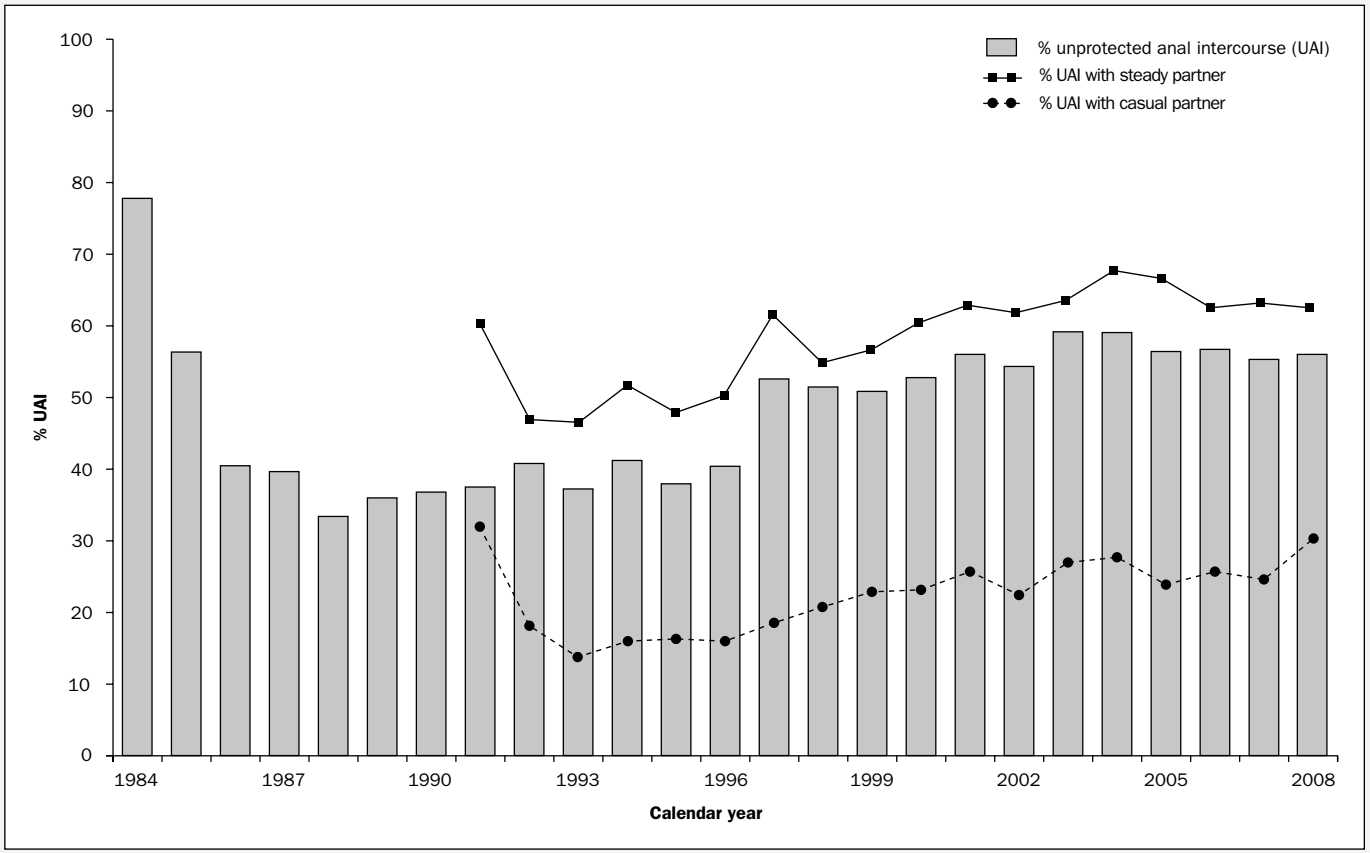


Figure 7.3: Trends in unprotected anal intercourse in the past 6 months among HIV-negative HM from the Amsterdam Cohort Study 1984-2008.

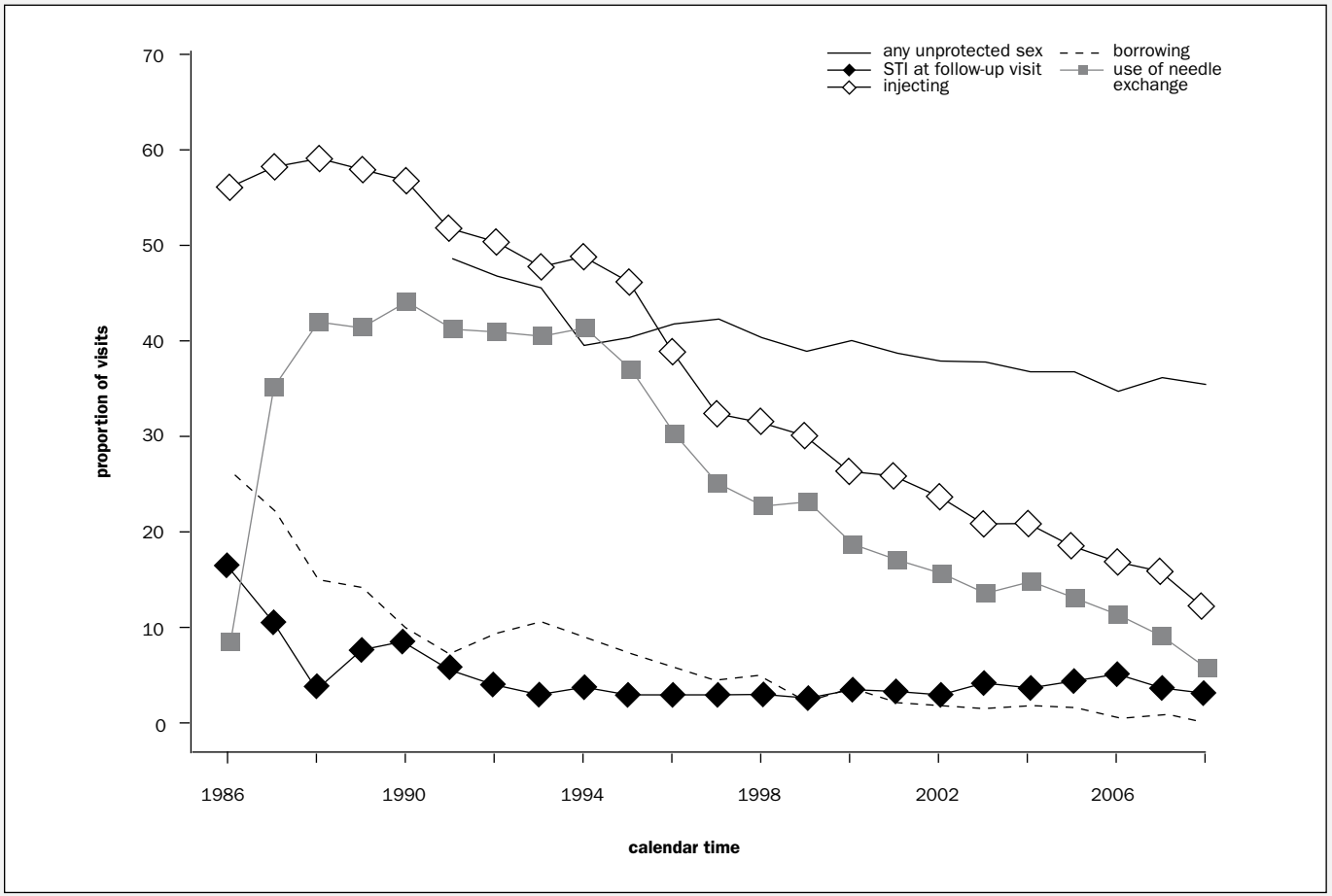


Figure 7.4: Proportion of visits per calendar year at which injecting and sexual high risk behaviour was reported among 1315 DU who were HIV-negative on ACS entry, 1986-2008.

8. Curaçao

Ard van Sighem, Luuk Gras, Gonneke Hermanides, Ashley Duits

Since 2005, the Stichting HIV Monitoring (SHM) collects data of HIV-infected patients who are followed at the St. Elisabeth Hospitaal or at the Stichting Rode Kruis Bloedbank in Willemstad, Curaçao. The total HIV-infected population recorded in Curaçao was 586 patients, including 482 (82.3%) patients who were still alive as of 1 June 2009 and 104 (17.7%) who had died before 1 June 2009. Compared to last year, this showed an increase of 139 patients[1]. Of the 482 patients who were still alive, 39 (8.1%) had no data recorded in the year preceding 1 June 2009. The total follow-up since HIV diagnosis was 3338 person-years for the entire population, including 2960 person-years for those still alive and 378 person-years for those who died. Of the 586 patients, a majority of 529 (90.3%) were infected with HIV-1. Two patients were infected with HIV-2, and seroreactivity to both HIV-1 and HIV-2 was found in 6 patients. For 49 (8.4%) patients, serologic results were not yet known or recorded in the database of the SHM. In total, 94 (16.0%) patients were diagnosed in or before 1995; of those, 32 (34%) were in the group of deceased patients (Table 8.1). Between 1996 and 2009, 432 patients were diagnosed, 373 (86.3%) of whom were still alive, corresponding to an average of 31 diagnoses per year. The majority of the patients were male, were infected via heterosexual contact, and originated from the Netherlands Antilles and Aruba (Table 8.2).

For 321 (54.8%) patients, the most likely country of infection was known. Most patients, 283 (88.2%), were reported to have been infected in the Netherlands Antilles, whereas 18 (5.6%) were infected in Haiti or the Dominican Republic. Of the 259 patients born in the Netherlands Antilles with a known country of infection, 247 (95.4%) were infected in the Netherlands Antilles. Of the 17 patients from the Dominican Republic and the 23 patients from Haiti with a known country infection, 13 and 13, respectively, were infected in the Netherlands Antilles, whilst the other patients were most likely infected in their country of birth. The HIV-1 subtype was known for 103 (17.6%) patients; all of them harboured a subtype B strain. In total, 380 (64.8%) patients were tested for hepatitis B, and 318 (54.3%) were tested for hepatitis C. Of those tested, 29 (7.6%) patients were co-infected with hepatitis B, and 4 (1.3%) patients had hepatitis C.

The median age at diagnosis was 38.0 (Interquartile range [IQR], 30.7-46.7) years and did not differ between patients who were still alive and those who had died (p=0.2). Only 46 (7.8%) patients presented with an AIDS-defining event. However, at the start of combination antiretroviral therapy (cART), 78 (13.3%) had experienced an AIDS event in the previous year. Median CD4 cell counts at diagnosis, known for 206 patients, were 321 (101-499) cells/mm^3 and did not change over time (p=0.9). Median RNA levels were 4.5 (IQR, 4.0-5.1) $\log_{10}$ copies/ml in 125 patients with a viral load measurement at diagnosis and likewise did not change over time (p=0.9). In the population that was still alive, CD4 counts increased from 332 (IQR, 117-520) cells/mm^3 at diagnosis to 385 (252-586) cells/mm^3 at present.

Between 2001 and 2009, the frequency of RNA measurements was 1.86 (95% confidence interval [CI], 1.80-1.91) per year. The frequencies of CD4 measurements were slightly higher, 2.06 (95% CI, 2.00-2.12), whilst the overall visit frequency was 2.55 (2.49-2.61) per year. Frequencies increased over time at an average rate of 0.05/year[2].

In total, 381 (65.0%) patients started cART, but the exact date of start was not known for 9 of those patients. The most frequently used initial regimens in the 372

patients who started cART in or after 1995 were lopinavir + zidovudine + lamivudine (162 patients, 43.5%), nelfinavir + stavudine + lamivudine (91 patients, 24.5%), efavirenz + tenofovir + emtricitabine (32 patients, 8.6%), and indinavir + zidovudine + lamivudine (25 patients, 6.7%). The prescription of these antiretroviral regimens changed over calendar time (Figure 8.1). At the beginning of 2009, 43% of the patients on cART were using lopinavir + zidovudine + lamivudine, whilst 9% of the patients used a combination of nevirapine + zidovudine + lamivudine, and 15% were on a combination of efavirenz + tenofovir + emtricitabine.

In total, 339 (91.1%) out of the 372 patients who started cART did so whilst being antiretroviral treatment-naïve, whereas the other 33 patients had been treated with non-cART regimens before start of cART. After 6 months of cART, CD4 cell counts had increased by more than 150 cells/mm^3 for 51% of the patients; after 2 years, this proportion had increased to 79% (Figure 8.2a). A viral-load level below 500 copies/ml was achieved within 6 months in 79% of the patients (Figure 8.2b).

In the group of 259 patients who started cART whilst being antiretroviral therapy-naïve and who were still in follow-up as of 1 June 2009, CD4 counts stabilised at a level of approximately 400 cells/mm^3 after 2 years of cART (Figure 8.2c). The proportion of patients with a viral load below 500 copies/ml, however, decreased from 75% at 48 weeks after start of cART to a level between 50% and 60% after 5 years (Figure 8.2d). This decreasing ability to suppress viral load was probably a consequence of the limited number of therapy options available in Curaçao. As shown previously, just 3 or 4 regimens accounted for the majority of all those administered in Curaçao. Ritonavir, which is used to achieve optimal blood levels of protease inhibitors, was not available in Curaçao, except in a fixed-dose combination with lopinavir. Hence, the number of boosted protease-containing regimens was limited. Non-nucleoside reverse transcriptase inhibitors became increasingly available from 2007 onwards, and they are currently administered to approximately 25% of the treated population.

The median time between start of cART and the first switch in therapy was 2.0 (IQR, 0.6-4.8) years. Of the 97 patients who discontinued their first regimen and started a new regimen after a period without treatment, 51 (53%) were restarted on their initial regimen. The annual proportion of previously therapy-naïve patients who failed on cART varied between 16% and 28% between 2000 and 2008 and was on average 22%. In total, 106 genotypic sequences were obtained after the start of cART in 79 out of 372 (21.2%) patients who started cART. Of these 79 patients, 30 had high-level resistance to nelfinavir, and 20 patients had resistance to saquinavir. Resistance to the non-nucleoside reverse transcriptase inhibitors nevirapine and efavirenz was observed in 17 and 13 patients, respectively. High-level resistance to lamivudine and emtricitabine was found in 43 patients, whilst resistance to zidovudine and stavudine was found in 17 patients. In 37 patients with a sequence available within 1 year after diagnosis and before the start of antiretroviral treatment, no infections with drug-resistant virus strains were observed.

Prospective follow-up in Curaçao started in 2006. In total, 468 patients were still alive as of 1 January 2006 or were diagnosed with HIV after that date. Three years later, 24 of these patients had died, and 94% (95% CI, 91-96) were still alive according to a Kaplan–Meier estimate. At the moment, the possibilities for survival analyses in Curaçao are still limited. For example, an analysis investigating survival from start of cART onwards may be biased since patients who started cART and were lost to follow-up before the registration programme in Curaçao began would be less likely to be included in the database than patients who would still be in follow-up at the start of the registration programme.

Table 8.1: Annual number of diagnoses in Curaçao stratified by gender and survival status as of 1 June 2009.

	alive, in follow-up		alive, lost to follow-up		dead		total	
	men	women	men	women	men	women	men	women
≤1995	37	21	2	2	25	7	64	30
1996	9	10	1	0	0	1	10	11
1997	8	10	1	0	6	2	15	12
1998	12	4	3	0	4	1	19	5
1999	16	6	1	0	1	1	18	7
2000	14	10	1	3	5	0	20	13
2001	8	12	2	0	4	3	14	15
2002	19	10	3	1	5	1	27	12
2003	23	14	2	2	9	1	34	17
2004	10	9	2	1	7	2	19	12
2005	19	10	1	0	2	2	22	12
2006	20	15	0	0	1	0	21	15
2007	24	7	0	0	1	0	25	7
2008	25	16	0	0	0	0	25	16
2009	6	3	0	0	0	0	6	3
total	259	157	19	9	70	21	339	187
unknown	20	16	6	5	5	8	31	29

Table 8.2: Characteristics of the HIV-infected population in Curaçao as registered by the SHM.

		alive, N=482		dead, N=104		total, N=586	
		N / median	% / IQR	N / median	% / IQR	N / median	% / IQR
gender, male		295	61.2	75	72.1	370	63.1
transmission	MSM	91	18.9	11	10.6	102	17.4
	heterosexual	323	67.0	68	65.4	391	66.7
	other/unknown	68	14.1	25	24.0	93	15.9
country of birth	Antilles	357	74.1	92	88.5	449	76.6
	Haiti	57	11.8	7	6.7	64	10.9
	Dominican Republic	29	6.0	3	2.9	32	5.5
treated with cART		326	67.6	55	52.9	381	65.0
diagnosis	CD4 (cells/mm^3)	332	117-520	99	46-315	321	101-499
	RNA (log_{10} copies/ml)	4.5	4.0-5.1	5.3	4.8-5.6	4.5	4.0-5.1
	age (years)	37.9	30.5-46.2	39.3	32.1-51.0	38.0	30.7-46.7
	AIDS	27	5.6	19	18.3	46	7.8
	time to cART	1.5	0.3-4.9	1.0	0.2-3.0	1.5	0.3-4.8
	follow-up (years)	5.2	1.6-9.8	2.1	0.2-5.7	4.4	1.1-9.0
start of cART	CD4 (cells/mm^3)	139	50-240	64	7-153	128	46-230
	RNA (log_{10} copies/ml)	5.0	4.5-5.5	5.2	4.5-5.6	5.0	4.5-5.5
	age (years)	41.9	35.1-50.6	43.3	36.6-55.6	42.2	35.2-51.3
	AIDS	52	10.8	26	25.0	78	13.3
	follow-up (years)	3.8	1.5-7.7	1.8	0.5-4.3	3.5	1.3-7.4
present (1 June 2009)	CD4 (cells/mm^3)	385	252-586	-	-	385	252-586
	RNA <500 copies/ml[a]	211	54.5	-	-	211	54.5
	age (years)	45.0	38.2-52.9	-	-	45.0	38.2-52.9

SHM: Stichting HIV Monitoring; IQR: interquartile range; MSM: men having sex with men; cART: combination antiretroviral therapy; [a]available for 387 patients still alive and for 22 patients who died.

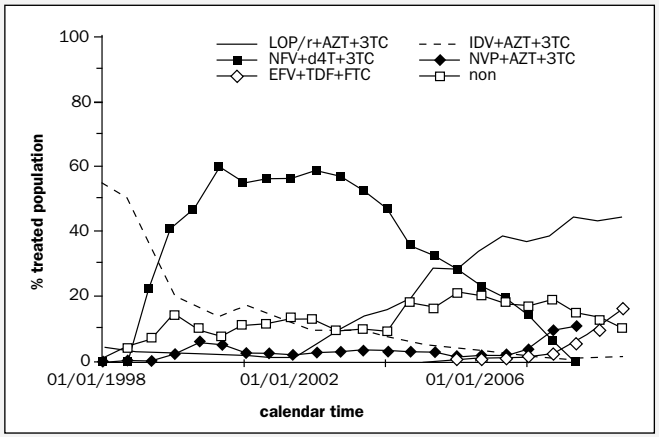


Figure 8.1: Percentage of patients treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. The proportion of patients using IDV + AZT + 3TC decreased from 54% in 1998 to 0% after 2007. This decrease was counterbalanced by an increase in the proportion of patients treated with NFV + d4T + 3TC. From 2002 onwards, a combination of LOP/r + AZT + 3TC was increasingly used, and 43% of the patients on cART were on this regimen at the beginning of 2009. At that time, 9% of the patients used a combination of NVP + AZT + 3TC, and 15% were on a combination of EFV + TDF + FTC. After 2004, 10 to 20% of the patients who ever started cART were (temporarily) not being treated. AZT: zidovudine; 3TC: lamivudine; d4T: stavudine; IDV: indinavir; LOP/r: ritonavir-boosted lopinavir; NFV: nelfinavir; NVP: nevirapine; EFV: efavirenz; TDF: tenofovir; FTC: emtricitabine.

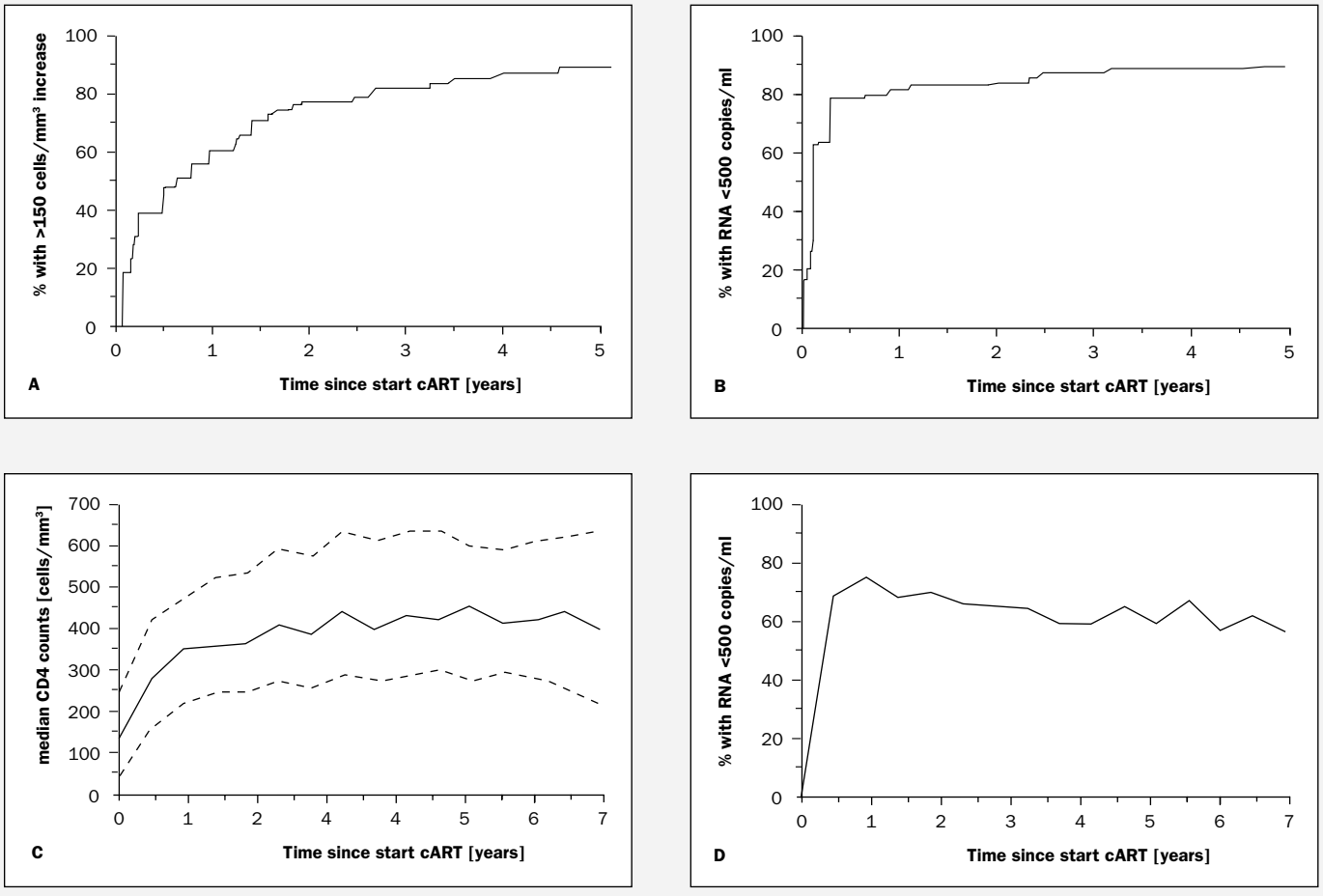


Figure 8.2: (a) The proportion of patients with a CD4 cell increase of more than 150 cells/mm^3 after start of combination antiretroviral therapy (cART) was 51% after 6 months and increased to 79% after 2 years, whilst (b) 79% of patients reached, but not necessarily maintained, HIV RNA below 500 copies/ml within 6 months. (c) Median CD4 cell counts (solid line; dotted lines: interquartile range) increased from 140 (IQR, 49-243) cells/mm^3 at start of cART to 276 (155-413) cells/mm^3 after 24 weeks and stabilised at a level of approximately 400 cells/mm^3 after 2 years. (d) The proportion of patients with HIV RNA levels <500 copies/ml was 69% after 24 weeks and 75% after 48 weeks and gradually declined to a level between 50% and 60% after 5 years. In all plots, only previously therapy-naïve patients are considered; (a) and (b) represent time-to-event analyses; (c) and (d) include patients who were still in follow-up as of 1 June 2009.

list of tables & figures

references

1. L. Gras *et al.*, "Monitoring of Human Immunodeficiency Virus (HIV) Infection in the Netherlands" (Stichting HIV Monitoring, Amsterdam, 2008).
2. D. Bezemer *et al.*, *Aids* **22**, 1071 (2008).
3. J. W. Mellors *et al.*, *Ann. Intern. Med.* **126**, 946 (1997).
4. M. J. Wawer *et al.*, *J. Infect. Dis.* **191**, 1403 (2005).
5. Y. Gali *et al.*, *Virology* **364**, 140 (2007).
6. N. Lohse, A. B. Hansen, J. Gerstoft, N. Obel, *J. Antimicrob. Chemother.* **60**, 461 (2007).
7. A. van Sighem *et al.*, *J. Acquir. Immune. Defic. Syndr.* **40**, 212 (2005).
8. L. Gras *et al.*, "Monitoring of Human Immunodeficiency Virus (HIV) Infection in the Netherlands" (Stichting HIV Monitoring, Amsterdam, 2007).
9. C. Smit *et al.*, *J. Acquir. Immune. Defic. Syndr.* **47**, 221 (2008).
10. R. Weber *et al.*, *Arch. Intern. Med.* **166**, 1632 (2006).
11. C. H. van den Berg *et al.*, *J. Viral Hepat.* **16**, 239 (2009).
12. T. J. van de Laar *et al.*, *J. Infect. Dis.* **196**, 230 (2007).
13. G. V. Matthews *et al.*, *Clin. Infect. Dis.* **48**, 650 (2009).
14. S. Dominguez *et al.*, *Aids* **20**, 1157 (2006).
15. K. Weigand, W. Stremmel, J. Encke, *World J. Gastroenterol.* **13**, 1897 (2007).
16. A. H. Greenbaum, L. E. Wilson, J. C. Keruly, R. D. Moore, K. A. Gebo, *Aids* **22**, 2331 (2008).
17. P. Nieuwkerk, E. Gisolf, M. Sprangers, S. Danner, *Antivir. Ther.* **6**, 97 (2001).
18. T. C. Quinn *et al.*, *N. Engl. J. Med.* **342**, 921 (2000).
19. K. Modjarrad, E. Chamot, S. H. Vermund, *Aids* **22**, 2179 (2008).
20. P. Vernazza, B. Hirschel, E. Bernasconi, M. Flepp, *Bulletin des médecins suisses* **89**, 165 (2008).
21. D. P. Wilson, M. G. Law, A. E. Grulich, D. A. Cooper, J. M. Kaldor, *Lancet* **372**, 314 (2008).
22. G. P. Garnett, B. Gazzard, *Lancet* **372**, 270 (2008).
23. M. Sturmer, H. W. Doerr, A. Berger, P. Gute, *Antivir. Ther.* **13**, 729 (2008).
24. B. G. Gazzard, *HIV. Med.* **9**, 563 (2008).
25. Centers for Disease Control and Prevention. www.cdc.gov/hiv/. 2008.
26. M. Bofill *et al.*, *Clin. Exp. Immunol.* **88**, 243 (1992).
27. E. Kassa *et al.*, *Aids* **13**, 381 (1999).
28. A. Mocroft *et al.*, *AIDS Res. Hum. Retroviruses* **21**, 743 (2005).
29. P. Bonfanti *et al.*, *J. Acquir. Immune. Defic. Syndr.* **23**, 236 (2000).
30. M. A. d'Arminio *et al.*, *Aids* **14**, 499 (2000).
31. O. Kirk *et al.*, *HIV. Med.* **2**, 43 (2001).
32. D. Burger *et al.*, *Br. J. Clin. Pharmacol.* **61**, 148 (2006).
33. "Monitoring of human immunodeficiency virus type 1 (HIV-1) infection in the Netherlands" (Stichting HIV Monitoring, Amsterdam, 2001).
34. M. E. O'Brien, R. A. Clark, C. L. Besch, L. Myers, P. Kissinger, *Jaids-Journal of Acquired Immune Deficiency Syndromes* **34**, 407 (2003).
35. V. von Wyl *et al.*, *Clin. Infect. Dis.* **48**, 979 (2009).
36. V. D. Lima *et al.*, *J. Infect. Dis.* **198**, 51 (2008).
37. S. Yerly *et al.*, *Aids* **21**, 2223 (2007).
38. W. P. Bannister *et al.*, *J. Acquir. Immune. Defic. Syndr.* **48**, 324 (2008).
39. P. Recordon-Pinson *et al.*, *Antivir. Ther.* **14**, 551 (2009).
40. M. Egger *et al.*, *Lancet* **360**, 119 (2002).
41. A. I. van Sighem *et al.*, *Aids* **17**, 2227 (2003).
42. M. May *et al.*, *Aids* **21**, 1185 (2007).
43. G. Chene *et al.*, *Lancet* **362**, 679 (2003).
44. R. B. Effros *et al.*, *Clin. Infect. Dis.* **47**, 542 (2008).
45. N. H. Dukers *et al.*, *Aids* **21**, 491 (2007).
46. A. E. Grulich, M. T. van Leeuwen, M. O. Falster, C. M. Vajdic, *Lancet* **370**, 59 (2007).
47. A. K. Chaturvedi *et al.*, *Aids* **21**, 207 (2007).
48. G. D. Kirk *et al.*, *Clin. Infect. Dis.* **45**, 103 (2007).
49. S. C. Darby *et al.*, *Lancet* **350**, 1425 (1997).
50. V. A. Triant, H. Lee, C. Hadigan, S. K. Grinspoon, *J. Clin. Endocrinol. Metab* **92**, 2506 (2007).
51. A. I. Choi *et al.*, *J. Am. Soc. Nephrol.* **18**, 2968 (2007).
52. M. Mary-Krause, L. Cotte, A. Simon, M. Partisani, D. Costagliola, *Aids* **17**, 2479 (2003).
53. L. Desquilbet *et al.*, *J. Gerontol. A Biol. Sci. Med. Sci.* **62**, 1279 (2007).
54. L. Gras *et al.*, *PLoS. ONE.* **4**, e7365 (2009).
55. C. Fraser, T. D. Hollingsworth, R. Chapman, F. de Wolf, W. P. Hanage, *Proc. Natl. Acad. Sci. U. S. A* **104**, 17441 (2007).
56. C. Smit, T. B. Hallett, J. Lange, G. Garnett, F. de Wolf, *PLoS. ONE.* **3**, e1949 (2008).
57. J. A. Freeman, J. C. Hobart, E. D. Playford, B. Undy, A. J. Thompson, *J. Neurol. Neurosurg. Psychiatry* **76**, 723 (2005).
58. J. K. Schneider, A. Deenan, *Appl. Nurs. Res.* **17**, 125 (2004).
59. G. Favalli *et al.*, *Eur. J. Cancer* **36**, 1125 (2000).
60. J. J. Allison *et al.*, *Jt. Comm J. Qual. Improv.* **26**, 115 (2000).
61. L. D. Cassidy, G. M. Marsh, M. K. Holleran, L. S. Ruhl, *Am. J. Manag. Care* **8**, 787 (2002).
62. L. Gras *et al.*, "Monitoring of Human Immunodeficiency Virus (HIV) Infection in the Netherlands" (Stichting HIV Monitoring, Amsterdam, 2006).
63. N. Black, *Lancet* **353**, 1205 (1999).

64. N. Black, *BMJ* **326**, 2 (2003).
65. A. Mocroft *et al.*, *Aids* **16**, 1663 (2002).
66. F. J. Palella, Jr. *et al.*, *J. Acquir. Immune. Defic. Syndr.* **43**, 27 (2006).
67. J. E. Sackoff, D. B. Hanna, M. R. Pfeiffer, L. V. Torian, *Ann. Intern. Med.* **145**, 397 (2006).
68. C. Smit *et al.*, *Aids* **20**, 741 (2006).
69. N. A. Hessol *et al.*, *Clin. Infect. Dis.* **44**, 287 (2007).
70. C. Lewden *et al.*, paper presented at the 14th Conference on Retroviruses and Opportunistic Infections. Los Angeles, CA, 2007).
71. F. Bonnet *et al.*, *HIV. Med.* **8**, 547 (2007).
72. A. N. Phillips, J. Neaton, J. D. Lundgren, *Aids* **22**, 2409 (2008).
73. M. J. Koziel, M. G. Peters, *N. Engl. J. Med.* **356**, 1445 (2007).
74. M. S. Sulkowski *et al.*, *Aids* **19**, 585 (2005).
75. C. S. Graham *et al.*, *Clin. Infect. Dis.* **33**, 562 (2001).
76. H. Al-Mohri, T. Murphy, Y. Lu, R. G. Lalonde, M. B. Klein, *J. Acquir. Immune. Defic. Syndr.* **44**, 463 (2007).
77. M. Puoti *et al.*, *J. Infect. Dis.* **183**, 134 (2001).
78. J. T. Herbeck *et al.*, *PLoS. ONE.* **3**, e1525 (2008).
79. V. Muller *et al.*, *Aids* **20**, 889 (2006).
80. P. Troude *et al.*, *Aids* **23**, 1261 (2009).
81. M. Dorrucci, G. Rezza, K. Porter, A. Phillips, *J. Infect. Dis.* **195**, 525 (2007).
82. V. Muller *et al.*, *PLoS. Pathog.* **5**, e1000454 (2009).
83. R. M. Troyer *et al.*, *J. Virol.* **79**, 9006 (2005).
84. M. E. Quinones-Mateu *et al.*, *J. Virol.* **74**, 9222 (2000).
85. K. K. Arien *et al.*, *Aids* **19**, 1555 (2005).
86. P. J. Kanki *et al.*, *J. Infect. Dis.* **179**, 68 (1999).
87. N. Kiwanuka *et al.*, *J. Infect. Dis.* **197**, 707 (2008).
88. A. Vasan *et al.*, *Clin. Infect. Dis.* **42**, 843 (2006).
89. R. Galli, L. Merrick, M. Friesenhahn, R. Ziermann, *J. Clin. Virol.* **34**, 245 (2005).
90. D. G. Murphy, L. Cote, M. Fauvel, P. Rene, J. Vincelette, *J. Clin. Microbiol.* **38**, 4034 (2000).
91. A. Berger *et al.*, *J. Clin. Virol.* **33**, 43 (2005).
92. B. P. Griffith, M. O. Rigsby, R. B. Garner, M. M. Gordon, T. M. Chacko, *J. Clin. Microbiol.* **35**, 3288 (1997).
93. D. W. Notermans *et al.*, *AIDS Res. Hum. Retroviruses* **16**, 1507 (2000).
94. C. C. Ginocchio *et al.*, *J. Clin. Microbiol.* **35**, 2886 (1997).
95. S. M. Bruisten *et al.*, *J. Virol. Methods* **67**, 199 (1997).
96. M. Dorrucci, A. N. Phillips, B. Longo, G. Rezza, *Aids* **19**, 331 (2005).
97. N. Crum-Cianflone *et al.*, *Clin. Infect. Dis.* **48**, 1285 (2009).
98. I. P. Keet *et al.*, *Aids* **10**, 1601 (1996).
99. N. Galai *et al.*, *Am. J. Epidemiol.* **143**, 278 (1996).
100. W. H. Levering *et al.*, *Cytometry B Clin. Cytom.* **74**, 79 (2008).
101. C. F. Kelley, J. D. Barbour, F. M. Hecht, *J. Acquir. Immune. Defic. Syndr.* **45**, 445 (2007).
102. J. Branger, J. T. van der Meer, R. J. van Ketel, S. Jurriaans, J. M. Prins, *Sex Transm. Dis.* (2008).
103. I. G. Stolte, N. H. Dukers, R. B. Geskus, R. A. Coutinho, J. B. de Wit, *Aids* **18**, 303 (2004).
104. R. L. Heijman *et al.*, *Sex Transm. Infect.* **85**, 249 (2009).
105. F. D. H. Koedijk *et al.*, "Sexually transmitted infections, including HIV, in the Netherlands in 2008" (RIVM report 210261004/2008, Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, 2009).
106. N. H. Dukers-Muijrers, A. M. Niekamp, M. M. Vergoossen, C. J. Hoebe, *Sex Transm. Infect.* **85**, 226 (2009).
107. I. G. Stolte, N. H. Dukers, J. B. de Wit, J. S. Fennema, R. A. Coutinho, *Sex Transm. Infect.* **77**, 184 (2001).
108. T. D. Hollingsworth, R. M. Anderson, C. Fraser, *J. Infect. Dis.* **198**, 687 (2008).
109. J. Tang *et al.*, *AIDS Res. Hum. Retroviruses* **20**, 19 (2004).
110. Y. Kawashima *et al.*, *Nature* **458**, 641 (2009).
111. L. Gras *et al.*, *PLoS. ONE.* **4**, e7365 (2009).
112. UNAIDS, "2006 Report on the global AIDS epidemic" (UNAIDS/06.13E, Joint United Nations Programme on HIV/AIDS (UNAIDS), 2006).
113. K. Boer *et al.*, *BJOG.* **114**, 148 (2007).
114. A. K. van der Bij *et al.*, *Ned. Tijdschr. Geneeskd.* **147**, 1232 (2003).
115. D. K. Mulder-Folkerts *et al.*, *Ned. Tijdschr. Geneeskd.* **148**, 2035 (2004).
116. B. H. van Benthem *et al.*, *Aids* **14**, 2171 (2000).
117. E. R. Cooper *et al.*, *J. Acquir. Immune. Defic. Syndr.* **29**, 484 (2002).
118. B. L. Rowland, S. T. Vermillion, D. E. Soper, *Am. J. Obstet. Gynecol.* **185**, 327 (2001).
119. J. S. Stringer, D. J. Rouse, R. L. Goldenberg, *JAMA* **281**, 1946 (1999).
120. F. Fourquet, J. Le Chenadec, M. J. Mayaux, L. Meyer, *Aids* **15**, 2193 (2001).
121. UNICEF. Young people and HIV/AIDS, opportunity in crisis. 2002.
122. UK Register of HIV seroconverters steering committee. *Aids* **12**, 659 (1998).
123. B. A. Koblin *et al.*, *Am. J. Epidemiol.* **150**, 1026 (1999).
124. D. Morgan *et al.*, *Aids* **16**, 597 (2002).
125. Y. Salhi, D. Costagliola, *J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol.* **16**, 409 (1997).
126. S. Grabar *et al.*, *Aids* **23**, 1163 (2009).

127. J. B. Dinoso, S. Y. Kim, R. F. Siliciano, J. N. Blankson, *Clin. Infect. Dis.* **47**, 102 (2008).
128. F. Pereyra *et al.*, *J. Infect. Dis.* **200**, 984 (2009).
129. Y. Madec, F. Boufassa, K. Porter, L. Meyer, *Aids* **19**, 2001 (2005).
130. The CoDe project. Website of the Copenhagen HIV Programma (CHIP). www.cphiv.dk/CoDe/tabid/55/Default.aspx. Accessed: 30-10-2009.
131. P. K. Andersen, S. Z. Abildstrom, S. Rosthoj, *Stat. Methods Med. Res.* **11**, 203 (2002).
132. S. Rosthoj, P. K. Andersen, S. Z. Abildstrom, *Comput. Methods Programs Biomed.* **74**, 69 (2004).
133. C. Lewden *et al.*, *J. Acquir. Immune. Defic. Syndr.* **48**, 590 (2008).
134. N. F. Crum *et al.*, *J. Acquir. Immune. Defic. Syndr.* **41**, 194 (2006).
135. P. Price *et al.*, *J. Clin. Virol.* **22**, 279 (2001).
136. A. Mocroft *et al.*, *Clin. Infect. Dis.* **48**, 1138 (2009).
137. Incidence of cancer. Website of the Association of Comprehensive Cancer Centres. www.ikcnet.nl/page.php?nav_id=41&id=2748, 30-10-2009.
138. T. Ferry *et al.*, *J. Acquir. Immune. Defic. Syndr.* **51**, 407 (2009).
139. L. Gras *et al.*, *J. Acquir. Immune Defic. Syndr.* **45**, 183 (2007).
140. J. D. Siliciano, R. F. Siliciano, *J. Antimicrob. Chemother.* **54**, 6 (2004).
141. M. Buffet *et al.*, *J. Clin. Virol.* **33**, 60 (2005).
142. G. H. Friedland, A. Williams, *Aids* **13 Suppl 1**, S61 (1999).
143. G. F. Vanhove, J. M. Schapiro, M. A. Winters, T. C. Merigan, T. F. Blaschke, *JAMA* **276**, 1955 (1996).
144. D. R. Kuritzkes, *AIDS Patient. Care STDS.* **18**, 259 (2004).
145. The antiretroviral therapy cohort collaboration (ART-cc), *Aids* 23, 2199 (2009).
146. C. J. Smith *et al.*, *J. Infect. Dis.* **190**, 1860 (2004).
147. P. R. Harrigan *et al.*, *J. Infect. Dis.* **191**, 339 (2005).
148. S. Napravnik *et al.*, *J. Acquir. Immune. Defic. Syndr.* **40**, 34 (2005).
149. S. Grabar *et al.*, *J. Acquir. Immune. Defic. Syndr.* **39**, 284 (2005).
150. O. Coll *et al.*, *J. Acquir. Immune. Defic. Syndr. Hum. Retrovirol.* **14**, 26 (1997).
151. S. Timmermans *et al.*, *Aids* **19**, 795 (2005).
152. P. K. Siiteri, D. P. Stites, *Biol. Reprod.* **26**, 1 (1982).
153. European Collaborative Study, *Clin. Infect. Dis.* **40**, 458 (2005).
154. C. Tempelman *et al.*, *Ned. Tijdschr. Geneeskd.* **148**, 2021 (2004).
155. M. Bunders, M. Cortina-Borja, M. L. Newell, *Pediatr. Infect. Dis. J.* **24**, 595 (2005).
156. A. M. van Rossum, P. L. Fraaij, R. de Groot, *Lancet Infect. Dis.* **2**, 93 (2002).
157. D. M. Gibb *et al.*, *Lancet* **355**, 1331 (2000).
158. V. A. Johnson *et al.*, *Top. HIV. Med.* **16**, 138 (2008).
159. S. Y. Rhee *et al.*, *Nucleic Acids Res.* **31**, 298 (2003).
160. D. Lincoln, K. Petoumenos, G. J. Dore, *HIV. Med.* **4**, 241 (2003).
161. C. H. van den Berg *et al.*, *Eur. J. Epidemiol.* **22**, 183 (2007).
162. A. Rauch *et al.*, *Clin. Infect. Dis.* **41**, 395 (2005).
163. G. Rooney, R. J. Gilson, *Sex Transm. Infect.* **74**, 399 (1998).
164. L. Ruiz *et al.*, *Aids* **21**, 169 (2007).
165. L. B. Seeff *et al.*, *Ann. Intern. Med.* **132**, 105 (2000).
166. M. G. Brook, R. Gilson, E. Wilkins, *HIV. Med.* **6 Suppl 2**, 84 (2005).
167. V. Soriano *et al.*, *Aids* **19**, 221 (2005).
168. T. Lee, M. Nunez, *HIV. Clin. Trials* **10**, 153 (2009).

acknowledgements

Treating physicians

(*Site coordinating physicians)

Academisch Medisch Centrum bij de Universiteit van Amsterdam - Amsterdam:
Dr. J.M. Prins*, Drs. J.C. Bos, Dr. J.K.M. Eeftinck-Schattenkerk (until Febr. 2009) Dr. S.E. Geerlings, Dr. M.H. Godfried, Prof. dr. J.M.A. Lange, Dr. J.T.M. van der Meer, Dr. F.J.B. Nellen, Dr. T. van der Poll, Prof. dr. P. Reiss, Drs. S.U.C. Sankatsing, Drs. M. van der Valk, Drs. J.N. Vermeulen, Drs. S.M.E. Vrouenraets, Dr. M. van Vugt, Dr. F.W.M.N. Wit.
Academisch Ziekenhuis Maastricht - Maastricht:
Dr. G. Schreij*, Dr. S. van der Geest, Dr. A. Oude Lashof, Dr. S. Lowe.
Catharina Ziekenhuis - Eindhoven:
Dr. B. Bravenboer*, Drs. M.J.H. Pronk.
Emma Kinderziekenhuis - AMC Amsterdam:
Prof. dr. T.W. Kuijpers, Drs. D. Pajkrt, Dr. H.J. Scherpbier.
Erasmus MC - Rotterdam:
Dr. M.E. van der Ende*, Drs. H. Bax, Drs. M. van der Feltz, Dr. L.B.S. Gelinck, Dr. J.L. Nouwen, Dr. B.J.A. Rijnders, Dr. E.D. de Ruiter, Dr. L. Slobbe, Drs. C.A.M. Schurink, Dr. A. Verbon, Dr. T.E.M.S. de Vries-Sluijs.
Erasmus MC - Sophia - Rotterdam:
Dr. G. Driessen, Dr. N.G. Hartwig,
Flevoziekenhuis - Almere:
Dr. J. Branger, Drs. M.H. Hoogewerf.
Haga Ziekenhuis, locatie Leyenburg - Den Haag:
Dr. R.H. Kauffmann*, Dr. E.F. Schippers.
Isala Klinieken - Zwolle:
Dr. P.H.P. Groeneveld*, Dr. M.A. Alleman.
Kennemer Gasthuis - Haarlem:
Prof. dr. R.W. ten Kate*, Dr. R. Soetekouw.
Leids Universitair Medisch Centrum - Leiden:
Dr. F.P. Kroon*, Dr. S.M. Arend, Drs. M.G.J. de Boer, Prof. dr. P.J. van den Broek, Prof. dr. J.T. van Dissel, Drs. C. van Nieuwkoop.
Maasstadziekenhuis - locatie Clara - Rotterdam:
Dr. J.G. den Hollander*.
Medisch Centrum Alkmaar - Alkmaar:
Dr. W. Bronsveld*, Dr. K. Pogany.
Medisch Centrum Haaglanden - locatie Westeinde - Den Haag:
Dr. R. Vriesendorp*, Dr. E.M.S. Leyten.
Medisch Centrum Leeuwarden - Leeuwarden:
Dr. D. van Houte*, Dr. M.B. Polée, Dr. M.G.A. van Vonderen.
Medisch Spectrum Twente - Enschede:
Dr. C.H.H. ten Napel*, Dr. G.J. Kootstra.
Onze Lieve Vrouwe Gasthuis - Amsterdam.
Prof. dr. K. Brinkman*, Drs. G.E.L. van den Berk, Dr. W.L. Blok, Dr. P.H.J. Frissen, Drs. W.E.M. Schouten.
St. Medisch Centrum Jan van Goyen - Amsterdam:
Dr. A. van Eeden*, Dr. D.W.M. Verhagen.
Slotervaart Ziekenhuis - Amsterdam:
Dr. J.W. Mulder*, Dr. E.C.M. van Gorp, Dr. J. Wagenaar, Dr. S. Weijer.
St. Elisabeth Ziekenhuis - Tilburg:
Dr. J.R. Juttmann*, Dr. M.E.E. van Kasteren.
St. Lucas Andreas Ziekenhuis - Amsterdam:
Dr. J. Veenstra*, Dr. K.D. Lettinga.
Universitair Medisch Centrum St. Radboud - Nijmegen:
Dr. P.P. Koopmans*, Drs. A.M. Brouwer, Dr. A.S.M. Dofferhoff, Dr. M. van der Flier, Prof. dr. R. de Groot, Drs. H.J.M. ter Hofstede, Dr. M. Keuter, Dr. A.J.A.M. van der Ven.
Universitair Medisch Centrum Groningen - Groningen:
Dr. H.G. Sprenger*, Dr. S. van Assen, Dr. C.J. Stek.
Universitair Medisch Centrum Groningen - Beatrix Kliniek - Groningen:
Dr. R. Doedens, Dr. E.H. Scholvinck.
Universitair Medisch Centrum Utrecht - Utrecht:
Prof. dr. I.M. Hoepelman*, Prof. dr. M.J.M. Bonten, Dr. P.M. Ellerbroek, Drs. E. Hoornenborg, Drs. C.A.J.J. Jaspers, Drs. L.J. Maarschalk-Ellerbroek, Dr. T. Mudrikova, Dr. J.J. Oosterheert, Dr. E.J.G. Peters, Dr. M.M.E. Schneider, Drs. M.W.M. Wassenberg.
Wilhelmina Kinderziekenhuis - UMC Utrecht:
Dr. S.P.M. Geelen, Dr. T.F.W. Wolfs.
VU Medisch Centrum - Amsterdam:
Prof. dr. S.A. Danner*, Dr. M.A. van Agtmael, Drs. W.F.W. Bierman, Drs. F.A.P. Claessen, Drs. M.E. Hillebrand, Drs. E.V. de Jong, Drs. W. Kortmann, Dr. R.M. Perenboom, Drs. E.A. bij de Vaate.
Ziekenhuis Rijnstate - Arnhem:
Dr. C. Richter*, Drs. J. van der Berg, Dr. E.H. Gisolf.
Ziekenhuis Walcheren - Vlissingen:
Dr. A.A. Tanis*.
St. Elisabeth Hospitaal/Stichting Rode Kruis Bloedbank - Willemstad, Curaçao:
Dr. A.J. Duits, Dr. A. Durand, Dr. F. Muskiet, Dr. R. Voigt, Dr. K. Winkel.

Virologists

Academisch Medisch Centrum bij de Universiteit van Amsterdam – Amsterdam:
Dr. N.K.T. Back, M.E.G. Bakker, Dr. H.L. Zaaijer.
Prof. dr. B. Berkhout, Dr. S. Jurriaans.
CLB Stichting Sanquin Bloedvoorziening - Amsterdam:
Dr. Th. Cuijpers.
Onze Lieve Vrouwe Gasthuis - Amsterdam:
Dr. P.J.G.M. Rietra, Dr. K.J. Roozendaal.
Slotervaart Ziekenhuis - Amsterdam:
Drs. W. Pauw, Drs. P.H.M. Smits, Dr. A.P. van Zanten.
VU Medisch Centrum – Amsterdam:
Dr. B.M.E. von Blomberg, Dr. A. Pettersson, Dr. P. Savelkoul.
Ziekenhuis Rijnstate – Arnhem:
Dr. C.M.A. Swanink.
HAGA, ziekenhuis, locatie Leyenburg - Den Haag:
Dr. P.F.H. Franck, Dr. A.S. Lampe.
Medisch Centrum Haaglanden,
locatie Westeinde - Den Haag:
Drs. C.L. Jansen.
Streeklaboratorium Twente - Enschede:
Dr. R. Hendriks.
Streeklaboratorium Groningen - Groningen:
Dr. C.A. Benne.
Streeklaboratorium Volksgezondheid Kennemerland - Haarlem:
Dr. J. Schirm, Dr. D. Veenendaal.
Laboratorium voor de Volksgezondheid in Friesland - Leeuwarden:
Dr. H. Storm, Drs. J. Weel, Drs. J.H. van Zeijl.
Leids Universitair Medisch Centrum - Leiden:
Dr. H.C.J. Claas, Prof. dr. A.C.M. Kroes.
Academisch Ziekenhuis Maastricht - Maastricht:
Prof. dr. C.A.M.V.A. Bruggeman, Drs. V.J. Goossens.
Universitair Medisch Centrum St. Radboud - Nijmegen:
Prof. dr. J.M.D. Galama, Dr. W.J.G. Melchers, Dr. Verduyn-Lunel.
Erasmus MC - Rotterdam:
Dr. C.A.B. Boucher, Dr. G.J.J. van Doornum, Dr. H.G.M. Niesters,
Prof. dr. A.D.M.E. Osterhaus, Dr. M. Schutten.
St. Elisabeth Ziekenhuis - Tilburg:
Dr. A.G.M. Buiting.
Universitair Medisch Centrum Utrecht - Utrecht:
Dr. E. Boel, Dr. R. Schuurman.
Catharina Ziekenhuis - Eindhoven:
Dr. A.F. Jansz, Drs. M. Wulf.

Pharmacologists

Medisch Centrum Alkmaar - Alkmaar:
Dr. A. Veldkamp.
Slotervaart Ziekenhuis - Amsterdam:
Prof. dr. J.H. Beijnen, Dr. A.D.R. Huitema.
Universitair Medisch Centrum St. Radboud - Nijmegen:
Dr. D.M. Burger.
Academisch Medisch Centrum bij de Universiteit van Amsterdam – Amsterdam:
Drs. H.J.M. van Kan.

HIV Treatment Centres

Academisch Medisch Centrum bij de Universiteit van Amsterdam,
Meibergdreef 9, 1105 AZ Amsterdam;
Academisch Ziekenhuis Maastricht,
P. Debyelaan 25, 6229 HX Maastricht;
Catharina Ziekenhuis,
Postbus 1350, 5602 ZA Eindhoven;
Emmakinderziekenhuis, AMC Amsterdam,
Meibergdreef 9, 1105 AZ Amsterdam;
Erasmus MC,
Dr. Molewaterplein 40, 3015 GD Rotterdam;
Flevoziekenhuis,
Hospitaalweg 1, 1315 RA Almere;
HAGA, locatie Leyenburg,
Leyweg 275, 2545 CH Den Haag;
Isala Klinieken, locatie Sophia,
Dokter van Heesweg 2, 8025 AB Zwolle;
Kennemer Gasthuis, locatie EG,
Boerhaavelaan 22, 2000 AK Haarlem;
Leids Universitair Medisch Centrum,
Rijnsburgerweg 10, 2333 AA Leiden;
Medisch Centrum Alkmaar,
Wilhelminalaan 12, 1815 JD Alkmaar;
Medisch Centrum Haaglanden, locatie Westeinde,
Lijnbaan 32, 2512 VA Den Haag;
Medisch Centrum Leeuwarden, locatie Zuid,
H. Dunantweg 2, 8934 AD Leeuwarden;
Maasstad ziekenhuis, locatie Clara,
Olympiaweg 350, 3078 HT Rotterdam;
Medisch Spectrum Twente,
Postbus 50, 7500 KA Enschede;

Onze Lieve Vrouwe Gasthuis, locatie Oosterpark,
1e Oosterparkstraat 179, 1091 HA Amsterdam;
Onze Lieve Vrouwe Gasthuis, locatie Prinsengracht,
Prinsengracht 769, 1017 JZ Amsterdam;
St. Medisch Centrum Jan van Goyen,
Jan van Goyenkade 1, 1075 HN Amsterdam;
Slotervaartziekenhuis,
Louwesweg 6, 1066 CE Amsterdam;
E**rasmus MC - Sophia**,
Dr. Molenwaterplein 40, 3015 GD Rotterdam;
St. Elisabeth Ziekenhuis,
Hilvarenbeekseweg 60, 5022 GC Tilburg;
St. Lucas Andreas Ziekenhuis,
Postbus 9243, 1006 AE Amsterdam;
Streekziekenhuis Walcheren,
Koudekerkseweg 88, 4382 EE Vlissingen;
Universitair Medisch Centrum Groningen,
Oostersingel 59, 9715 EZ Groningen;
Universitair Medisch Centrum Groningen – Beatrix Kliniek,
Oostersingel 59, 9715 EZ Groningen;
Universitair Medisch Centrum St. Radboud,
Postbus 9101, 6500 HB Nijmegen;
Universitair Medisch Centrum Utrecht,
Heidelberglaan 100, 3584 CX Utrecht;
VU Medisch Centrum,
De Boelelaan 1117, 1081 HV Amsterdam;
Wilhelmina Kinderziekenhuis Utrecht,
Postbus 85090, 3508 AB Utrecht;
Ziekenhuis Rijnstate,
Wagnerlaan 55, 6815 AD Arnhem;
Stichting Rode Kruis Bloedbank, Huize Batavia,
Pater Euwensweg 36, Willemstad, Curaçao;
St. Elisabeth Hospitaal,
Breedestraat 193 (0), Willemstad, Curaçao.

Other institutions involved

CLB, Stichting Sanquin Bloedvoorziening,
Plesmanlaan 125, 1066 CX Amsterdam;
Laboratorium voor de Volksgezondheid in Friesland,
Postbus 21020, 8900 JA Leeuwarden;
Streeklaboratorium voor de Volksgezondheid voor Groningen en Drenthe,
Van Ketwich Verschuurlaan 92, 9821 SW Groningen;
Streeklaboratorium Volksgezondheid Kennemerland,
Boerhaavelaan 26, 2035 RE Haarlem;
Streeklaboratorium Twente-Enschede,
Burg. Edo Bergsmalaan 1, 7512 AD Enschede.

Governing Board of the Stichting HIV Monitoring 2009

NVAB nominated:
Prof. dr. S.A. Danner, Chairman (until October 21, 2009),
VU University Amsterdam, Amsterdam, The Netherlands
Dr. F.P. Kroon, Chairman (from October 21, 2009),
Leiden University Medical Centre, Leiden, The Netherlands
Ministry of Health, Welfare and Sport:
Prof. dr. R.A. Coutinho, observer,
Centre for Infectious Disease Control, Bilthoven, The Netherlands
AMC-UvA nominated:
Prof. dr. J. Goudsmit, member (until October 21, 2009),
Crucell BV, Leiden, The Netherlands
Prof. dr. K. Stronks, member, (from October 21, 2009),
Academic Medical Centre of the University of Amsterdam, Amsterdam,
The Netherlands
NFU nominated:
Prof. dr. L.J. Gunning-Schepers, member (until October 21, 2009),
Academic Medical Centre of the University of Amsterdam, Amsterdam,
The Netherlands
Dr. R.J.M. Hopstaken, member (from October 2009),
Academic Medical Centre of the University of Amsterdam, Amsterdam,
The Netherlands
NVZ nominated:
Dr. D.J. Hemrika, Secretary (until October 21, 2009),
Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
Drs. J.C.H.G. Arts, member (from October 21, 2009),
Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands
Zorgverzekeraars Nederland nominated:
Drs. A.J. Lamping, Treasurer,
Zorgverzekeraars Nederland, Zeist, The Netherlands
HIV Vereniging Nederland nominated:
Dhr. H.G.P.M. van Rooij MD, member
GGD Nederland nominated:
Drs. P. van der Velpen, member (from October 21, 2009),
GGD Amsterdam, Amsterdam, The Netherlands
AGIS nominated:
Drs. M.I. Verstappen, member (from October 21, 2009),
AGIS, Amersfoort, The Netherlands

Advisory Board of Stichting HIV Monitoring

Prof. dr. J.M.A. Lange (chairman), AMC, Dept. of Internal Medicine, Amsterdam
Dr. F.P. Kroon (vice chairman), LUMC, Dept. of Internal Medicine, Leiden
Prof. dr. Sir R.M. Anderson, Imperial College, Faculty of Medicine, Dept. of Infectious Disease Epidemiology, London, United Kingdom
Prof. dr. M. Egger, University of Bern, Switzerland / Bristol, United Kingdom
Prof. MD. D.R. Kuritzkes, Brigham and Women's Hospital, Section of Retroviral Therapeutics, Cambridge, U.S.A.
Prof. dr. J. Lundgren, Copenhagen HIV Programme, Denmark
Dhr. C. Rümke, Dutch HIV Association, Amsterdam
Prof. dr. J. Schuitemaker, AMC, Dept. of Internal Medicine, Amsterdam

Working group Members of Stichting HIV Monitoring

Dr. M.E. van der Ende (chairman), Erasmus Medical Centre, Dept. of Internal Medicine, Rotterdam
Dr. K. Boer, AMC, Dept. of Obstretrics/Gynaecology, Amsterdam
Dr. C.A.B. Boucher, Erasmus Medical Centre, Dept. of Internal Medicine, Rotterdam
Dr. F.C. van Leth, KNCV Tuberculosis Foundation, The Hague
Dr. W.M.C. Mulder, Dutch HIV Association, Amsterdam
Prof. dr. P. Reiss, AMC, Dept. of Internal Medicine, Amsterdam

Working group Reviewers of Stichting HIV Monitoring

Dr. N.K.T. Back, AMC, Lab. Exp. Virology, Amsterdam
Prof. dr. K. Brinkman, Onze Lieve Vrouwe Gasthuis, location Oosterpark, Dept. of Internal Medicine, Amsterdam
Dr. D.M. Burger (subgr. Pharmacology), UMCN – St. Radboud, Dept. of Clinical Pharmacy, Nijmegen
Dr. H.C.J. Claas, LUMC, Clinical Virological Laboratory, Leiden
Dr. G.J.J. Doornum, Erasmus Medical Centre, Dept. of Virology, Rotterdam
Prof. dr. J.M.D. Galama, UMCN - St. Radboud, Dept. of Medical Microbiology, Nijmegen
Dr. S.P.M. Geelen, UMCU-WKZ, Dept. of Paediatrics, Utrecht
Prof. dr. A.I.M. Hoepelman, UMCU, Dept. of Virology, Utrecht
Dr. S. Jurriaans, AMC, Lab. Exp. Virology, Amsterdam
Dr. J.R. Juttmann, St. Elisabeth Hospital, Dept. of Internal Medicine, Tilburg
Dr. R. Kauffmann, HAGA Ziekenhuis, location Leyenburg, The Hague
Dr. R.P. Koopmans, UMCN – St. Radboud, Dept. of Internal Medicine, Nijmegen
Prof. dr. A.C.M. Kroes, LUMC, Clinical Virological Laboratory, Leiden
Prof. dr. T.W. Kuijpers, AMC, Dept. of Paediatrics, Amsterdam
Dr. W.J.G. Melchers, UMCN - St. Radboud, Dept. of Medical Microbiology, Nijmegen
Dr. C.H.H. ten Napel, Medisch Spectrum Twente, Dept. of Internal Medicine, Enschede
Prof. dr. J.M. Prins, AMC, Dept. of Internal Medicine, Amsterdam
Dr. P. Savelkoul, VU Medical Centre, Dept. of Medical Microbiology, Amsterdam
Dr. G. Schreij, Academic Hospital, Dept. of Internal Medicine, Maastricht
Dr. R. Schuurman, UMCU, Dept. of Virology, Utrecht
Dr. H.G. Sprenger, Academic Hospital, Dept. of Internal Medicine, Groningen
Dr. A. Wensing, UMCU, Dept. of Virology, Utrecht

Stichting HIV Monitoring

Director

Prof. dr. F. de Wolf

Senior researchers

Dr. D.O. Bezemer
Drs. L.A.J. Gras
Dr. A.I. van Sighem
Dr. Ir. C. Smit

PhD students

Drs. A.M. Kesselring
Drs. S. Zhang

Manager Patient Data & Quality Control

Drs. S. Zaheri, Manager Patient Data & Quality Control

Patient Registration

R.F. Beard

Data Monitoring

Drs. S. Grivell
Drs. J.M.T. van der Heijden
Drs. M.M.J. Hillebregt
Drs. V. Kimmel
Drs. B. Slieker
Drs. C.A.H. Welling

Data collection

Academisch Medisch Centrum bij de Universiteit van Amsterdam – Amsterdam:
C.R.E. Lodewijk, Y.M.C. Ruijs-Tiggelman, D.P. Veenenberg-Benschop, L.G.M. de Groot-Berndsen, T. Woudstra (from August 2009).
Academisch Ziekenhuis Maastricht:
R. Vergoossens, R. Ackens (until October 2009), M.E. Todor (from September 2009).
Catharina Ziekenhuis - Eindhoven:
B. Korsten, S. de Munnik.
Erasmus Medisch Centrum - Rotterdam:
C. Kam-van de Berg, A. de Oude, T. Royaards (until August 2009), P. Hokhles, J. de Groot (from September 2009), F. Broekman.
Haga Ziekenhuis, location Leyenburg – The Hague:
G. van der Hut.
Isala Klinieken - Zwolle:
A. van den Berg, A.G.W. Hulzen.
Kennemer Gasthuis - Haarlem:
N. Bermon.
Leids Universitair Medisch Centrum - Leiden:
M.J. van Broekhoven-Kruijne.
Medisch Centrum Alkmaar - Alkmaar:
D. Pronk, F.A. van Truijen-Oud.
Medisch Centrum Haaglanden, location Westeinde – The Hague:
Y.M.C. Ruijs-Tiggelman.
Medisch Centrum Leeuwarden - Leeuwarden:
S. Rotteveel.
Maasstadziekenhuis - locatie Clara - Rotterdam:
D. Haazer.
Medisch Spectrum Twente - Enschede:
E. Lucas.
Onze Lieve Vrouwe Gasthuis, Amsterdam:
B.M. Peeck, E.M. Tuijn-de Bruin, M. van den Akker.
Stichting Medisch Centrum Jan van Goyen - Amsterdam:
M. van den Akker, Y.M. Bakker.
Slotervaart Ziekenhuis - Amsterdam:
E. Oudmaijer-Sanders, Y.M. Bakker.
St. Elisabeth Ziekenhuis - Tilburg:
R. Santegoets, B. van der Ven, M. Kuipers, B. de Kruijf-van de Wiel.
St. Lucas Andreas Ziekenhuis – Amsterdam:
M. Spelbrink.
Universitair Medisch Centrum – St Radboud - Nijmegen:
M. Meeuwissen, A. van Rijk.
Universitair Medisch Centrum Groningen - Groningen:
J. Huizinga (until May 2009), C.I. Nieuwenhout.
Universitair Medisch Centrum Utrecht - Utrecht:
H. Nieuwenhuis, M. Gras (from September 2009).
VU Medisch Centrum – Amsterdam:
L.G.M. de Groot-Berndsen.
Ziekenhuis Rijnstate - Arnhem:
C.W.A.J. Deurloo-van Wanrooy.
Ziekenhuis Walcheren - Vlissingen:
J. Bom, Y.M. Bakker.
Flevoziekenhuis - Almere
L.G.M. de Groot-Berndsen.
St. Elisabeth Hospitaal/Stichting Rode Kruis Bloedbank - Willemstad, Curaçao:
K. Laurant, Y.M.C. Ruijs-Tiggelman.

Manager Office, Administration, Communication

D. de Boer

Personnel & Administration

I.H.M. de Boer
Drs. H.J.M. van Noort

Communication

Drs. S.M.H. Huiberts (until August, 2009)
Drs. C.M.M. Knoop (from August, 2009)

Office

M.M.T. Koenen Bsc
Drs. G.E. Scholte

publications 2009

Publications

Does short-term virologic failure translate to clinical events in antiretroviral-naïve patients initiating antiretroviral therapy in clinical practice?
Antiretroviral Therapy Cohort Collaboration (ART-CC), Mugavero MJ, May M, Harris R, Saag MS, Costagliola D, Egger M, Phillips A, Günthard HF, Dabis F, Hogg R, De Wolf F, Fatkenheuer G, Gill MJ, Justice A, D'Arminio Monforte A, Lampe F, Miró JM, Staszewski S, Sterne JA.
AIDS. 2008 Nov 30;22(18):2481-92.

Lower perceived necessity of HAART predicts lower treatment adherence and worse virological response in the ATHENA cohort
De Boer-van der Kolk IM, Sprangers MA, Van der Ende M, Schreij G, De Wolf F, Nieuwkerk PT.
J Acquir Immune Defic Syndr. 2008 Dec 1;49(4):460-2

Absence of a relation between efavirenz plasma concentrations and toxicity-driven efavirenz discontinuations in the EuroSIDA study
Van Luin M, Bannister WP, Mocroft A, Reiss P, Di Perri G, Peytavin G, Molto J, Karlson A, Castagna A, Beniowski M, Lundgren JD, Burger DM; EuroSIDA Study Group.
Antivir Ther. 2009;14(1):75-83.

Variable impact on mortality of AIDS-defining events diagnosed during combination antiretroviral therapy: not all AIDS-defining conditions are created equal
Antiretroviral Therapy Cohort Collaboration (ART-CC), Mocroft A, Sterne JA, Egger M, May M, Grabar S, Furrer H, Sabin C, Fatkenheuer G, Justice A, Reiss P, D'Arminio Monforte A, Gill J, Hogg R, Bonnet F, Kitahata M, Staszewski S, Casabona J, Harris R, Saag M.
Clin Infect Dis. 2009 Apr 15;48(8):1138-51.

Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: a collaborative analysis of 18 HIV cohort studies
When To Start Consortium, Sterne JA, May M, Costagliola D, De Wolf F, Phillips AN, Harris R, Funk MJ, Geskus RB, Gill J, Dabis F, Miró JM, Justice AC, Ledergerber B, Fätkenheuer G, Hogg RS, Monforte AD, Saag M, Smith C, Staszewski S, Egger M, Cole SR.
Lancet. 2009 Apr 18;373(9672):1352-63. Epub 2009 Apr 8.

Clinical experience with the combined use of lopinavir/ritonavir and rifampicin
L'homme RF, Nijland HM, Gras L, Aarnoutse RE, Van Crevel R, Boeree M, Brinkman K, Prins JM, Juttmann JR, Burger DM.
AIDS. 2009 Apr 27;27(7):863-5.

Estimating the public health impact of the effect of herpes simplex virus suppressive therapy on plasma HIV-1 viral load
Baggaley RF, Griffin JT, Chapman R, Hollingsworth TD, Nagot N, Delany S, Mayaud P, De Wolf F, Fraser C, Ghani AC, Weiss HA.
AIDS. 2009 May 15;23(8):1005-13.

Baseline lipid levels rather than the presence of reported body shape changes determine the degree of improvement in lipid levels after switching to atazanavir
Van Vonderen MG, Gras L, Wit F, Brinkman K, Van der Ende ME, Hoepelman AI, De Wolf F, Reiss P.
HIV Clin Trials. 2009 May-June;10(3):168-80.

Reemergence of the HIV epidemic among men who have sex with men in North America, Western Europe, and Australia, 1996-2005
Sullivan PS, Hamouda O, Delpech V, Geduld JE, Prejean J, Semaille C, Kaldor J, Folch C, Op de Coul E, Marcus U, Hughes G, Archibald CP, Cazein F, McDonald A, Casabona J, Van Sighem A, Fenton KA; Annecy MSM Epidemiology Study Group.
Ann Epidemiol. 2009 June;19(6):423-31.

Efavirenz Dose Reduction Is Safe in Patients With High Plasma Concentrations and May Prevent Efavirenz Discontinuations
Van Luin M, Gras L, Richter C, Ende ME, Prins JM, Wolf FD, Burger DM, Wit FW.
J Acquir Immune Defic Syndr. 2009 July 10 52:240–245

Which method of adherence measurement is most suitable for daily use to predict virological failure among immigrant and non-immigrant HIV-1 infected patients?
Nellen JFJB, Nieuwkerk PT, Burger DM, Wibaut M, Gras L, Prins JM.
AIDS Care July 2009 21 (7); 842 - 850

Risk factors for treatment-limiting toxicities in patients starting nevirapine-containing antiretroviral therapy
Kesselring AM, Wit FW, Sabin CA, Lundgren JD, Gill MJ, Gatell JM, Rauch A, Montaner JS, De Wolf F, Reiss P, Mocroft A; Nevirapine Toxicity Multicohort Collaboration.
AIDS. 2009 August 24;23(13):1689-99.

Effect of Baseline CD4 Cell Counts on the Clinical Significance of Short-Term Immunologic Response to Antiretroviral Therapy in Individuals With Virologic Suppression
Moore DM, Harris R, Lima V, Hogg B, May M, Yip B, Justice A, Costagliola D, Elzi L, Mugavero MJ, D'Arminio Monforte A, Sabin C, Podzamczer D, Fätkenheuer G, Staszewski S, Gill J, Sterne JAC; The Antiretroviral Therapy Cohort Collaboration.
J Acquir Immune Defic Syndr. 2009 November 1 52(3):357-63

A comparison of three computational modelling methods for the prediction of virological response to combination HIV therapy.
Wang D, Larder B, Revell A, Montaner J, Harrigan R, De Wolf F, Lange J, Wegner S, Ruiz L, Pérez-Elías MJ, Emery S, Gatell J, D'Arminio Monforte A, Torti C, Zazzi M, Lane C.
Artif Intell Med. 2009 September;47(1):63-74.

The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals
The HIV-CAUSAL Collaboration. *Epub ahead of print, AIDS. 2009 September 18*

Prognosis of patients treated with cART from 36 months after initiation, according to current and previous CD4 cell count and plasma HIV-1 RNA measurements
Lanoy E, May M, Mocroft A, Phillips A, Justice A, Chêne G, Sterling T, D'Arminio Monforte A, Force L, Gill J, Harris R, Hogg RS, Rockstroh J, Saag M, Khyakin P, Sterne ACJ, Costagliola D; The antiretroviral therapy cohort collaboration (ART-CC).
AIDS. 2009 October 23;23(16):2199-2208

Prognosis of HIV-associated non-Hodgkin lymphoma in patients starting combination antiretroviral therapy
Bohlius J, Schmidlin K, Costagliola D, Fätkenheuer G, May M, Murillo AMC, Mocroft A, Bonnet F, Clifford G, Touloumi G, Miro JM, Chene G, Ludgren J, Egger M; Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study group.
AIDS. 2009 September 24;23(15):2029-37

Mortality of HIV-infected patients starting potent antiretroviral therapy: comparison with the general population in nine industrialized countries
Zwahlen M, Harris R, May M, Hogg R, Costagliola D, De Wolf F, Gill F, Fätkenheuer G, Lewden C, Saag M, Staszewski S, D'Arminio Monforte A, Casabona J, Lampe F, Justice A, Von Wyl V, Egger M. The Antiretroviral Therapy Cohort Collaboration
International Journal of Epidemiology. October 2009

Viral load levels measured at set-point have risen over the last decade of the HIV epidemic in the Netherlands
Gras L, Jurriaans S, Bakker M, Van Sighem A, Bezemer D, Fraser C, Lange J, Prins JM, Berkhout B, De Wolf F, on behalf of the ATHENA national observational cohort study
PLoS One. 2009 October 7;4(10):e7365.

Sexually transmitted infections, including HIV, in the Netherlands in 2008
Koedijk FDH, Vriend HJ, Van Veen MG, Op de Coul ELM, Van den Broek IVF, Van Sighem A, Verheij RA, Van der Sande MAB.
National Institute for Public Health and the Environment, Bilthoven, 2009
RIVM report number 210261005

Accepted articles

Health-related quality of life independently predicts survival among HIV infected patients on HAART in the ATHENA-cohort
De Boer-van der Kolk IM, Sprangers MAG, Smit C, De Wolf F, Prins JM, Nieuwkerk PT
CID.

Transmission Networks of Resistant HIV-1 among Men Who Have Sex with Men in the Netherlands
Bezemer D, Van Sighem A, Lukashov V, Van der Hoek L, Back N, Schuurman R, Boucher C, Claas E, Boerlijst MC, Coutinho R, De Wolf F, for the ATHENA observational cohort
AIDS.

Poster presentations

Stable HIV-1 Epidemic among Heterosexual Men and Women in the Netherlands
Van Sighem A, Fraser C, Bezemer D, Jurriaans S, Garnett G, De Wolf F
16th Conference on Retroviruses and Opportunistic Infections, Montréal, Canada, 8-11 February 2009

Different Rates of Discontinuation because of Toxicities According to CD4 Counts and Prior ART in Patients Starting Nevirapine-based cART: Nevirapine Toxicity Multicohort Collaboration
Kesselring A, Wit F, Sabin C, Lundgren JD, Gill J, Gatell J, Rauch A, Montaner J, De Wolf F, Reiss P, Mocroft A, on behalf of the Nevirapine Toxicity Multicohort Collaboration.
16th Conference on Retroviruses and Opportunistic Infections, Montréal, Canada, 8-11 February 2009

Set Point HIV-1 Viral Load Is Higher in Patients in the Netherlands in More Recent Years
Gras L, Jurriaans S, Fraser C, Van Sighem A, Bezemer D, Bakker M, Smit C, Prins J, Berkhout B, De Wolf F
16th Conference on Retroviruses and Opportunistic Infections, Montréal, Canada, 8-11 February 2009

Transmission Networks of Resistant HIV-1 among Men Who Have Sex with Men in the Netherlands
Bezemer D, Van Sighem A, Lukashov V, Van der Hoek L, Jurriaans S, Schuurman R, Boucher C, Claas E, Coutinho R, De Wolf F
16th Conference on Retroviruses and Opportunistic Infections, Montréal, Canada, 8-11 February 2009

Modelling 27 Years of the HIV-1 Epidemic amongst Men Having Sex with Men: The Netherlands
Bezemer D, De Wolf F, Boerlijst MC, Van Sighem A, Fraser C
16th Conference on Retroviruses and Opportunistic Infections, Montréal, Canada, 8-11 February 2009

Risk of extensive triple-class virologic failure of the three original antiretroviral drug classes among people followed from therapy initiation with NNRTI or ritonavir-boosted Protease Inhibitor regimens
Lodwick R and Plato II projectteam of COHERE
16th Conference on Retroviruses and Opportunistic Infections, Montréal, Canada, 8-11 February 2009

Side effects of HAART in HIV-1 infected pregnant and non-pregnant women; pregnancy is associated with hepatotoxicity, while ethnicity is associated with rash
Snijdewind I, Smit C, Godfried M, Nellen J, Boer K, De Wolf F, Van der Ende I
16th Conference on Retroviruses and Opportunistic Infections, Montréal, Canada, 8-11 February 2009

Newly acquired hepatitis C infection causes a cellular immune response amongst HIV infected individuals
Smit C, Arends J, Gras L, Van Sighem A, Lange J, Hoepelman A, De Wolf F
16th International Workshop on HIV Observational Databases, Lisbon, Portugal, 26-28 March 2009

A novel method of estimating the number of people living with HIV/AIDS in the Netherlands
Van Sighem A, Fraser C, Bezemer D, Garnett G, De Wolf F
16th International Workshop on HIV Observational Databases, Lisbon, Portugal, 26-28 March 2009

Lower HIV RNA measurement frequency introduces misclassification of episodes of viraemia in initially successfully treated patients
Gras L, Smit C, Van Sighem A, De Wolf F, for the ATHENA observational cohort
16th International Workshop on HIV Observational Databases, Lisbon, Portugal, 26-28 March 2009

Immune restoration and onset of new AIDS-defining events after starting cART in HIV-1 infected immigrants from sub-Saharan Africa in the Netherlands
Kesselring AM, Gras L, Wit FW, Smit C, Geerlings SE, Mulder JW, Schreij G, Sprenger HG, Reiss P, De Wolf F
16th International Workshop on HIV Observational Databases, Lisbon, Portugal, 26-28 March 2009

Interaction between hepatitis B and C in HIV infected patients; risk of dying among patients with a triple infection
Smit C, Arends JE, De Wolf F, Hoepelman AIM
Annual Meeting of the European Association for the Study of the Liver (EASL), Copenhagen, Denmark, 22-26 April 2009

Measuring the quality of data in the HIV Monitoring Foundation Athena database
Hillebregt M, De Lange-de Klerk E, Knol D, De Wolf F, Smit C
Wetenschappelijk Epidemiologisch Onderzoek Nederland (WEON), Amsterdam, the Netherlands, 11-12 June 2009

Presence of drug resistance during the course of treatment in patients who developed virologic failure to the three original classes of antiretroviral drug
De Wolf F, on behalf of the PLATO II Project Team of COHERE
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

HIV-related Hodgkin lymphoma in the era of HAART: Incidence and survival in a European multi-cohort study, preliminary results
Bohlius J, for the cancer Working Group of COHERE
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

Viral load outcome after virologic failure of the three original antiretroviral drug classes in 2000-2007
Costagliola D, for the PLATO II Project Team of COHERE
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

Viral load levels measured at set-point have risen over the last decade of the HIV epidemic in the Netherlands
Gras L, Jurriaans S, Bakker M, Van Sighem A, Bezemer D, Fraser C, Lange J, Prins J, Berkhout B, De Wolf F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Serious non-AIDS events are increasingly more common than AIDS events in the HIV-1 cART treated population
Gras L, Kesselring A, Smit C, Van Sighem A, De Wolf F, for the ATHENA national observational cohort
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Immunodeficiency is a risk factor for non-AIDS defining malignancies in HIV-1 infected patients on combination antiretroviral therapy
Kesselring A, Gras L, Smit C, De Wolf F, Reiss P, Wit F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Estimating the number of people living with HIV/AIDS in the Netherlands
Van Sighem A, Fraser C, Bezemer D, Garnett G, De Wolf F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals
Van Sighem A, Gras L, Reiss, Brinkman K , De Wolf F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Significant increase in the number of HIV-infected homosexual men, co-infected with hepatitis C
Welling C, Smit C, Van der Meer J, Brinkman K, Hoepelman I, De Wolf F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

The effectiveness of national first trimester opt-out HIV screening in the Netherlands
Boer K, Smit C, Van der Flier M, De Wolf F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Effectiveness of antenatal screening for HIV, hepatitis B and syphilis in the Netherlands
Op de Coul E, Van Weert Y, Oomen P, Smit C, Van der Ploeg K, Van der Sande M
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Oral presentations

Ageing with HIV
Van Sighem A
Expertmeeting "Ouder worden met hiv", Amsterdam, Netherlands, 11 January 2009

Controlling the hiv epidemic in the Netherlands
Van Sighem A, De Wolf A, Bezemer D, Hollingsworth D, Garnett G, Fraser C
16th International Workshop on HIV Observational Databases, Lisbon, Portugal, 26-28 March 2009
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

Limited impact of episodes of viremia on the risk of non-AIDS events amongst successfully treated patients
Zhang S, Van Sighem A, Reiss P, Gras L, Smit C, De Wolf F
16th International Workshop on HIV Observational Databases, Lisbon, Portugal, 26-28 March 2009
Amsterdam Cohort meeting, Amsterdam, May 2009

Trend in antiretrovirale therapie (ART) regimes; Draagt ART bij aan de preventie van HIV-1 infectie?
De Wolf F
HIV Intervention Monitoring deel V Curaçao, 18-20 April 2009

De rol van Stichting HIV Monitoring bij onderzoek: late presentatie in kliniek zorgt voor gelimiteerd effect van ART
De Wolf F
HIV Intervention Monitoring deel V Curaçao, 18-20 April 2009

HIV in NL schatting-1
Van Sighem A
Expertmeeting soa & hiv surveillance, Bilthoven, the Netherlands, 12 June 2009

Verschuiving van de hepatitis C epidemie onder HIV-patienten; van injecterend drugsgebruik naar homoseksueel contact
Welling C, De Wolf F, Smit C
Wetenschappelijk Epidemiologisch Onderzoek Nederland (WEON), Amsterdam, the Netherlands, 11-12 June 2009

Longer duration of exposure to immunodeficiency and detectable viremia both are risk factors for non-AIDS defining malignancies in HIV-1 infected patients on combination antiretroviral therapy
Kesselring A, Gras L, Smit C, De Wolf F, Reiss P, Wit F
5th IAS Conference on HIV Pathogenesis, Treatment and Prevention, Cape Town, South Africa, 19-22 July 2009

Immuno-virological response to triple NRTI and boosted PI in treatment-naïve HIV-2-infected patients
The ACHIEV2E collaboration study group.
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

Mortality rates of elderly HIV-infected adult treated with antiretroviral are closer to general population than in younger patients
Lewden C on behalf of the COHERE Mortality Working Group
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

CD4 count, viral suppression, prophylaxis and the risk of primary pneumocystis pneumonia in the cart era - The Collaboration of Observational HIV Epidemiological Research Europe (COHERE)
Mocroft A, for the Opportunistic Infections Working Group
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

CD4 Count, viral suppression, prophylaxis and the risk of recurrent pneumocystis pneumonia in the cART Era - The Collaboration of Observational HIV Epidemiological Research Europe (COHERE)
Mocroft A, for the Opportunistic Infections Working Group
12th European AIDS Conference (EACS), Cologne, Germany, 11-14 November 2009

Transmission networks of (resistant) HIV-1 among MSM in the Netherlands
Bezemer D, Van Sighem A, Lukashov V, Van der Hoek L, Back N, Schuurman R, Boucher C, Claas E, Boerlijst M, Coutinho R, De Wolf F, ATHENA observational cohort
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

In patients on cART without an undetectable viral load measured in the last three months the use of condoms is crucial to reduce HIV transmission
Smit C, Hallett T, Garnett G, De Wolf F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

Episodes of HIV viremia and the risk of non-AIDS events amongst successfully treated patients
Zhang S, Van Sighem A, Gras L, Smit C, Prins J, Kauffmann R, Richter C, Reiss P, De Wolf F
NCHIV 2009, Amsterdam, the Netherlands, 24 November 2009

colophon

Authors
Luuk Gras, Ard van Sighem, Colette Smit, Sima Zaheri, Ineke Stolte, Hanneke Schuitemaker, Frank de Wolf

Co-authors
Gonneke Hermanides, Ashley Duits, Bianca Slieker, Camiel Welling

Mission
Stichting HIV Monitoring 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.

Requests for copies should be made to:
Stichting HIV Monitoring
Academic Medical Centre of the University of Amsterdam
Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands
Voice: +31 20 5664172
Fax: +31 20 5669189
E-mail: hiv.monitoring@amc.uva.nl
Website: www.hiv-monitoring.nl

Visiting address:
Stichting HIV Monitoring
Hogeschool van Amsterdam
Tafelbergweg 51
1105 BD Amsterdam, The Netherlands

Correspondence to:
Frank de Wolf
E-mail: f.dewolf@amc.nl

ISBN: 978-94-90540-01-2
First edition: November 2009
Editing: Sally H. Ebeling, Dover, MA, USA
Art Direction: Guus Ottens, Aan de Bak BV, Haarlem
DTP: Studio Zest, Amsterdam
Print: MullerVisual, Amsterdam