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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

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Introduction

In its annual report on the HIV monitoring programme in the Netherlands, the HIV Monitoring Foundation (HMF) provides information on trends over time in the epidemic and the effect of treatment of HIV. This year's report confirms the increase in the number of HIV diagnoses amongst men who have sex with men, and it shows the steady improvement in the effect of antiretroviral treatment, with changes in mortality patterns that reflect an increase in non-AIDS-related causes of death in the chronically HIV-infected population who receive lifelong treatment.

The HIV Monitoring Foundation is assigned by the Dutch Minister of Health, Welfare and Sport to monitor HIV in the Netherlands and to contribute to the quality of HIV care. Its target groups are primarily the HIV-treating physicians who work in one 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 HMF, and, in case of approved research proposals, 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 its yearly report not only contributes to the development of HIV care and prevention policies, but also 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 changes in the data quality assessment now being implemented. A section on the HIV monitoring programme follows, with the chapters describing in more detail 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 antiretroviral combination therapy (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, the HIV nurse-consultants and the staff of various diagnostic laboratories and facilities in the HIV treatment centres, and the data collecting and monitoring staff both in and outside the HIV Monitoring Foundation. 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.

Frank de Wolf, MD, PhD
Director HIV Monitoring Foundation

summary & recommendations

Summary

Frank de Wolf

Trends in the epidemic

The cumulative number of individuals living in the Netherlands and registered with the HIV Monitoring Foundation (HMF) as having an HIV infection has increased by 1696 since June 2007, to a total of 14,960. As of the 1st of June 2008, 11,349 of these persons (76%) are still being followed in one of the 25 HIV Treatment Centres in the Netherlands.

In previous years, the annual number of newly registered HIV-infected individuals has varied by approximately 1200, but this year's increase is substantially higher. When the distribution of the year of HIV diagnosis of the individuals registered between 2007 and 2008 is compared with distributions reported for the previous years, no significant differences are evident: 70% to 75% of the newly registered persons were diagnosed with HIV in either the same year of registration with the HMF or the year before. This finding, together with an increase in the absolute number and proportion of newly diagnosed individuals with a known last HIV-negative test date, indicates that the time between infection and diagnosis and entry into care has been shortened due to an improved HIV testing policy[1]; consequently, a rise in recent HIV infections has become apparent.

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[2,3]. Amongst other factors, shortening the time between HIV transmission and diagnosis plays an important role in containing ongoing HIV transmission[4]. Another factor involved in ongoing transmission may be the amount of virus circulating in an individual unaware of his or her infection. In a study of 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. Interestingly, preliminary results show 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 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 contribute 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. Vertical transmission and transmission through injecting drug use or blood products account for only 5% of the infections amongst the population in follow-up as of 1 June 2008. The annual number of HIV diagnoses amongst MSM has almost doubled since 1996, to 665 in 2007. The proportion of MSM in the annual number of new HIV diagnoses started to increase in2003 and reached its highest point (68.9%) in 2008. In contrast, both the absolute number and the proportion of men and women who were infected through heterosexual contact has decreased since 2003.

The decrease in the annual number of individuals who acquired HIV through heterosexual contact parallels that of the number of diagnoses amongst persons originating from sub-Saharan Africa and is consistent with the decrease in the number of sub-Saharan Africans immigrating to the Netherlands. It seems, however, that the annual number of HIV-infected sub-Saharan Africans diagnosed in the Netherlands has

stabilised since 2006. Almost half of women with HIV now originate from sub-Saharan Africa and a quarter from the Netherlands; for men, approximately one-third is 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 one quarter of the population currently in follow-up is 50 years of age or older. In the coming years, the age of the population will continue to increase, and by 2015, an estimated 37.7% of the patients in follow-up will be more than 50 years[6]. 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.

There was an increase in the prevalence of hepatitis C virus (HCV) co-infections amongst the MSM in follow-up as of 1 June 2008; 7.0% had co-infection with hepatitis C, compared to 5.8% last year[6]. This increase is in accord with those recently reported[7,8] and probably related to the observed increase in sexual risk behaviour after the introduction of cART[4,9]. In addition, improved HCV testing may contribute to the increased prevalence. The clinical implications of HCV/HIV co-infection can be far-reaching, since co-infection complicates treatment of HIV and progression to liver disease is accelerated compared to that in HCV-mono-infected persons. Moreover, we found an increased death risk for HIV/HCV co-infected patients, a result that confirms a previous study[10]. In our study, we found a higher risk of dying amongst HIV/HCV co-infected patients as compared to patients solely infected with HCV, suggesting that HIV alters the progression of HCV disease. A study by Weber and colleques[10,11] has shown similar results.

Trends in treatment

By June 2008, approximately 80% of the registered HIV-infected population were on combination antiretroviral therapy (cART). At that time, more than half of all treated patients were using a regimen containing tenofovir. In addition, an increasing proportion of patients were using emtricitabine instead of lamivudine, probably because of its availability in a fixed-dose combination with tenofovir. Tenofovir-containing and emtricitabine-containing regimens were prescribed to three-quarters of the patients starting cART between 1 June 2007 and 31 May 2008. Almost half of the patients started with a combination of tenofovir, emtricitabine, and efavirenz, which is now available as a fixed-dose, once-daily pill. No changes have been observed in the total treated population with respect to the administration of nevirapine, lopinavir, and atazanavir, but efavirenz-containing regimens have gained popularity. Also in first-line cART, efavirenz-containing regimens have been used more often.

Treatment success

Progression to AIDS and death among HIV-infected patients has declined substantially since cART was introduced in 1996[12-14]. Consequently, the infected population is aging; a large proportion of patients is currently older than 50 years. Nevertheless, the life expectancy of HIV-infected patients is still lower than that of the general population. Further improvement may be achieved by revised guidelines ensuring a timely start of cART[15] and an effective short-term response to first-line cART[16].

At 24 weeks after commencing cART, we found that almost 80% of the antiretroviral therapy-naïve patients reach an HIV-1 RNA level of less than 50 copies/ml plasma. During the following weeks, that percentage slowly increased, rising to almost 90% after 240 weeks. It was even higher when patients were continuously on cART without interrupting treatment.

Restoration of CD4 cell counts to levels found in non-infected individuals appears to be feasible after 5 years, if cART is started when counts are above 400 cells/mm^3. However, the median CD4 cell counts at the start of cART in the therapy-naïve population is still much lower, i.e., 210 cells/mm^3 in those starting in 2007, with an improved median count after 5 years; although, it is still below 500 cells, which is approximately half of the count found in non-infected individuals. In addition, restoration of CD4 cell counts is reported to depend on age, with younger people achieving a better result than older people when plasma HIV-1 RNA levels are suppressed to below 50 copies/ml.

Treatment failure

The annual proportion of pre-treated patients who failed on cART declined from 49% in 1997 to 14% in 2007 and, so far, to 10% in 2008. During the same period, the proportion of previously therapy-naïve patients who experienced failure remained between 6% and 9%.

Toxicity is the most frequently registered reason for interrupting or changing cART[6]. The incidence of changing the initial regimen due to toxicity is highest in the 3 months following the start of cART. However, the frequency with which regimens are changed following toxic responses has decreased over time; compared to patients starting cART before 2000, fewer needed to change their cART regimen between 2002 and 2007. Women were more likely to interrupt and change regimen because of toxicity than men[17-19].

Results from our study regarding the frequency and clinical consequences of short episodes of HIV vireamia amongst antiretroviral therapy-naïve patients who were initially successfully treated with cART showed 16% interrupted cART at least once, 35% experienced at least one episode of vireamia, and 9.6% had at least one episode of high-level (i.e. >1000 HIV-1 RNA copies/ml plasma) vireamia. Cumulative exposure to treatment interruptions was associated with a worse outcome for death, AIDS, and immunologic response, as was exposure to episodes of high-level vireamia. Episodes of low-level (50-1000 copies/ml) viremia were not associated with death or AIDS, and episodes <3 months were associated with a favourable immunologic response.

Resistance

Resistance of HIV to antiretroviral drugs, if measured when antiretroviral therapy fails to suppress virus production, is found in 95% of the pre-treated and 79% of the therapy-naïve patients. Percentages of genetic resistance measurements in the therapy-experienced group of patients increased from 9% in 1996 to 27% in 2007, but in the therapy-naïve group the percentages decreased from 34% in 2003 to 18% in 2007.

The prevalence of resistance to specific antiretroviral drugs has changed over a period of time in correlation with changes in the use of antiretroviral drugs. Thus, the prevalence of resistance to non-nucleoside reverse transcriptase inhibitors (NNRTIs) has increased, whilst resistance to the first generation of protease inhibitors (PIs) has declined. The prevalences of high-level resistance to nucleoside reverse transcriptase inhibitors (NRTIs) and NNRTIs fit quite well with a recent study in France, but prevalences of PI resistance were lower in our cohort[20]. Resistance to newer drugs like tenofovir and lopinavir remained at a low level, despite increasingly frequent use of these drugs in recent years. A new NNRTI, etravirine, has recently become available for antiretroviral treatment in the Netherlands. This drug has antiretroviral activity even when the virus is highly resistant to the other NNRTIs efavirenz and nevirapine.

It has been found that almost 10% of the patients failing on antiretroviral therapy harbour virus strains with high-level resistance to at least one antiretroviral drug. This percentage is probably an underestimation

since a resistance test is performed in only 30% of the patients failing on therapy. Also, other cohorts with more frequent sampling for resistance have found prevalences between 20% and 30%[21, 22]. Compared to 2007, the proportion of patients with resistance has slightly decreased, but the absolute number of patients harbouring resistant virus has increased from 1064 to 1112[6].

The rate of transmission of intermediate and high-level drug-resistant HIV-1 virus in the Netherlands remains low: 3.2% of recently infected patients and 4.3% of newly diagnosed patients after 2001 were infected with a strain that was resistant to at least one antiretroviral drug. These proportions tended to be lower than those observed in other Western countries[23-28]. Prevalences of major resistance-associated mutations were higher in both patient groups. Apparently, the presence of major resistance-associated mutations is not necessarily a sign of full resistance. As was found in Switzerland, we did not observe an increase in transmitted drug-resistant HIV-1 over time[27].

Trends in morbidity and mortality

In total, 4109 cases of AIDS and 1281 deaths were recorded up to 1st June 2008; 1323 AIDS cases were diagnosed, and 1107 deaths were recorded after the start of cART. The average mortality rate was 1.39 per 100 person-years, and it decreased slightly from 1.94 in 2007 to 1.17 in 2008. The average AIDS incidence was 2.5 per 100 person-years, declining from 9.1 in 1996 to 1.4 in 2008. In the total group that ever started cART, the incidence of new AIDS cases declined dramatically from 14.7 in 1996 to 1.25 in 2008; the mortality rate declined from 4.6 in 1996 to 1.15 in 2008.

AIDS was still the major cause of death, although the proportion amongst all causes of death decreased from 39% before 2004 to 29% after 2004. Non-AIDS-defining causes of death have increased since the introduction of cART. Non-AIDS-defining malignancies, liver failure and HBV/HCV co-infection, cardiovascular diseases, and non-AIDS-defining infections are most frequently registered, next to non-natural causes of death, which in most cases is suicide.

The increase in the incidence of death due to non-AIDS-defining malignancies and cardiovascular complications with a longer time on cART, as well as the higher proportion of deaths due to malignancy and cardiovascular diseases seen in our cohort of treated patients after 1 January 2004, may be associated with the aging of the HIV-infected population. The distribution of non-AIDS causes of death has come to resemble more closely that seen in the general population, an observation also made in other cohorts[29-31].

However, the incidence of non-AIDS-defining cancer and cardiovascular disease in HIV-infected patients after starting cART is higher than in the general population, as has been shown by others[32-36]. In addition to the higher risk of non-AIDS-defining causes of death in HIV-infected patients compared to that in the general population, we found an association of a lower latest CD4 cell count with a higher incidence of non-AIDS-defining causes of death, which may indicate that immunodeficiency plays a role in the risk of fatal non-AIDS events. The rate of death due to non-AIDS causes decreased with a higher latest CD4 cell count, although it declined to a lesser extent than the rate due to AIDS[37].

Immunodeficiency and HIV infection itself aside, lifestyle, older age, exposure to certain antiretroviral drugs or drug classes, and co-infection may also play a role in causing premature deaths. Each of these has a separate effect on the incidence of serious diseases, and it will be a challenge for future studies to disentangle them to gain a better understanding of the mechanisms of the diseases.

General conclusions and recommendations

The HIV-infected homosexual population has continued to grow since 1996. The increasing proportion of recently HIV-infected patients means that the time from infection to diagnosis is shortened. It also indicates that the majority of new infections are taking place during that same period. To be able to further contain the spread of HIV in the MSM population, prevention measures focussing on risk behaviour from the time of infection to diagnosis remain of utmost importance[4]. New preventive approaches are needed, as are studies of factors predictive for delaying testing and entry into care.

The number of infections amongst heterosexuals is decreasing, but this is mainly due to a decreasing contribution of imported infections from sub-Saharan Africa. As the decrease in the annual number of new HIV diagnoses amongst persons from sub-Saharan Africa is stabilising, monitoring of this particular group will help to recognise changes in the heterosexual epidemic in the Netherlands and develop preventive measures aimed specifically at this group.

Since the introduction of cART in 1996, its efficacy has increased. Moreover, the incidence of toxicity-driven therapy changes has decreased in more recent calendar years. Achieving CD4 cell counts comparable to those in non-infected individuals seems feasible, but only when cART is started at much higher baseline CD4 counts than is currently done. Thus, testing policies aimed at early diagnosis of HIV infection are of importance not only for public health, but also for individual patient care.

Failure of cART has become less frequent over time, to approximately 10% of the treated population. When it fails, resistance is found in approximately 80% of the cases. The low frequency of cART failure, combined with the presumed high-level contribution of infected individuals in their pre-cART period to the transmission of HIV, may explain the low level of transmission of drug-resistant strains of the virus. However, the low level of resistance testing may imply that the level of resistance transmission is underestimated. Transmitted resistance amongst patients infected with a non-B infection, who are typically of sub-Saharan origin, appears to be limited as well. However, the roll-out of widely available antiretroviral treatment in Africa will undoubtedly increase the prevalence of drug resistance in that area. This drug resistance could subsequently lead to an increase in transmitted resistance in Africa and also in the migrant population in the Netherlands. An improved resistance testing scheme is needed to adequately follow changes in the level of resistance transmission.

In patients with a prolonged and uninterrupted period of time on cART and an accompanying rise in CD4 cell count, there is a shift from AIDS-related to non-AIDS-related causes of death. Death due to non-AIDS causes is likely to be immunodeficiency-related, albeit to a lesser degree than death due to AIDS. To further reduce the mortality and morbidity, it is important to diagnose and treat HIV-infected patients at an earlier stage. In addition, large studies are needed to better understand the relationship between chronic HIV infection and the development of non-AIDS-related diseases and to disentangle aging from both antiretroviral treatment and chronic immune activation by low-level HIV production as possible mechanisms accounting for the increase in non-AIDS-related causes of death.

data quality

1. Predictors of missing data

Sima Zaheri, Mariska Hillebregt

Introduction

Since 2002, data (appendix 1) of all HIV-infected patients who are registered and followed longitudinally in one of the 25 HIV treatment centres in the Netherlands have been collected by staff in these centres who are specifically appointed to collect information from patients' medical files and to enter it on site in the ATHENA (AIDS Therapy Evaluation in the Netherlands) database. Data monitors at the HIV Monitoring Foundation (HMF) maintain the data set and process data for subsequent analysis.

Maintenance and improvement of the quality of this longitudinal clinical data set is a main concern. Controlling the quality of data obtained from patients is crucial for all clinical research [38-42], and source data verification (SDV) is the usual approach. However, because of the large population size of ATHENA, 100% SDV is not feasible. Therefore, customized procedures [43, 44] for improving the quality of data have been implemented. These procedures contain SDV of endpoints essential for key data analysis.

Obviously, the onset of AIDS is frequently used as an endpoint in HIV/AIDS studies. Therefore, the quality of data of clinical symptoms that are registered as related to HIV, i.e., U.S. Centers for Disease Control and Prevention (CDC)-B and CDC-C events, is highly important. We previously examined the quality of data collection by studying the validity of the data. In that study, data were extracted from the clinic charts of two anonymous outpatients by 38 data collectors. The analysis revealed that the one CDC event that had to be extracted by the data collectors was correctly collected in only 60% of the cases (standard deviation [SD] 13%). Moreover, focusing on the start and stop date of the CDC-C event showed an even higher rate of error. Since SDV of all CDC events is not feasible, in order to efficiently improve the quality of CDC event data, we investigated in another controlled study whether low CD4 cell counts, which are clinically associated with a higher incidence of opportunistic infections[45], could be a predictor for poor data quality of CDC events.

Methods

We selected data from patients with two consecutive initial CD4 measurements of <50 cells/mm^3, assuming that they would have the highest incidence of CDC events and more complex medical files. The selection yielded 600 patients, and of those, 48 patients were randomly chosen. Subsequently, data from patients with initial CD4 cell counts of ≥200 cells/mm^3 were selected for comparison. The limit of 200 CD4 cell counts was chosen to increase the statistical power of the analysis. To exclude differences in demographic characteristics of patients included in this analysis, each patient with low CD4 cell counts was matched with two patients from the group with CD4 cell counts of ≥200 cells/mm^3 on the basis of age, gender, outpatient clinic, and the year of inclusion (Table 1.1). Data collected for the two groups of patients were selected for quality control by SDV. The numbers of missing, surplus, correct, and incorrect events per patient were determined by the data monitors. An incorrect score was based on missing, surplus, or incorrect event description; incorrect start and stop date; and incorrect degree of diagnostic certainty. The score for diagnostic certainty consisted of possible, presumptive, and definitive categories. The more evidence for the diagnosis of a CDC event, the higher the diagnostic certainty should be scored.

Finally, the results of SDV were entered into a Microsoft Access database to be analysed by SAS® version 9.1 (statistical analyses software).

Analysis

The Wilcoxon rank sum test was used to determine the significance of the difference in the number of (missing) CDC events between the two groups.

Results

Data obtained from 144 patients showed 138 CDC events in the case group (N=48) and 45 events in the control group (N=96). SDV revealed 32 missed events in the case group and 9 in the control (P=0.0008). The total number of CDC events after SDV in the group with low CD4 cell counts [151] was significantly higher than that in the control group [49] (P=< 0.0001). The mean number of CDC events per patient was 3.14 in the group with low CD4 cell counts and 0.51 in the control (Table 1.2). The number of surplus collected CDC events was 19 in the case group and 9 in the control.

For each patient, the number of correct and incorrect events was scored as described in the Methods section. The percentage of correctly collected CDC events was 57% for the case group and 60% for the control. On closer inspection, the percentages of incorrectly collected description and start and stop dates and the diagnosis certainty level of CDC events were higher in the group with low CD4 cell counts.

Discussion

The results of the analyses of key data such as CDC-defined HIV-related events depend on the quality of the collected data. Collection of CDC event data is highly sensitive to error because the data collectors extract diagnostic data from various sources, such as pathology, radiology and bacteriology reports. Besides training data collectors in the correct use and understanding of the diagnostic results, efficient use of SDV can improve the quality of CDC event data. One possible approach to improvement is the restriction of source data verification to data likely to have a higher frequency of errors on collection. The objective of this study was to find a predictor for errors in CDC event data.

Like in many other studies [46, 45], we show that patients with low initial CD4 cell counts had significantly more CDC events than patients with higher CD4 cell counts. Collection of data for patients with low CD4 counts showed a significantly higher number of missing CDC events. The percentage of incorrect data was also higher. The higher percentage of missing and incorrect data could be explained by the fact that the more CDC events that are to be collected, the more various diagnostic data should be extracted by the data collectors. Subsequently, patients with low CD4 counts have potentially more complex medical files, and their files are more sensitive to errors in data collection.

The percentage of missing CDC events (21%) seems high, which can lead to misclassification of patients in our studies that are based on such data. Consequently, the effect of CD4 cell counts could be underestimated, for example, in survival analyses or in studies where CD4 cell count is used as a parameter to predict clinical benefit or lack of it after treatment, therapy, or intervention.

In conclusion, SDV of data from all patients with initial CD4 cell counts of < 50 cells/ mm^3 should be included in our procedures for data quality improvement. Furthermore, the approach described in this case study will be used to investigate other predictors for errors in endpoints for key data analysis to further optimize our procedures for data quality improvement.

	Case (N=48)	Control (N=96)
Median (range) age	45 (26- 77)	44 (24 -66)
N men	37	74
N women	11	22
Median (range)	2002	2002
enrol date	(1998 – 2007)	(1998 – 2008)
Median (range)		
first cd4 count	10 (0 - 47)	421 (200- 1430)

Table 1.1: Demographic characteristics of patients included in the analysis

	Patients with 2 consecutive initial CD4 measurements <50 cells/mm^3 (N=48)	Patients with initial CD4 measurements of of >200 cells/mm^3 (N=96)	P-value
CDC events			
CDC events before monitoring	138	45	
Missing CDC events	32	9	0.0008 *
Surplus collected CDC events	19	5	0.0030 *
CDC events after monitoring	151	49	<0.0001 *
Mean CDC events	3.14	0.51	
Data collection			
% correct	57%	60%	
Data collection detailed			
Incorrect CDC event	33%	30%	
Incorrect start date	45%	38%	
Incorrect stop date	47%	40%	
Incorrect degree of certainty	46%	36%	

* Wilcoxon rank sum test

Table 1.2: Results of source data verification: a comparison of CDC event data quality of patient's with initial low CD4 cells and the control group

Appendix 1: Data collected by the HIV Monitoring Foundation

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 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 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*	
	Creatinin 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 10e9/l	
	Thrombocytes <150 10e9/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
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. Trends in baseline characteristics

Ard van Sighem

Introduction

As of 1 June 2008, the total HIV-infected population registered in the database of the HIV Monitoring Foundation was 15,407. Of these patients, 447 (2.9%) were being followed in Willemstad in Curaçao, and these patients are described in more detail in chapter 9. In this chapter, demographic and clinical characteristics of the population currently in follow-up are presented. In addition, this chapter presents changes over time in characteristics of the population at the time of diagnosis and at the time of the start of combination antiretroviral therapy (cART).

Methods

Two groups of patients were considered. The first group consisted of HIV-1-infected patients who were alive as of 1 June 2008, were 13 years of age or older, and were still in follow-up. A patient was considered as still in follow-up if data had been collected in the preceding year. The second population comprised all HIV-1-infected patients diagnosed at 13 years of age or more with a known year of HIV diagnosis.

Patients were classified according to their transmission risk category, including men who acquired their infection via homosexual contact (men having sex with men [MSM]), men and women infected via heterosexual contact, injection drug use (IDU), contact with infected blood or blood products including needle accidents, vertical transmission, or other or unknown transmission routes. Countries of origin were grouped together in 12 regions: the Netherlands, Western Europe excluding the Netherlands, Central Europe, Eastern Europe, South/Southeast Asia, North Africa and the Middle East, sub-Saharan Africa, North America, Latin America, the Caribbean, Australia and New Zealand, and the Pacific Islands.

CD4+ and CD8+ T cell counts and plasma HIV RNA levels at diagnosis were taken as the measurements closest to the time of diagnosis and prior to the start of therapy within the first 12 weeks after the diagnosis was made. Counts and plasma viral load at the start of cART were determined closest to the date at which cART was started, within a time interval of 12 weeks before and 1 week (0 weeks for RNA) after the start date. Measurements at 24 and 48 weeks after the start of cART were defined as the measurements closest to these time points within an interval of 12 weeks before or thereafter. The disease stage according to the Centers for Disease Control (CDC) at a specific time point was defined as the most serious CDC event occurring, at most, one year before and 4 weeks after the time point[47]. Hepatitis B (HBV) co-infection was defined as a positive HBV surface antigen (HBsAg) test or a positive envelope antigen (HBeAg) test. Hepatitis C (HCV) infection was defined by a positive HCV antibody test or a positive result of an HCV RNA test.

HIV-1 subtypes were determined by comparing the nucleotide sequences of protease and reverse transcriptase (RT) with a representative set of reference sequences from the Los Alamos National Laboratory sequence database. Sequences were assigned a specific subtype when the cluster containing the sequences and a reference sequence in a phylogenetic analysis exceeded 85%. Sequences that could not be classified as a specific non-B subtype or a circulating recombinant form (CRF) were labeled “other non-B”. The circulating recombinant forms designated as CRF01_AE and CRF02_AG were referred to as AE and AG.

Changes over calendar time were assessed by studying changes in the patient characteristics at diagnosis or at the start of cART. Proportions were compared by a chi-square test or, if sample sizes were small, by Fisher's exact test. Differences in age, T cell counts, and RNA levels were tested with Wilcoxon-Mann-Whitney and chi-square nonparametric tests. The significance of proportional changes over time was assessed with Poisson regression modeling linear in time. For continuous variables, medians were reported with the interquartile range (IQR); changes over time were studied with a linear median regression model. For changes over time, p values refer to the slope of the linear model. Because of the large number of patients, p values were often smaller than 0.001 and generally only values larger than 0.001 are reported.

Results

Total population

The total HIV-infected population in the Netherlands registered by the HMF consisted of 14,960 patients with a total follow-up of 107,131 person-years since diagnosis. Of these patients, 14,407 (96.3%, 2007: 12,958) were infected with HIV-1, and 79 (0.5%, 2007: 78) were infected with HIV-2. For 112 (0.7%, 2007: 95) patients, seroreactivity to both HIV-1 and HIV-2 was found, and for 362 patients (2.4%, 2007: 133) serologic results were inconclusive or not (yet) known.

Population currently in follow-up

The majority of the 11,349 patients in follow-up as of 1 June 2008 were men (8929 or 78.7%) who originated from the Netherlands (6645 or 58.6%) and were infected via homosexual contact (6479 or 57.2%). In total, 1505 (16.9%) men and 2124 (87.8%) women were infected via heterosexual contact, whereas patients infected via injection drug use accounted for 3.2% of the population (Table 2.1).

The current median age of the population was 43.9 (IQR, 37.2-51.1) years, and men were generally older than women, that is, 45.3 (38.9-52.4) years of age for men compared to 38.4 (31.9-45.7) years for women. The age of the population in follow-up increased over calendar time (Figure 2.1). In 1986, 74% of the patients in follow-up were younger than 30 years of age, whereas 0.8% were 50 years or older. In 2008, only 10% of the patients were younger than 30 years and 26% were older than 50 years of age.

cART was administered to 9136 (80.5%) patients, whilst 40 (0.4%) patients received a non-cART regimen, and 2173 (19.1%) were not yet treated. The number of patients not yet treated was higher amongst men than women, being 1840 (20.6%) and 333 (13.8%), respectively.

The four most frequently used regimens as of 1 June 2008 were tenofovir + emtricitabine + efavirenz (1340 patients, 14.7%), tenofovir + emtricitabine + nevirapine (704 patients, 7.7%), zidovudine + lamivudine + nevirapine (679 patients, 7.4%), and tenofovir + lamivudine + nevirapine (537 patients, 5.9%), accounting for 35.7% of all regimens (Table 2.2). As of 1 June 2007, these regimens accounted for 31.6% of all those given. Between 1 June 2007 and 1 June 2008, the proportion of patients using tenofovir increased from 48.2% to 55.1%, and the proportion using emtricitabine increased from 22.5% to 33.1%. On the other hand, the use of lamivudine decreased from 65.0% to 56.1%, and zidovudine use decreased from 31.6% to 24.9%. As of 1 June 2008, the most frequent additions to the backbone were nevirapine (28.8%, 2007: 29.7%, $p=0.2$), efavirenz (29.6%, 2007: 27.3%, $p<0.001$), lopinavir (17.3%, 2007: 16.2%, $p=0.07$), and atazanavir (11.6%; 2007: 11.0%, $p=0.2$).

The most recently measured CD4 cell counts were 480 (IQR, 340-650) cells/mm^3 for the male population and 493 (350-680) cells/mm^3 for the female population ($p=0.01$). CD8 cell counts were 950 (IQR, 680-1300) cells/mm^3 for men and 830 (610-1110) cells/mm^3 for

women (p<0.001). In the total population, 8283 (73.0%) patients had a plasma viral load <500 copies/ml. One or more AIDS-defining events had been diagnosed in 2856 (25.2%) patients; about half of those patients, 1510 (13.3% of the total population), had an AIDS diagnosis at or within four weeks after their HIV diagnosis.

The HIV-1 subtype could be determined for 3835 (33.8%) patients, including 3089 men and 746 women. The majority (2992, 78.0%) were infected with a subtype B strain. This subtype was more frequently observed in men (2693, 87.2%) than in women (299, 40.1%). Other frequently observed subtypes were AG (250, 6.5%), C (194, 5.1%), A (109, 2.8%), and AE (100, 2.6%).

The median time since diagnosis was 6.7 (IQR, 3.0-11.8) years for men and 6.4 (3.4-10.5) years for women (p=0.06). In total, 2745 (24.2%) patients had been diagnosed in the 3 years before 1 June 2008; this proportion was higher for men (24.9%) than for women (21.4%, p<0.001). Also, a larger proportion of men (2980, 33.4%) than women (635, 26.2%) received their HIV diagnosis more than 10 years previously (p<0.001).

A total of 10,575 (93.2%) were tested for HBsAg or HBeAg; 893 (7.9%) tested positive. HBV was most prevalent amongst injection drug users, of whom 36 (10.7% of the 336 tested) were co-infected. The HBV prevalence was 9.0% (545 of 6057 tested) amongst homosexual men (p=0.3 compared to IDU). Amongst heterosexually infected patients, the overall prevalence was 7.2%, significantly higher amongst men (9.0%) than amongst women (6.0%) (p<0.001). The prevalence of HBV was 2.8% (30 of 1081 patients tested) amongst heterosexually infected patients originating from the Netherlands, 6.3% (21 of 313 tested) for patients from Latin America, 10.8% (153 of 1418 tested) for patients from sub-Saharan Africa, and 12.1% (8 of 66 tested) for patients from Central or Eastern Europe.

The HCV status was known for 9932 (87.5%) patients, of whom 1055 (10.6%) were HCV-positive. Co-infection with both HBV and HCV was found in 107 patients. The HCV prevalence was highest amongst injection drug users, of whom 327 (94.2% of the 347 tested) were co-infected with HCV. In the population infected via heterosexual contact, the HCV prevalence was 5.7% for men and 5.2% for women (p=0.5). The prevalence was higher amongst homosexual men (p=0.003), of whom 404 out of 5760 tested (7.0%) were HCV-positive. In the group of homosexual men, the HCV prevalence was 8.6% in patients seen in hospitals in Amsterdam and 5.3% in patients followed in other hospitals (p<0.001). The HCV prevalence was higher amongst those infected by blood-blood contact (32%; 43% for men, 12.0% for women) and amongst those for whom the route of transmission was unknown (19.4%; 13.5% for men, 47% for women).

Trends over time – diagnosis

The total number of HIV-infected individuals registered in one of the 25 HIV treatment centres increased by 1696 to a total of 14,960 with more than 100,000 person years of follow-up; 14,169 patients had a known year of HIV-1 diagnosis and were diagnosed at 13 years of age or more. Of these patients, 11,115 (78.4%) were men, and 3054 (21.6%) were women. The majority of the patients, 7996 (56.4%), originated from the Netherlands, whilst 2370 (16.7%) were of sub-Saharan African origin. In total, 3420 (24.1%) patients were diagnosed in 1995 or before.

Men having sex with men (MSM)

For 7779 (70.0%) of the 11,115 men with an HIV-1 diagnosis, the reported mode of transmission was homosexual contact. The majority of these patients, 5672 (72.9%), were diagnosed in 1996 or later. The annual number of diagnoses amongst MSM was 367 in 1996; the number decreased to 320 in 1998 and then steadily increased to 665 in 2007 (Table 2.3).

The proportion of MSM in the annual tally decreased from 58.1% in 1996 to a nadir of 44.1% in 2003; thereafter, it increased to 68.9% in 2008 (Figure 2.2). Most of the MSM, 5668 (72.9%), were of Dutch origin, whereas 743 (9.6%) originated from other European countries, including 501 (6.4%) from Latin America, 226 (2.9%) from the Caribbean, and 211 (2.7%) from South and Southeast Asia. These proportions did not change over time (p=0.4).

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 359 (160-550) and 920 (620-1340) 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 the other patients. CD4 counts were higher in Dutch patients (360 [166-560] cells/mm^3) compared with those in other patients (330 [150-520] cells/mm^3) (p=0.002). Also, CD8 cell counts were higher in Dutch patients (930 [640-1362] cells/mm^3), compared with those in patients from other countries (900 [600-1270] cells/mm^3) (p=0.01). Median CD4 cell counts increased from 250 (IQR, 90-420) cells/mm^3 in 1996 to 420 (230-597) cells/mm^3 in 2007.

The median age at diagnosis was 37.9 (IQR, 31.8-44.9) 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 39.2 (33.5-46.4) years. For Dutch patients, the median age at diagnosis increased from 37.0 (IQR, 31.7-45.5) years in 1996 to 40.8 (33.8-47.7) years in 2007, whereas it increased for patients from other regions from 32.9 (30.0-39.2) to 36.3 (29.7-41.7) years. An AIDS-defining event at diagnosis was found in 53 (8.0%) of the 665 patients diagnosed in 2007, whereas 565 (85.0%) had no evidence of a CDC event.

In total, 1122 (19.8%) 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 37 out of 367 (10.1%) in 1996 to 211 out of 665 (31.7%) in 2007 and to 55 out of 195 (28.2%) in 2008. The proportion of patients with a recent infection was higher amongst patients of Dutch origin (20.6%) than amongst patients from other countries (17.4%, p=0.007). A recent infection was found in 627 out of 2860 (21.9%) patients who were 38 years of age or younger at diagnosis. In 2812 patients older than 38 years, a recent infection was less common, occurring in 495 (17.6%, p<0.001).

For patients with a recent infection, median CD4 and CD8 counts at diagnosis were 510 (360-683) and 1010 (720-1470) cells/mm^3, which did not change over time (p=0.9). CD4 and CD8 counts were lower for patients without recent infection, specifically, 310 (120-500) and 900 (600-1300) cells/mm^3, respectively. For patients without recent infection, CD4 counts increased from 220 (80-400) cells/mm^3 in 1996 to 359 (180-550) cells/mm^3 in 2007. The number of patients who ever had a negative HIV test increased from 86 (23.4%) in 1996 to 376 (56.5%) in 2007, and it was 199 (61.0%) in 2008.

For 5725 (73.6%) patients, the most likely country of infection was known. A majority, 5092 (88.9%), were infected in the Netherlands. The proportion of patients infected in the Netherlands increased from 238 out of 272 (87.5%) in 1996 to 495 out of 533 (92.9%) in 2007. For 4345 (96.4%) of the 4508 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 117 of 190 (62%) patients originating from the Netherlands Antilles or Aruba and for 134 of 219 (61%) patients from Suriname. Of the 117 from the Antilles, 23 (20%) were infected there, and 87 (74%) were infected in the Netherlands, whilst of the

134 patients from Suriname, 12 (9%) were infected in Suriname and 119 (89%) in the Netherlands.

The HIV-1 subtype could be determined for 2701 (34.7%) MSM. Of these, 2596 (96.1%) were infected with subtype B, and the proportion of patients infected with a subtype B strain decreased over time between 1996 and 2008 (p=0.003). Other subtypes found in homosexual men were AE (36 patients, 1.3%), AG (26 patients, 1.0%), C (18 patients), A (17 patients), G (3 patients), and other subtypes (5 patients).

Heterosexual men and women

Of the 4598 patients infected via heterosexual contact, 1945 (13.7% of the total population and 42.3% of the heterosexual group) were men, and 2653 (18.7% of the total population and 57.7% of the heterosexual group) were women. The proportion of heterosexual men in the annual number of diagnosed patients varied slightly over time; it increased from 13.3% in 1996 to 17.7% between 2000 and 2003 and decreased thereafter to 10.2% in 2008 (Figure 2.2). For heterosexual women, a similar, although more pronounced, pattern was observed: 12.5% in 1996; 25.0% between 2000 and 2003; and a decrease to 12.7% in 2008. Between 2000 and 2005, the mean annual number of diagnoses was 167 for men and 241 for women, and for both sexes it increased on average by 8.1 diagnoses yearly (p=0.005). From 2006 on, the number of diagnoses decreased, and 148 men and 173 women were diagnosed in 2006. For 2007, 119 diagnoses amongst men and 173 amongst women have been reported so far.

The most frequently reported regions of origin for heterosexual men were the Netherlands (725 patients, 37.3%) and sub-Saharan Africa (688, 35.4%). Other regions were Latin America (198 patients, 10.2%), Europe excluding the Netherlands (130, 6.9%), and the Caribbean (104 patients, 5.3%). Almost half of the heterosexual women originated from sub-Saharan Africa (1312 patients, 49.5%), whilst 649 (24.5%) patients were from the Netherlands. The proportion of women originating from the Caribbean (152, 5.7%) and Latin America (241, 9.1%) was similar to that of men, whilst 149 (5.6%) female patients originated from South/ Southeast Asia and 110 (4.1%) from Europe excluding the Netherlands.

Between 1996 and 2002, the proportion of patients originating from sub-Saharan Africa increased from 33.1% to 57.3%. Thereafter, this proportion declined to 39.6% (127 out of 321) in 2006. In 2007, 126 (43.2%) of the diagnoses were amongst sub-Saharan Africans. This pattern was counterbalanced by a decrease in the proportion of Dutch patients from 41.7% in 1996 to a nadir of 19.0% in 2001, with a subsequent increase to 32.2% in 2007.

The median CD4 cell counts at diagnosis were 200 (IQR, 53-400) cells/mm^3 for heterosexual men and 294 (129-490) cells/mm^3 for heterosexual women. Median CD8 cell counts were 800 (500-1140) cells/mm^3 and did not differ between men and women (p=0.5). 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 30.9 (IQR, 25.5-37.5) years, compared to 37.2 (31.3-44.6) years for men.

Age, 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. On the other hand, men and women from sub-Saharan Africa were generally younger and had lower CD4 cell counts than their Dutch counterparts. The median age was 29.2 (IQR, 24.3-34.4) years for women from sub-Saharan Africa and 33.9 (28.0-38.8) years for men from sub-Saharan Africa, whereas for Dutch women the median age was 35.2 (28.0-45.7) years and for Dutch men the median age was 40.8 (33.9-50.2) years.

CD4 counts were 260 (IQR, 130-410) cells/mm^3 for sub-Saharan African women and 160 (70-313) cells/mm^3 for sub-Saharan African men, whereas they were 281 (70-500) for heterosexual men from the Netherlands and 430 (160-650) cells/mm^3 for heterosexual women from the Netherlands. Patients from Latin America, the Caribbean, and South/Southeast Asia likewise had lower CD4 counts than Dutch patients. 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 90 (IQR, 30-380) cells/mm^3 in 1996 to 270 (50-510) cells/mm^3 in 2007 in the male population. In the female population, CD4 counts were 260 (150-425) cells/mm^3 in 1996 and 304 (140-500) cells/mm^3 in 2007, but this increase was not statistically significant (p=0.7). The median age at diagnosis of the entire heterosexual population increased from 33.1 (27.3-38.4) years in 1996 to 37.5 (29.2-44.2) years in 2007 ($p<0.001$).

Between 1996 and 2008, 705 (17.7%) patients presented with an AIDS-defining event, whereas 278 (7.0%) patients had a CDC-B event. The proportion of male patients with AIDS was 22.5% (381 out of 1694), which differed from the proportion of female patients, 14.2% (324 out of 2278). Proportions did not change over time ($p>0.3$).

Of the 3972 heterosexuals diagnosed between 1996 and 2008, 207 (5.2%) had a negative HIV test within 18 months prior to HIV diagnosis, whilst 616 (15.5%) ever had a negative test. These proportions were similar for men and women ($p>0.5$). Of the 1272 patients originating from the Netherlands and the rest of Europe, 288 (22.6%) ever had a negative test, and 108 (8.5%) had a negative test in the 18 months prior to diagnosis, whereas for the 2700 patients born outside Europe, 328 (12.1%) ever had a negative test, and 99 (3.7%) had a recent infection. The proportion of patients with a recent infection tended to increase over time from 4.3% in 1996 to 5.1% in 2007 (p=0.02). Likewise, the proportion of patients with a negative HIV test at any time before diagnosis increased from 15.3% in 1996 to 21.9% in 2007 ($p<0.001$).

The most likely country of infection was recorded for 3297 (71.7%) patients, including 1332 (68.4%) men and 1965 (74.1%) women. Of the 3297 patients, 1443 (43.8%) were infected in the Netherlands, and 1333 (40.4%) were infected in sub-Saharan Africa. The majority of the patients infected in the Netherlands (880, 61.0%) also originated from the Netherlands, whilst 163 (11.3%) originated from sub-Saharan Africa, 151 (10.5%) from Suriname, and 68 (4.7%) from the Netherlands Antilles or Aruba. Of the patients who were infected in sub-Saharan Africa, 1227 (92.0%) were also born in sub-Saharan Africa, whereas 94 (7.1%) originated from the Netherlands. Of the 138 patients from the Netherlands Antilles and Aruba, 65 (47%) were infected in their home country, as were 62 (28%) of 218 patients from Suriname. More men than women of Dutch origin were infected abroad: 157 (28.7%) men compared to 68 (12.2%) women. Of these 225 patients, 61 (27.1%, 59 men) were infected in Thailand and 17 (7.6%) in Kenya.

Of the 1328 (28.9%) patients with a known HIV-1 subtype, 594 (44.7%) originated from sub-Saharan Africa and 734 (55.3%) from other regions. The most prevalent subtype amongst patients from other regions was B (527 patients, 71.8%). Other reported subtypes were AE (58 patients, 7.9%), AG (46, 6.3%), C (33, 4.5%), A (26, 3.5%), G (15, 2.0%), D (8, 1.1%), F (4, 0.5%), and other non-B subtypes (17, 2.3%). Subtype B was found in only 12 (2.0%) patients from sub-Saharan Africa. The most frequent subtypes other than B amongst sub-Saharan Africans were AG (196, 33.0%), C (152, 25.6%),

A (76, 12.8%), G (41, 6.9%), D (36, 6.1%), F (15, 2.5%), and other non-B subtypes (66, 11.1%).

Injection drug users (IDU)

For 659 (4.7%) patients, including 478 (72.5%) men and 181 (27.5%) women, the reported mode of transmission was injection drug use. The majority of the patients (397, 60.2%) were infected before 1996; only 116 (17.6%) patients were infected in or after 2000. Of the IDUs, 415 (63.0%) of the patients originated from the Netherlands, and 126 (19.1%) were born in other Western European countries.

Of the 262 patients diagnosed in or after 1996, 88 (33.6%) were followed in a hospital in Amsterdam, 77 (29.4%) in another hospital in the Randstad, and 65 (24.8%) patients in the southern part of the Netherlands, in particular Maastricht (49 patients, 18.7%). The median age at diagnosis was 37.8 (IQR, 32.3-43.0) years. Median CD4 counts, CD8 counts and viral load were 280 (IQR, 90-510) cells/mm^3, 810 (480-1182) cells/mm^3, and 4.7 (4.0-5.2) $\log_{10}$ copies/ml, respectively. There were no differences between men and women and between patients of Dutch origin and patients originating outside the Netherlands. However, patients from outside the Netherlands were younger than those of Dutch origin: the age of non-Dutch patients was 33.9 (IQR, 26.2-40.8) years compared with 39.3 (35.1-43.4) years for those of Dutch origin. An AIDS event was found in 34 (13.0%) of the IDUs, whereas 210 (80.2%) were asymptomatic at diagnosis.

The most likely country of infection was reported for 543 (82.4%) patients. The majority (464, 85.5%) were infected in the Netherlands, whereas 48 (8.8%) patients were infected in other Western European countries. Of the IDUs diagnosed from 1996 on, 13 (5.0%) patients had a recent infection, whereas 47 (17.9%) patients ever had a negative HIV test. Subtype B was the most frequently reported HIV subtype; 153 (91.1%) of the 168 with a known subtype were infected with this strain.

Trends over time – start of cART

Amongst the 14,169 patients with a known year of HIV-1 diagnosis, 11,325 (79.9%) started cART. Of these patients, 2323 (20.5%) had been treated with mono- or dual antiretroviral therapy before starting cART, whilst 9002 (79.5%) started cART as therapy-naïve patients. For the total population, the median age at the start of cART was 38.0 (IQR, 32.0-45.2) years, but men were generally older than women; the men were 39.5 (33.7-46.5) years of age compared to the age of 32.6 (27.6-39.0) years for women. The median time between diagnosis and the start of cART for patients diagnosed in 1996 or later was 0.26 (IQR, 0.10-1.23) years for men and 0.23 (0.09-0.84) years for women ($p<0.001$).

The median CD4 cell count in men at the start of cART was 190 (IQR, 80-297) cells/mm^3 and the median CD8 cell count in men was 854 (560-1270) cells/mm^3; the median CD4 count in women at the start was 210 (100-340) cells/mm^3, and the median CD8 count in women was 755 (490-1110) cells/mm^3. After 24 weeks of cART, CD4 counts had increased to 310 (IQR, 180-460) cells/mm^3 in men and 340 (210-510) in women. In previously therapy-naïve patients, CD4 cell counts rose from 190 (IQR, 80-294) cells/mm^3 at start of cART to 330 (200-473) at 24 weeks in men and from 213 (102-340) to 360 (220-530) in women. The median CD4 count increased further to 370 (IQR, 236-530) cells/mm^3 in men and 388 (260-560) in women at 48 weeks after the start of cART. After 24 weeks, CD8 counts were 960 (IQR, 690-1300) cells/mm^3 in men and 840 (620-1210) in women, whereas they were 960 (685-1320) cells/mm^3 in men and 860 (620-1200) in women after 48 weeks.

In the therapy-naïve population, median CD4 cell counts at the start of cART were 200 (IQR, 90-318) cells/mm^3 in 1996, and they decreased to 180 (70-324) in 2000 ($p=0.003$). Between 2000 and 2005, CD4 cell

counts were 180 (IQR, 70-290) cells/mm^3. Thereafter, CD4 counts increased to 230 (IQR, 140-280) cells/mm^3 in 2008 ($p<0.001$).

At 24 weeks, 84.4% (6247 of 7402) of men and 79.6% (1701 of 2136) of women whose RNA levels were measured reached levels below 500 copies/ml. At 48 weeks after the start of cART, these proportions were 83.1% (5785 out of 6961) for men and 74.6% (1471 out of 1973) for women. For therapy-naïve patients, 90.1% of the men and 82.4% of the women had levels below 500 copies/ml at 24 weeks, whilst these levels were found for 63.0% of men and 64.7% of women in the pre-treated population.

A summary of the most frequent first-line cART combinations in the population from 1 June 2006 through 31 May 2007 and from 1 June 2007 through 31 May 2008 is shown in Table 2.2. In 2007-2008, tenofovir + emtricitabine + efavirenz was prescribed in 392 out of 809 (48.5%) cases, compared to 291 out of 837 (34.8%) in 2006-2007. Overall, the prescription of tenofovir increased from 555 cases (66.3%) in 2006-2007 to 628 cases (77.6%, $p<0.001$) in 2007-2008. Emtricitabine was part of 443 (52.9%) initial regimens in 2006-2007 and 611 (75.5%) in 2007-2008 ($p<0.001$), whereas the use of lamivudine decreased from 394 (47.1%) to 199 (24.6%) patients ($p<0.001$). Also, zidovudine was a less frequent option: 183 (21.9%) patients in 2006-2007 received it, compared to 98 (12.1%) patients in 2007-2008 ($p<0.001$).

The most frequent additions in 2007-2008 were efavirenz (483 patients, 59.7%), lopinavir (163, 20.1%), nevirapine (125, 15.5%) and atazanavir (50, 6.2%). Compared to 2006-2007, the proportion of patients using nevirapine (13.4%, $p=0.2$), lopinavir (21.7%, $p=0.4$) and atazanavir (8.0%, $p=0.1$) did not differ. However, the proportion of patients starting efavirenz (45.4%, $p<0.001$) was lower in 2006-2007 than in 2007-2008.

Discussion

Since 2007, the HIV-infected population in the Netherlands as registered by the HIV Monitoring Foundation has increased by 1696 patients, to a total of 14,960 patients with more than 100,000 person-years of follow-up[6]. Three-quarters of the population were still in follow-up as of 1 June 2008. This proportion is probably an underestimation because for some patients the backlog in data collection was more than one year.

The increase in the number of registered patients is remarkable as the number was approximately 1200 in previous years. On closer inspection, newly registered patients with HIV-1 diagnoses in 2006 or later accounted for 72% of the increase, patients diagnosed between 1996 and 2005 accounted for 9%, and those diagnosed before 1996 accounted for 3%. Compared to 2007, the number of patients without serologic results increased by 229, accounting for 14% of the 1696 patients. These patients generally were included in the HMF just before closure of the database.

Since the beginning of the HIV epidemic in the Netherlands, the age of the population living with HIV has increased, and one quarter of the population currently in follow-up is 50 years of age or more. In our previous report, it was shown that in succeeding years the age of the population would increase further, and by 2015, 37.7% of the patients in follow-up would be older than 50 years[6]. It is expected that treatment of HIV will be complicated by the increasing age of the population because of the appearance of age-related diseases and other non-HIV-related illnesses.

In recent years, the proportion of diagnosed patients who were infected via homosexual contact increased to almost 70%, whereas an estimated 25% were infected via heterosexual contact. The absolute number of diagnoses amongst homosexual men was more than 650 in 2007. When the backlog in registration is taken

into account, the real number of diagnoses in 2007 is expected to be approximately 15% higher, thus approaching 750 diagnoses annually. The absolute number of diagnoses amongst heterosexual men and women was in the order of 430 until 2005, and then it declined to a level of approximately 300 diagnoses annually.

Since 2002, the number of diagnoses amongst patients originating from sub-Saharan Africa has declined. This is consistent with the decreasing number of people emigrating from Africa to the Netherlands, as reported by Statistics Netherlands (http://statline.cbs.nl). After 2004, the number of immigrants from sub-Saharan Africa stabilised, and this probably was reflected in the HMF database by an apparent stabilisation of the number of diagnoses amongst sub-Saharan Africans from 2006 onward.

Both in homosexual men and in heterosexual men and women, the proportion of patients diagnosed with a recent infection increased, although the increase was more pronounced in homosexual men. This observation probably reflects the increasing frequency of testing as reported by sexually transmitted infection (STI) clinics[1]. Heterosexual patients originating from a European country were more likely to be diagnosed with a recent infection and more likely to ever have had a negative HIV test than patients originating from outside Europe. Even for European patients, however, the proportion with a recent infection or a negative test was lower amongst heterosexuals than amongst MSM.

By June 2008, approximately 805 of the HIV-infected population had started cART. More than half of all treated patients were using a regimen containing tenofovir. In addition, an increasing proportion of patients were receiving emtricitabine instead of lamivudine, probably because it is available in a fixed-dose combination with tenofovir. Tenofovir-containing and emtricitabine-containing regimens were prescribed for three-quarters of the patients starting cART between 1 June 2007 and 31 May 2008. Almost half of the patients started a combination of tenofovir, emtricitabine and efavirenz, which is now available as a fixed-dose, once-daily pill. In the total treated population, no changes were observed in the administration of nevirapine, lopinavir, and atazanavir, but efavirenz-containing regimens gained popularity. Also, in first-line cART, efavirenz-containing regimens were more often used.

Recently, an increase in the prevalence of HCV infections amongst homosexual men has been reported[7, 8]. This increase was also apparent in our data, since 7.0% of MSM in follow-up as of 1 June 2008 were co-infected with hepatitis C (8.6% in Amsterdam), compared to 5.8% last year[6]. This increase in HCV prevalence is probably related to the observed increase in high-risk sexual behaviour after the introduction of cART[4, 9]. The clinical implications of HCV/HIV co-infection can be far-reaching, because co-infection complicates treatment of HIV and accelerates progression to liver disease, when compared to the rate of progression in HCV-mono-infected patients.

In conclusion, despite a dozen years of cART, the annual growth of the HIV-infected homosexual population has only increased since 1996. The number of infections amongst heterosexuals is decreasing, but this is mainly due to a decreasing contribution of imported infections from sub-Saharan Africa. The growing proportion of patients recently infected with HIV means that the time from infection to diagnosis is shortened. Therefore, provided that risk behaviour is reduced after HIV diagnosis, there should be fewer transmissions per infected patient, which should lead to a reduction in the HIV epidemic in the long term.

	men (N=8929)		women (N=2420)		total (N=11,349)	
	N	%	N	%	N	%
transmission						
MSM	6497	72.8			6497	57.2
heterosexual	1505	16.9	2124	87.8	3629	32.0
IDU	259	2.9	105	4.3	364	3.2
blood (products)	106	1.2	60	2.5	166	1.5
vertical	17	0.2	20	0.8	37	0.3
other/unknown	545	6.1	111	4.6	656	5.8
age category (years)						
13-17	15	0.2	17	0.7	32	0.3
18-24	149	1.7	162	6.7	311	2.7
25-34	1111	12.4	649	26.8	1760	15.5
35-44	3219	36.1	933	38.6	4152	36.6
45-54	2858	32.0	481	19.9	3339	29.4
55-64	1264	14.2	131	5.4	1395	12.3
≥65	313	3.5	47	1.9	360	3.2
region of origin						
the Netherlands	5939	66.5	706	29.2	6645	58.6
sub-Saharan Africa	727	8.1	1045	43.2	1772	15.6
Western Europe	596	6.7	106	4.4	702	6.2
Latin America	611	6.8	210	8.7	821	7.2
Caribbean	306	3.4	120	5.0	426	3.8
years aware of HIV infection						
<1	699	7.8	141	5.8	840	7.4
1-2	1527	17.1	378	15.6	1905	16.8
3-4	1303	14.6	410	16.9	1713	15.1
5-10	2396	26.8	845	34.9	3241	28.6
>10	2980	33.4	635	26.2	3615	31.9
unknown	24	0.3	11	0.5	35	0.3

MSM: men having sex with men; IDU: injection drug use

Table 2.1: Characteristics of the HIV-infected population in follow-up as of 1 June 2008

	1 June 2008 (N=9136)		1 June 2007 (N=8333)	
cART in the entire population	N	%	N	%
TDF+FTC+EFV	1340	14.7	842	10.1
TDF+FTC+NVP	704	7.7	425	5.1
AZT+3TC+NVP	679	7.4	806	9.7
TDF+3TC+NVP	537	5.9	562	6.7
none	531	5.8	591	7.1
TDF+3TC+EFV	491	5.4	570	6.8
AZT+3TC+ABC	433	4.7	502	6.0
AZT+3TC+LOP/r	389	4.3	363	4.4
TDF+FTC+ATV/r	371	4.1	268	3.2
TDF+FTC+LOP/r	323	3.5	176	2.1
	2007-2008 (N=809)		**2006-2007 (N=837)**	
first-line cART	N	%	N	%
TDF+FTC+EFV	392	48.5	291	34.8
TDF+FTC+NVP	88	10.9	50	6.0
TDF+FTC+LOP/r	65	8.0	43	5.1
ABC+3TC+EFV	48	5.9	45	5.4
AZT+3TC+LOP/r	45	5.6	70	8.4
TDF+FTC+ATV/r	37	4.6	42	5.0
TDF+FTC+EFV+LOP/r	19	2.3	10	1.2
AZT+3TC+NVP	14	1.7	19	2.3
ABC+3TC+LOP/r	13	1.6	18	2.2
ABC+3TC+NVP	10	1.2	10	1.2

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).

Table 2.2: Overview of the most frequently used cART regimens in the entire treated populations as of 1 June 2008 and as of 1 June 2007 and in the populations starting cART between 1 June 2007 and 31 May 2008 and between 1 June 2006 and 31 May 2007

	MSM	Heterosexual		Injection drug use		Blood (products)		Other/unknown		Total
Year of diagnosis	Men	Men	Women	Men	Women	Men	Women	Men	Women	
1996	367	84	79	35	14	3	4	41	5	632
1997	423	106	126	42	7	8	3	50	7	772
1998	320	103	110	21	4	6	6	28	9	607
1999	333	101	137	17	6	8	4	31	5	642
2000	346	150	201	12	3	5	3	37	9	766
2001	417	159	226	13	6	8	2	48	7	886
2002	445	155	255	14	2	12	5	62	9	959
2003	436	174	266	18	4	7	4	66	13	988
2004	545	180	251	9	2	4	3	77	11	1082
2005	593	186	245	12	3	2	3	67	10	1121
2006	587	148	173	7	5	4	5	54	3	986
2007	665	119	173	5	1	2	5	47	8	1025
2008	195	29	36	0	0	1	1	17	4	283
total	**5672**	**1694**	**2278**	**205**	**57**	**70**	**48**	**625**	**100**	**10749**

MSM: men having sex with men

Table 2.3: Annual number of diagnoses since 1996 stratified by gender and transmission risk group

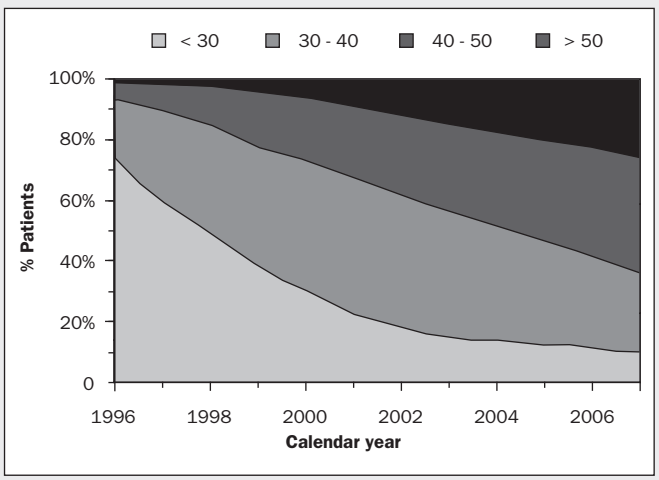


Figure 2.1: Proportion of patients in follow-up as of 1 July of each calendar year who were <30 years of age, 30 to 40 years, 40 to 50 years, or 50 years or older

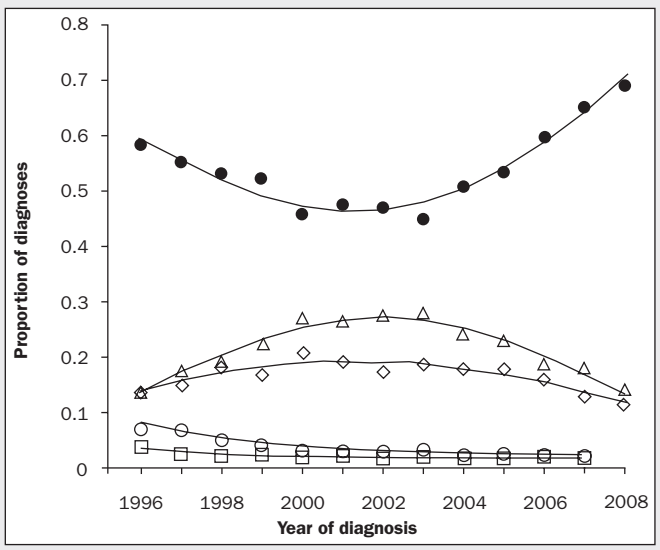


Figure 2.2: Annual proportion of diagnoses per transmission risk group

Dots represent homosexual men; triangles, heterosexual women; diamonds, heterosexual men; circles, injection drug users (men); squares, injection drug users (women); and lines, Poisson regression model quadratic in time

3. Causes of death

Luuk Gras / Ard van Sighem

Introduction

Combination antiretroviral therapy (cART) reduces mortality and morbidity rates in HIV-infected patients[12,14,44,48,49]. With a timely start of HIV-1-suppressing cART, the life expectancy of infected patients increases significantly, although still not to the level of the age- and gender-matched general population[50, 51]. Hence, HIV is gradually acquiring the characteristics of a chronic, rather than lethal, disease. As patients live longer, a significant proportion of deaths in HIV-1-infected patients are now caused by non-HIV-related events[12, 52].

In this chapter an update on annual mortality and morbidity rates is given, and changes in causes of death in the cART-treated population are described.

Methods

The total study population consisted of 14,347 HIV-1-infected patients with a known date of HIV diagnosis. From this population, a subpopulation of 11,416 (79.6%) patients was selected that comprised all patients who started cART between 1995 and 1 June 2008. All deaths and cases of AIDS (CDC-C events) occurring in the total population in 1996 or later were assessed.

Annual mortality and AIDS incidence rates were calculated as the number of deaths and AIDS cases per year divided by the total number of person-years (py) of follow-up during that year. Follow-up for each patient was divided into monthly intervals to study the effect of latest CD4 count, plasma viral load, and time after first starting cART on the incidence of the most frequent causes of death. The Poisson distribution was used to calculate 95% confidence intervals (CI) for rates. The significance of changes in rates over time was assessed with generalised linear models.

For the analysis of causes of death, a smaller subgroup of 10,135 antiretroviral therapy-naïve and pre-treated patients starting cART between July 1996 and December 2007 was selected. Patients less than 16 years of age and women who started cART during pregnancy were excluded. 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[53]. Differences in the proportion of causes of death occurring from 1996 through 2003 and from 2004 through 2007 were compared using chi-square p-values. This cut-off was chosen to include approximately 50% of the total deaths that occurred on either side of the cut-off.

Differences in causes of death between pre-treated and naïve patients were studied with the cumulative incidence function of competing causes of death[54, 55]. Information on causes of death in the general population in the Netherlands was obtained from Statistics Netherlands[56]. The only causes of death selected were those for which the definition was comparable to the definition used in this chapter. Annual incidence figures for men and women and each 5-year age group were calculated as the number of specific causes of death divided by the number of people alive on 1 January in each gender/age group. Cause-specific incidence figures were standardized according to the age distribution in HIV-1 infected male and female patients on 1 January 2004.

Results

Mortality and incidence of AIDS

In the total group of 14,347 patients with 92,123 person-years of follow-up since 1996, 1281 cases of death were recorded (Table 3.1). This number corresponded with an average mortality of 1.39 (95% CI 1.31-1.47) deaths per 100 py. The mortality slightly decreased over time ($p<0.001$), from 1.94 (1.55-2.40) in 1997 to 1.17

(0.84-1.58) in 2008 (Figure 3.1). When patients who had an AIDS diagnosis within 6 weeks after an HIV diagnosis (N=2172) were excluded, the overall mortality was reduced to 1.20 (1.12-1.28) per 100 py and did not change over time (p=0.08). When only patients diagnosed in or after 1996 were considered, the mortality was also lower, 1.04 (0.96-1.13), and it likewise did not change over time (p=0.3) (N=10,912, 55,421 py of follow-up, 576 cases of death).

For the total group, 4109 AIDS diagnoses were registered at or after HIV diagnosis. There were 2417 new AIDS diagnoses recorded 6 weeks or longer after an HIV diagnosis, of which 1956 (80.9%) were recorded in or after 1996. The total follow-up since 1996 until AIDS diagnosis was 78,273 person-years, yielding an average AIDS incidence of 2.50 (95% CI 2.39-2.61). From 1996 on, there has been a decline ($p<0.001$) in AIDS diagnoses per 100 py from 9.1 (8.0-10.2) in 1996 to 1.4 (1.1-1.6) in 2007 (Figure 3.1). After 2000, the AIDS incidence was 1.93 (1.82-2.05) per 100 py 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 2.04 (1.91-2.18) per 100 py (p=0.2 compared to all patients).

The population of patients starting cART consisted of 2358 patients with prior antiretroviral treatment (20,452 py of follow-up since 1996, 538 deaths) and 9058 previously therapy-naïve patients (46,814 py of follow-up, 569 deaths). Overall, the mortality rate declined from 4.6 (3.0-6.5) per 100 py in 1996 to 1.15 (0.94-1.40) in 2007 and 1.36 (0.97-1.87) in 2008. On average, the mortality after 2000 was 1.46 (1.36-1.57) and tended to decline over time (p=0.01). In the therapy-naïve population, mortality was lower than in the pre-treated population, that is, 1.18 (1.08-1.30) compared to 2.31 (2.06-2.59) per 100 py after 2000. Between 1996 and 2008, the overall mortality in the naïve population was 1.22 (1.12-1.32) per 100 py and did not change over time (p=0.2). When patients with an AIDS diagnosis in the year prior to the start of cART were excluded, the mortality rate was 0.89 (0.79-0.99) per 100 py in the previously therapy-naïve population and 2.13 (1.91-2.37) in the pre-treated population, and both rates did not change over calendar time ($p>0.1$).

In the total group who ever started cART, 1322 AIDS diagnoses were registered in 1996 or later during 61,649 person-years of follow-up after the start of cART. The incidence of new AIDS diagnoses decreased dramatically from 14.7 (11.9-18.1) in 1996 to 1.25 (0.93-1.42) in 2007. In the therapy-naïve population (43,538 py of follow-up), the overall incidence of AIDS was 1.89 (1.77-2.03) per 100 py, which was lower than in the pre-treated population for which the incidence was 2.74 (2.51-3.00) per 100 py. The AIDS incidence after 2000 was similar in the pre-treated and therapy-naïve populations, being 1.64 (1.41-1.89) and 1.65 (1.52-1.79) per 100 py, respectively (p=0.9), and it declined over time ($p<0.001$).

Cause of death

During 59,368 person-years of follow-up after initiation of cART between July 1996 and December 2007, 979 of 10,135 patients died (1.65 deaths per 100 py of follow-up, 95% CI 1.54-1.75). In total, 118 deaths (12.1%) could not be classified because of insufficient clinical data. AIDS as the cause of death was recorded in 335 patients (39% of all known causes of death), and non-AIDS causes of death were recorded in 526 patients (61%).

Table 3.2 shows the cause of death for 513 patients (52.4%) who died before 1 January 2004 and for 466 (47.6%) who died thereafter. AIDS-defining infection (130 patients) occurred just as frequently as AIDS-defining malignancy (124 patients), whilst 81 patients were recorded as having died because of AIDS but without further classification. Non-AIDS-defining malignancy was the cause of death in 132 patients, cardiovascular complications in 88 patients, and non-

AIDS-defining infection in 66 patients. The proportion of deaths due to AIDS during or after 2004 was significantly lower compared to that before 2004 (39 vs. 29%, p=0.0006), whilst the proportion of deaths due to non-AIDS cancers (10% vs. 17%, p=0.001) and cardiovascular disease (7% vs. 11%, p=0.01) was significantly higher in or after 2004. 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 (Interquartile range [IQR], 10-130) and 95 (30-200), respectively (p=0.001). The same trend was seen in non-AIDS-defining infections (median last CD4 count, 110 cells/mm^3 [IQR, 50-270]) and non-AIDS defining malignancies (median, 230 cells/mm^3 [120-415], p=0.02). The highest median CD4 counts prior to death were seen in patients who died by accident or violence (360 cells/mm^3 [IQR, 120-410]), substance abuse (350 cells/mm^3 [100-610]), and cardiovascular disease (320 cells/mm^3 [180-515]). Table 3.3 shows the incidence of the five most frequent causes of death (AIDS, non-AIDS malignancy, cardiovascular disease, non-AIDS infection, or liver failure with HCV or HBV co-infection) according to the latest CD4 count. The incidence of death due to AIDS was 158.8 / 1000 py (95% CI 134.0-186.9) for patients with a latest CD4 count of less than 50 cells/mm^3, compared to 2.7 (1.9-3.9) for those with a count between 200 and 350 cells/mm^3 (p<0.0001).
There was a clear association of a higher incidence of all five causes of death with a lower latest CD4 cell count. This effect was strongest for death due to AIDS and weakest for death due to cardiovascular disease.

As with latest CD4 count, there was a trend toward a higher incidence of death due to AIDS, non-AIDS malignancy, cardiovascular disease, non-AIDS infection, or liver failure with HCV or HBV co-infection, with a higher HIV-1 RNA concentration measured in the latest sample obtained (Table 3.4). For all five causes of death, the incidence was higher in patients on antiretroviral therapy with a plasma viral load ≥500 compared to <500 copies/ml. Also, in patients not on antiretroviral therapy, the incidences were higher in those having a plasma viral load between <100,000 compared to ≥100,000 copies/ml. Furthermore, there was a high incidence of death due to AIDS and non-AIDS malignancies in patients who were off antiretroviral therapy and for whom no latest plasma viral load off therapy was available. This was not seen in cases of death due to cardiovascular disease. In models adjusted for both latest CD4 count and plasma viral load, the association of higher latest CD4 count and increased risk of specific causes of death remained significant. There was a trend toward a higher risk of specific causes of death with higher latest plasma viral load (both on and off therapy), but this was only significant for death due to AIDS.

The Kaplan-Meier estimate of all-cause mortality 11 years after the start of cART was 10.6% in naïve patients and 23.6% in those who were pre-treated (p<0.0001). Figure 3.2 shows the cumulative incidence of the most frequent causes of death after starting cART for 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 first starting cART, whereas in naïve patients the cumulative incidence of these causes of death levelled off after the first 3 years after starting cART. In naïve patients, the incidence of death because of AIDS per 1000 py was 7.91 (95% CI 6.74-9.23) during the first 3 years after starting cART, 1.82 (1.22-2.61) between 3 and 7 years and further decreased to 0.82 (0.27-1.91) after 7 years. In contrast, the incidence of death due to non-AIDS malignancy increased with longer time after starting cART, 1.71 per 1000 py (1.19-2.38) during the first 3 years, 1.94 (1.32-2.77) between 3 and 7 years, and 3.43 (2.12-5.25) after 7 years. In pre-treated patients, the incidence of death due to AIDS also decreased with

longer time after starting cART, but it remained high at 4.62 (2.86-7.06) per 1000 py after 7 years from first starting cART.

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 3.5). On 1 January 2004, the male pre-treated patients had a mean age of 47.1 compared to 43.1 years in male therapy-naïve patients ($p<0.0001$). Therefore, the age standardized incidences of specific causes of death amongst pre-treated patients in Table 3.5 are higher than those in the naïve group. The incidence of death due to non-AIDS-defining cancer was 2.89 (95% CI 2.06-3.93) for pre-treated male patients and 1.77 (0.57-4.13) per 1000 py for female patients. This compares to 1.50 and 0.60 per 1000 py for the male and female age-standardized general population. Similarly, the incidence of death due to cardiovascular disease or suicide after starting cART was also higher compared to the age-standardized population. The risk of cardiovascular disease in female HIV-infected patients (only 1 death of a female was recorded) was comparable to that in the general female population. Although the incidence of death due to non-AIDS-defining cancer or cardiovascular disease was lower in naive patients compared to pre-treated, the incidence was still higher compared to the age-standardized population.

Discussion

Since 1996, the overall mortality in the HIV-infected population in the Netherlands has declined slightly to the present level of just above 1 death per 100 person-years of follow-up. This seemingly contradicts the sharp decline observed in the cART-treated population. However, this decline in mortality was only apparent in the pre-treated population, which constituted a mere 16% of the total HIV-infected population. Also, the decline in mortality in the cART-treated population should be interpreted with care; it 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.

Also, the incidence of AIDS was approximately 1 case per 100 person-years of follow-up. There appeared to be a decline in incidence of AIDS after 2000, but this might in part have been due to a backlog in registration of AIDS-defining events.

Of all deaths after the start of cART, 61% had non-AIDS-defining causes. Non-AIDS-defining causes of death (in particular, death following a non-AIDS-defining malignancy) comprised the largest category in patients who had been on cART for a longer period of time (more than 4 years). As treatment has turned HIV infection into a chronic disease, causes of death in the aging 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 after 1 January 2004 in our cohort of treated patients and in other cohorts[29-31]. However, we also found that the incidence of non-AIDS-defining cancer and cardiovascular disease in HIV-infected patients after starting cART is higher than in the general population. This has also been shown for myocardial infarction and certain non-AIDS-defining cancers in other studies[32-36].

In addition to the higher risk of non-AIDS-defining causes of death in HIV-infected patients compared to that in the general population, the association of a lower latest CD4 count and a higher incidence of non-AIDS-defining causes of death also indicates that immunodeficiency may play a role in the risk of

fatal non-AIDS events. The rate of death due to non-AIDS causes decreased with higher latest CD4 count, although to a lesser extent than death due to AIDS, which was similar to others' findings[37]. Regarding specific causes of death, the association of a higher latest CD4 count with lower incidence of fatal disease for fatal non-AIDS-defining cancers was found in some[37, 57, 58] studies, but not in others[59-61]. Likewise, studies have shown an association of hepatic and non-AIDS infections with lower latest CD4 counts[11, 62]. Even with high CD4 counts (≥350 cells/mm^3), the higher the count the lower the risk of fatal and non-fatal events [63-65]. We also found a trend toward a higher incidence of death due to non-AIDS causes with a higher plasma viral load. Large collaborative studies are needed to confirm this association and to determine whether this trend is independent of that of an increased risk of non-AIDS death with higher CD4 counts. Unpublished data from the SMART (Strategies for Management of Antiretroviral Therapy) study suggest that the effect of latest viral load might be independent of latest CD4 count in deaths due to cardiovascular, hepatic, and renal disease. The probable explanation for the finding of a high incidence of death due to AIDS and non-AIDS malignancy in patients not on antiretroviral therapy with no available value for latest plasma viral load off therapy is that it concerns patients who were not using antiretroviral therapy shortly before they died. The more acute nature of death due to cardiovascular disease is reflected in the absence of such an effect in this specific cause of death. Taken together, these results suggest that to reduce mortality in HIV-infected patients further it would be beneficial to start cART at an earlier stage, e.g., 350 cells/mm^3. It has been shown that restoration of CD4 counts to levels seen in the uninfected population is possible, but it involves long continuous use of cART[66].

A limitation of observational data is that it is not always possible to adjust for all known risk factors for each co-morbidity. For example, data on past or current smoking is incompletely collected in the ATHENA cohort. Furthermore, the high number of patients in whom the cause of death was unknown hampers drawing firmer conclusions. Insight into the causes of death is crucial to better target interventions, and, therefore, continued monitoring of causes of death, preferably as judged by a panel including physicians, should continue.

Apart from immunodeficiency and HIV infection itself, lifestyle, older age, exposure to certain antiretroviral drugs or drug classes, and co-infection may also play a role in premature deaths. These are each separate effects on the incidence of serious diseases, and it will be a challenge for future studies to disentangle them to gain a better understanding of the mechanisms of the diseases.

In summary, in patients with an increased duration of time on cART and an accompanying rise in CD4 count, there is a shift from AIDS-related to non-AIDS-related causes of death. Death due to non-AIDS causes is likely to be immunodeficiency-related, albeit to a lesser extent than death due to AIDS. In order to further reduce the mortality and morbidity, it is important to diagnose and treat HIV-infected patients at an earlier stage.

	AIDS			death	
	total	≥ 6 weeks after diagnosis	after start of cART	total	after start of cART
≤1995	734	461	1	1	-
1996	355	285	90	43	29
1997	304	179	128	85	69
1998	248	133	112	84	74
1999	234	134	115	91	89
2000	242	113	87	81	78
2001	256	145	97	78	77
2002	293	153	120	121	84
2003	284	140	110	140	118
2004	277	165	112	143	127
2005	336	186	122	140	125
2006	268	159	112	112	99
2007	231	129	90	120	99
2008	47	35	27	42	39
	4109	**2417**	**1323**	**1281**	**1107**

cART: combination antiretroviral therapy

Table 3.1: Annual number of patients with AIDS and number of patient deaths

		<2004		≥2004		Median last CD4
		N	%	N	%	count (IQR)
Total		513	100.0	466	100.0	
Death due to AIDS defining causes		201	39.2	134	28.8	60 (20-150)
	Infection	83	16.2	47	10.1	50 (10-130)
	Malignancy	67	13.1	57	12.2	95 (30-200)
	AIDS, not specified	51	9.9	30	6.4	50 (10-130)
Non-AIDS-defining malignancy		52	10.1	80	17.2	230 (120-415)
Non-AIDS-defining infection		41	8.0	25	5.4	110 (50-270)
Liver failure / cirrhosis and HBV/HCV co-infection		20	3.9	31	6.7	190 (100-280)
Diabetes mellitus		1	0.2	3	0.6	270 (195-380)
Lactic acidosis		4	0.8	2	0.4	240 (70-310)
Cardiovascular complications		35	6.8	53	11.4	320 (180-515)
	MI	17	3.3	23	4.9	295 (160-510)
	Stroke	5	1.0	6	1.3	270 (180-900)
	Other ischemic heart disease	1	0.2	1	0.2	470 (360-570)
	Heart or vascular (other causes)	13	2.5	24	5.2	360 (200-450)
Lung related		9	1.8	11	2.4	165 (80-375)
Liver failure (without HBV/HCV)		4	0.8	2	0.4	110 (80-240)
Renal failure		5	1.0	2	0.4	310 (70-500)
Non-natural death		52	10.1	48	10.3	245 (100-455)
	Accident or other violent death	12	2.3	4	0.9	360 (120-410)
	Suicide	17	3.3	28	6.0	310 (210-600)
	Euthanasia	23	4.5	16	3.4	150 (40-280)
Substance abuse		11	2.1	4	0.9	350 (100-610)
Other cause*		15	2.9	11	2.4	200 (30-490)
Unknown		59	11.5	59	12.6	250 (100-500)

Table 3.2: Cause of death according to date of death before or after 1 January 2004

* Other causes include pancreatitis, haematological, respiratory, gastro-intestinal tract, gynaecological, and central nervous system disorders

HBV: hepatitis B virus; HCV: hepatitis C virus; MI: myocardial infarction; IQR: interquartile range

Cause of death	Latest CD4 count (cells/mm^3)	Deaths	PY	Incidence/ 1000 PY	(95% CI)
AIDS	<50	145	913	158.8	(134.0-186.9)
	50-200	121	6602	18.3	(15.2-21.9)
	200-350	34	12310	2.7	(1.9-3.9)
	350-500	15	13532	1.1	(0.6-1.8)
	≥500	9	24042	0.4	(0.2-0.7)
Non-AIDS	<50	13	913	14.2	(7.6-24.3)
malignancy	50-200	47	6602	7.1	(5.2-9.5)
	200-350	27	12310	2.2	(1.4-3.2)
	350-500	21	13532	1.6	(1.0-2.4)
	≥500	23	24042	1.0	(0.6-1.4)
Non-AIDS	<50	7	913	7.7	(3.1-15.8)
infection	50-200	17	6602	2.6	(1.5-4.1)
	200-350	17	12310	1.4	(0.8-2.2)
	350-500	5	13532	0.4	(0.1-0.9)
	≥500	3	24042	0.1	(0.03-0.4)
Cardiovascular	<50	4	913	4.4	(1.2-11.2)
disease	50-200	21	6602	3.2	(2.0-4.9)
	200-350	20	12310	1.6	(1.0-2.5)
	350-500	18	13532	1.3	(0.8-2.1)
	≥500	24	24042	1.0	(0.6-1.5)
Liver disease	<50	16	913	17.5	(10.0-28.5)
and HCV	50-200	31	6602	4.7	(3.2-6.7)
or HBV	200-350	6	12310	0.5	(0.2-1.1)
co-infection	350-500	9	13532	0.7	(0.3-1.3)
	≥500	3	24042	0.1	(0.03-0.4)

Table 3.3: Incidence after first starting cART of the five most frequent causes of death according to latest CD4 count in 10135 patients

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

Cause of death	Latest CD4 count (cells/mm^3)	Deaths	PY	Incidence/ 1000 PY	(95% CI)
AIDS	On trt, <500	126	46968	2.7	(1.7-2.6)
	On trt, ≥500	115	7058	16.3	(13.5-19.6)
	Off trt, <100,000	24	2804	8.6	(5.5-12.7)
	Off trt, ≥100,000	37	923	40.1	(28.2-55.3)
	Off trt, unknown	6	100	60.0	(22.0-130.7)
Non-AIDS	On trt, <500	100	46968	2.1	(1.7-2.6)
malignancy	On trt, ≥500	16	7058	2.3	(1.3-3.7)
	Off trt, <100,000	6	2804	2.1	(0.8-4.7)
	Off trt, ≥100,000	5	923	5.4	(1.8-12.6)
	Off trt, unknown	4	100	40.0	(10.9-102.5)
Non-AIDS	On trt, <500	28	46968	0.6	(0.4-0.9)
infection	On trt, ≥500	15	7058	2.1	(1.2-3.5)
	Off trt, <100,000	7	2804	2.5	(1.0-5.1)
	Off trt, ≥100,000	13	923	14.1	(7.5-24.1)
	Off trt, unknown	1	100	10.0	(0.3-55.7)
Cardiovascular	On trt, <500	68	46968	1.4	(1.1-1.8)
disease	On trt, ≥500	12	7058	1.7	(0.9-3.0)
	Off trt, <100,000	3	2804	1.1	(0.2-3.1)
	Off trt, ≥100,000	4	923	4.3	(1.2-11.1)
	Off trt, unknown	0	100	0.0	(0.0-36.9)
Liver disease	On trt, <500	34	46968	0.7	(0.5-1.0)
and HCV	On trt, ≥500	8	7058	1.1	(0.5-2.2)
or HBV	Off trt, <100,000	4	2804	6.0	(1.2-17.6)
co-infection	Off trt, ≥100,000	4	923	4.3	(1.2-11.1)
	Off trt, unknown	1	100	10.0	(0.3-55.7)

Table 3.4: Incidence after first starting cART of the five most frequent causes of death according to latest plasma HIV RNA concentration (copies/ml) and treatment status

pVL: plasma viral load; PY: person-years; trt: treatment; HCV: hepatitis C virus; HBV: hepatitis B virus

		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	♂	2.89 (2.06-3.93)	1.50*	2.41 (1.92-2.99)	1.22*
	♂	1.77 (0.57-4.13)	0.60*	0.48 (0.13-1.24)	0.64*
Cardiovascular disease	♂	2.74 (1.94-3.77)	1.09	1.42 (1.05-1.88)	0.89
	♂	0.00 (0.00-1.31)	0.24	0.12 (0.003-0.68)	0.24
CVA	♂	0.36 (0.12-0.84)	0.17	0.15 (0.05-0.34)	0.14
	♂	0.00 (0.00-1.31)	0.07	0.12 (0.003-0.68)	0.07
Myocardial infarction	♂	1.01 (0.55-1.69)	0.37	0.76 (0.49-1.11)	0.30
	♂	0.00 (0.00-1.31)	0.06	0.00 (0.00-0.44)	0.06
Suicide	♂	0.72 (0.35-1.33)	0.19	0.90 (0.61-1.28)	0.18
	♂	0.71 (0.09-2.56)	0.07	0.24 (0.03-0.80)	0.07

Table 3.5: Incidence of various causes of death in HIV-1 infected patients after starting cART compared to the age standardized general population

*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 cervix carcinoma

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

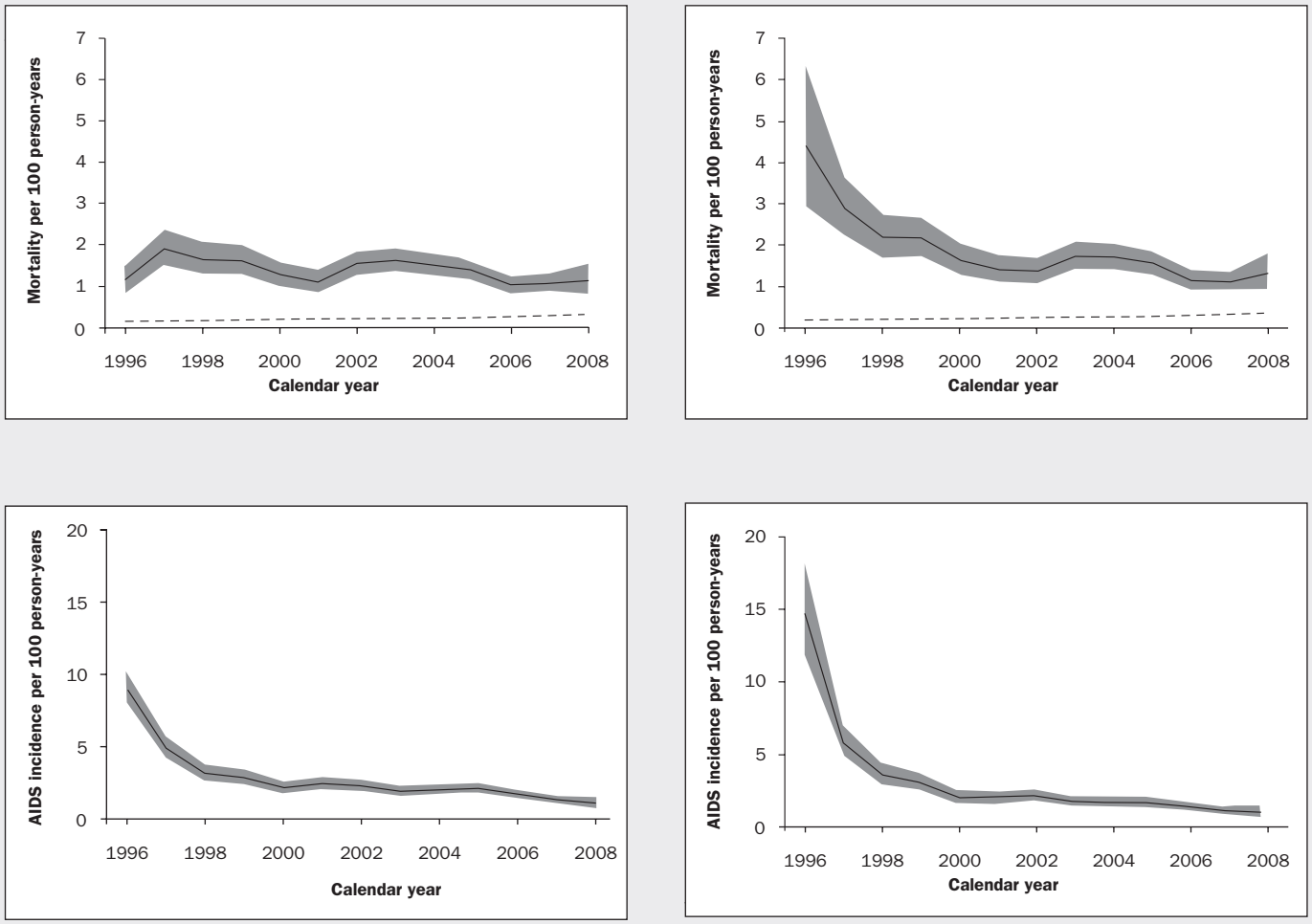


Figure 3.1: Mortality and incidence of AIDS as a function of calendar year after diagnosis (upper plots) and after start of cART (lower plots). The black lines represent the incidence, whilst the grey areas are the 95% confidence intervals. The dotted line is the mortality rate expected for age- and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

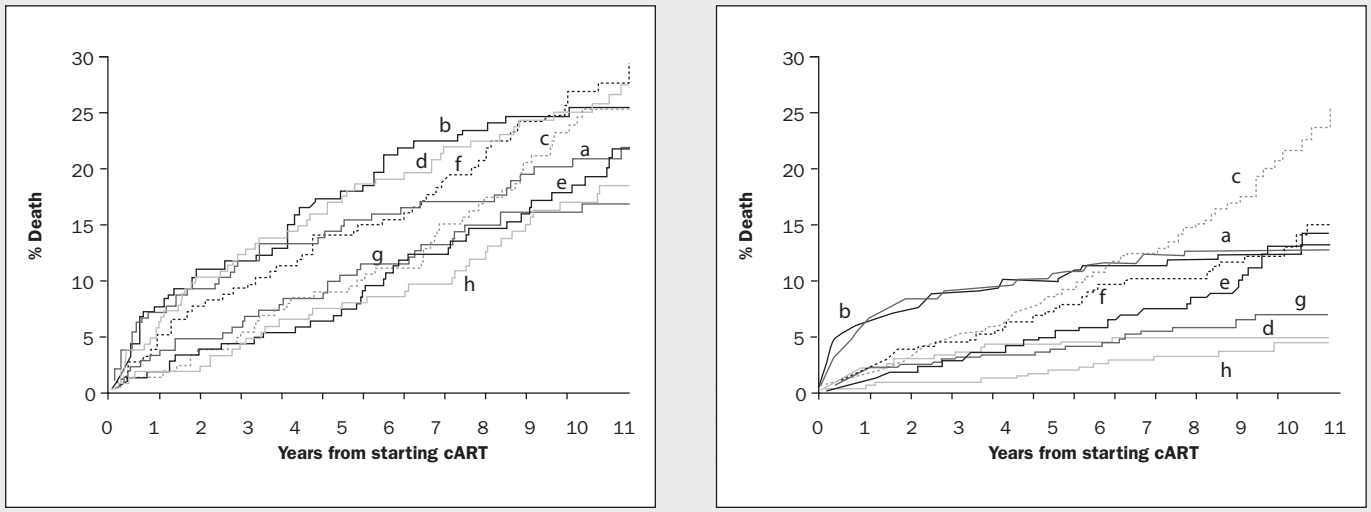


Figure 3.2: Cumulative incidence curves of death after starting combination antiretroviral therapy (cART) in 1975 pre-treated (left) and 8159 ART-naïve patients (right) according the Causes of Death in HIV (CoDe) scheme.

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 HCV or HBV co-infection

4. Hepatitis B and C co-infection

Colette Smit

Introduction

As a result of the shared routes of transmission, hepatitis B (HBV) and hepatitis C (HCV) are highly prevalent amongst HIV-infected patients. Approximately 10% of the HIV-infected patients are co-infected with HBV, whilst the prevalence of HCV co-infection ranges from 7% to as high as 82% in cases of a reported history of injecting drug use[67, 68]. Irrespective of co-infection with HIV, chronic HBV and HCV infection is associated with cirrhosis, liver failure, and cancer [69, 70]. However, HIV is known to accelerate the progression of HBV- and HCV-related liver disease, and in HIV-infected patients these viruses are an important cause of mortality[10, 71].
Screening for HBV and HCV of all HIV-infected patients is recommended. When testing for hepatitis B surface antigen (HBsAg) or hepatitis B surface antibody (anti-HBs) is negative, HBV vaccination should be offered. Unfortunately, this option is not available for HCV[72, 73].

In this chapter, we provide an update on the prevalence of HBV and HCV co-infection in the HIV-infected population in the Netherlands. In addition, we include results of our study of the impact of HBV and HCV co-infection on the progression to AIDS and death.

Study population and methods

The study population was composed of 9716 (83%) out of 11,720 HIV-infected patients who were at least 18 years old at the time of initiation of combination antiretroviral therapy (cART) and were tested for both HBV and HCV. Demographic and baseline characteristics of this population are summarised in Table 4.1.

Definition of HBV and HCV co-infection

HBV infection was defined by a positive result on an HBsAg test (EIA, Axsym). HCV infection was defined by a positive result on an HCV antibody test (EIA, Axsym) and preferably confirmed with a positive HCV RNA test (measured by a qualitative polymerase chain reaction). Patients who had a positive result on an HCV antibody test, but a negative result on an HCV RNA test were classified as HCV-negative.

Statistical analysis

Patients were subdivided into 3 groups: a) HIV-infected patients without either HBV or HCV infection, b) with HBV co-infection, and c) with HCV co-infection. HIV-infected patients who were co-infected with both HBV and HCV (n=36) were not included in the analysis. The chi-square and Mann-Whitney tests were used to assess the differences in the demographic and baseline characteristics amongst the three patient groups.
The effect of HBV and HCV co-infection on time to a first AIDS-defining event (CDC-C event) and death was assessed by a Cox proportional hazards model. Time to follow-up was from the date of cART initiation to that of last contact or most recent follow-up, an AIDS defining event or death, or 1 June 2008. Models were adjusted for age at cART initiation, sex, risk group, ethnicity, baseline CD4 cell count and HIV RNA levels.
Kaplan-Meier estimates of the probability of dying were plotted for the time to death and stratified by co-infection.

Results

In the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort, 83% of the patients were screened for both HBV and HCV co-infection in 2008; although not all patients are currently screened for co-infection, the proportion of patients being screened

has increased from 67% for HBV and from 64% for HCV in 2006 [74].

The prevalence of HBV amongst the 9716 HIV-infected patients screened was 6%; 7% of the patients were HCV co-infected (Table 4.1). The median age at cART initiation did not differ amongst the three groups. The majority of the HBV co-infected patients were infected with HIV by homosexual contact; amongst the HCV co-infected group, injecting drug use was the most likely route of HIV transmission. In all groups, the majority of patients were of Dutch origin.

At the time of cART initiation, HBV and HCV co-infected patients had significantly lower CD4 cell counts and after 24 weeks of cART compared with the patients infected only with HIV at baseline and 24 weeks after cART initiation. Compared to the HIV mono-infected patients, HCV co-infected patients had lower HIV RNA levels at baseline. However, 24 weeks after cART initiation, HIV RNA levels were significantly higher amongst the HCV co-infected patients (Table 4.1).

The impact of HBV and HCV co-infection on the progression to AIDS and death.

A total of 34% of the patients included in this analysis progressed to AIDS after cART initiation. The time to an AIDS event was not associated with HBV and HCV (p-value log-rank test: 0.62).

In total, 867 (9%) of the patients died during follow-up. The probability of dying was not the same for all patients (p-value log rank test: <0.0001, Figure 4.1). Ten years after cART initiation the all-cause mortality was 34% amongst the HCV co-infected patients (confidence interval [CI]: (30-39), whereas amongst the HBV co-infected patients it was 19% (CI: 15-25). The lowest mortality rate was in the HIV mono-infected patients, with 11% (CI: 10-12) over a period of 10 years after the start of cART.

The hazard ratios for progression to AIDS and death are presented in Table 4.2. HBV and HCV co-infection was not associated with progression to AIDS after adjustment for differences in age, sex, risk group, ethnicity, baseline CD4-cell count, and HIV RNA levels. Also, the adjusted risk of dying was not significantly higher for patients with HBV co-infection. However, the adjusted hazard ratio for death was 1.86 (CI: 0.35-2.85) for those who were co-infected with HCV.

Discussion

We described all-cause mortality in HIV-HBV or HIV-HCV co-infected patients. The risk of dying was highest amongst HIV-infected patients co-infected with HCV, whereas HBV co-infection was not associated with an increased death risk.

Our finding of an increased death risk for HIV-HCV co-infected individuals confirms the results of a previous study in which an increased risk of dying was found amongst HIV-HCV co-infected patients. In this study, the risk of dying amongst HIV-HCV co-infected patients was higher when compared with patients infected only with HCV, suggesting that HIV alters the HCV disease progression. A study by Weber and colleagues[10, 11] showed similar results. However, the impact of HCV co-infection on the risk of dying remains controversial[75]. Comparing mortality rates amongst HIV-HCV co-infected patients with those amongst HIV mono-infected patients, we found a higher all-cause mortality rate amongst the HCV co-infected patients, even after adjustment for differences between patient groups. In addition, in chapter 3 of this report we showed that a higher proportion of deaths has been liver-related in recent years, implying that the higher risk of all-cause mortality can be explained by the increased risk of liver-related death in co-infected patients. However, because CD4 cell counts at both baseline and 24 weeks after treatment initiation were lower in

the HCV co-infected patients, the underlying immune deficiency caused by HIV may also play a role[11, 76].

In our cohort, HBV co-infection did not increase the risk of dying. The effect of treatment with lamivudine on progression of HBV disease might explain this, since 49% of the HBV co-infected patients in our cohort were treated with this HBV-suppressing drug during follow-up [77].

To provide HCV treatment in a timely manner to HCV co-infected patients, the identification of HCV co-infection is important. This and the higher mortality risk amongst HCV co-infected patients, which may be reduced by HCV treatment, stresses the need for an HCV screening policy for all HIV-infected patients. In the ATHENA observational cohort, which is a registry of all HIV-infected patients followed in one of the country's 25 HIV treatment centres, screening of these patients for both HCV and HBV is still incomplete. This may also have biased the results of our present analysis, since we expected an overrepresentation of patients with clinical signs of HBV or HCV co-infection.

Acknowledgments
We thank Joop Arends for his clinical input.

		Total	HIV+	HIV+/HBV+	HIV+/HCV+
Demographic characteristics					
Number (%)		9716	8519 (88)	544 (6)	653 (7)
Age (median, IQR)*		39(32-45)	38(32-46)	37(32-44)	38 (34-44)
Gender	Male	7506 (78)	6587 (77)	435(86)	484(74)
	Female	2174 (22)	1932 (23)	73(14)	169(26)
Transmission category:	Homosexual	5134 (53)	4715 (55)	301 (17)	113 (17)
	Heterosexual	3274 (34)	3032 (36)	155 (13)	82 (13)
	IDU**	492 (5)	112 (1)	10 (53)	348 (53)
	Other/unknown	816 (8)	660 (8)	42 (17)	110 (17)
Region of origin:	Netherlands	5366 (55)	4712 (55)	230 (45)	402 (62)
	Europe	818 (8)	636 (7)	46 (8)	143 (22)
	Sub-Saharan	1628 (17)	1464 (17)	131 (26)	31 (8)
	Africa	1233 (13)	1136 (13)	55 (10)	37 (6)
	Latin America/Caribbean	671 (7)	571(7)	46(8)	50 (8)
	Other				
Number of AIDS events (%)		3299 (34)	2817 (33)	190 (37)	277 (42)
Number of deaths (%)		867 (9)	634(7)	57 (11)	165 (25)
CD4 cell count (x10^6 cells/l) (median, IQR)		190(80-300)	200(80-301)	170 (60-290)	180 (90-290)
HIV RNA levels (log_{10} copies/ml) (median, IQR)		4.9 (4.3-5.3)	4.9 (4.4-5.3)	4.8 (4.2-5.2)	4.7 (4.1-5.3)
24 weeks after cART initation					
CD4 cell count (x10^6 cells/l) (median, IQR)		320 (190-470)	326(190-480)	280 (160-431)	270 (170-430)
HIV RNA levels (log_{10} copies/ml) (median, IQR)		1.7 (1.7-2.6)	1.8 (1.7-2.6)	1.9 (1.7-2.6)	2..3 (1.7-2.7)

* IQR: interquartile range ** IDU: injecting drug use

Table 4.1: Demographic and baseline characteristics of HIV-infected patients with and without hepatitis co-infection

Co-infection	AIDS		Death	
	Crude HR[b] (95% CI)[c]	Adjusted HR[a,b] (95% CI)[c]	Crude HR[b] (95% CI)[c]	Adjusted HR[a,b] (95% CI)[c]
HIV	1	1	1	1
HIV/HBV	1.07 (0.92-1.24)	1.06 (0.88-1.26)	1.45 (1.10-1.91)	1.40 (0.97-2.01)
HIV/HCV	1.23 (1.09-1.40)	1.10 (0.89-1.34)	3.25 (2.73-3.62)	1.86 (1.35-2.85)

[a] adjusted for age at combination antiretroviral therapy (cART) initiation, sex, risk group, ethnicity, baseline CD4 cell count and HIV RNA levels.

[b] HR: Hazard ratio

[c] CI: 95% confidence interval

Table 4.2: Risk of an AIDS-defining event and death amongst HIV-infected patients with and without hepatitis co-infection

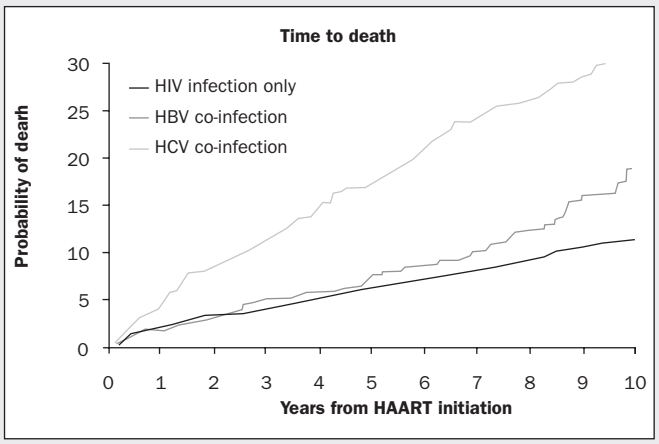


Figure 4.1: Probability of death during the first 10 years of combination retroviral therapy (cART) use, stratified by HBV and HCV co-infection

5. Pregnancies

Colette Smit

Introduction

Without intervention, the risk of mother-to-child transmission (MTCT) in HIV-infected pregnant women is 15 to 20% [78]. HIV-infected women with detectable HIV RNA levels have a high risk of vertical transmission [79]. From 1998 onward, HIV-infected pregnant women in the Netherlands have been treated with combination antiretroviral therapy (cART) to reduce viral load, especially at the point of delivery.

In addition, in January 2004, voluntary HIV-antibody testing of pregnant women on the basis of opting-out was introduced in the Netherlands [80]. Since then, a substantial proportion of women who were unaware that they were infected with HIV have been diagnosed while pregnant [81].

Here we report trends over a period of time in the number of HIV-infected women becoming pregnant, and we describe changes in demographic characteristics and antiretroviral treatment during pregnancy.

Methods

Study population

The study population consisted of 3447 HIV-infected women between the ages of 16 and 45 years, who were followed as part of the AIDS Therapy Evaluation in the Netherlands (ATHENA) observational cohort in one of the 25 HIV treatment centres in the Netherlands. All first and second pregnancies occurring after an HIV diagnosis in these women between 1998 and 2008 were included in the analyses.

Data for all registered HIV-infected pregnant women were collected according to the standard HIV monitoring protocol. In addition, pregnancy-related data were collected retrospectively for those women who became pregnant before 2006 and prospectively for those who have become pregnant since 2006. For the present study, data of pregnant women were included for analyses only in cases where the additional data was complete. A total of 1394 pregnancies were reported, and data on 936 pregnancies that occurred amongst 754 HIV-infected women between 1 January 1998 and 1 June 2008 were used for this purpose.

Statistical analysis

The number of pregnancies per calendar year was calculated per 1000 person-years (py). All women aged between 16 and 45 years were considered to be "at risk" for pregnancy, and this group of women was taken into account when calculating person-years, which were calculated from the time of the HIV diagnosis until the last visit, death, point when the patient was lost to follow-up, age of 45 years, or as of 1 January 2008. A Poisson regression model was used to test the effect of calendar year on the occurrence of pregnancy.

The chi-square test was used to look for differences in known HIV status before pregnancy between women of different geographic origin, and the Cochran-Armitage test for trend was used to evaluate changes over time.

The virologic trajectory during pregnancy was modelled using a random effect model. Its design allows for a random intercept for HIV RNA plasma levels per individual. We described time in weeks after the beginning of the pregnancy. When an HIV diagnosis was made during pregnancy, time was still described as weeks from the start of the pregnancy, but HIV RNA levels were missing for the first weeks of the pregnancy. Changes in HIV RNA levels were modelled piecewise. The slopes were allowed to change at weeks 20 and 28 of the pregnancy. If HIV RNA levels were below the quantification limit, we took half the quantification limit as the HIV RNA level. HIV RNA $\log_{10}$ values were used instead of absolute values.

Results

Out of the 3447 women who were being followed in the ATHENA observational cohort between 1998 and 2008, 754 became pregnant (22%). A total of 936 pregnancies occurred amongst these 754 women during that time. The median age during the first pregnancy was 29 years (interquartile range [IQR]: 24-33) and did not change over time. After being diagnosed with HIV, 150 women became pregnant for a second time; these women more often originated from sub-Saharan Africa, and 83% were already using cART before becoming pregnant for the second time. For 94% of the women, heterosexual contact was the route of HIV transmission. The region of origin for 456 (60%) women was sub-Saharan Africa, and 105 (14%) were Dutch (Table 5.1). The median age at the time of pregnancy varied between ethnic groups; women originating from the Netherlands were significantly older than non-Dutch women.

Incidence of pregnancy over time

Overall, the incidence of pregnancy amongst women aged between 16 and 45 years was 35 pregnancies per 1000 person-years (95% confidence interval [CI]: 32-38). The overall incidence and that according to geographic origin are presented in Figure 5.1. The overall incidence of pregnancy significantly increased from 27 per 1000 py in 1998 to 49 per 1000 py in 2005 and then decreased to 27 per 1000 py in 2006. The incidence was higher amongst women originating in sub-Saharan Africa, but declined from 66 per 1000 py in 1998 to 41 per 1000 py in 2006 ($p<0.001$). Amongst Dutch women, the number of pregnancies significantly increased from 15 per 1000 py in 1998 to 40 per 1000 py in 2005 and then strongly decreased to 10 per 1000 py in 2006.

HIV diagnosis during pregnancy

HIV was diagnosed during pregnancy in 52% of the women. The fraction of women unaware of their HIV status at the point of becoming pregnant did not significantly change over time. However, significant differences were found between women of different geographic origins. Dutch women were more often aware of being HIV-infected when they became pregnant (75%) than were non-Dutch women (50%) ($P<0.001$).

Treatment

Overall, 99% of the women were treated during their pregnancy; 272 (36%) received treatment after being diagnosed with HIV before their first pregnancy (Table 5.1), and 471 (62%) initiated cART during their first pregnancy. Of the women whose second pregnancy followed an HIV diagnosis, 83% were already receiving treatment. The proportion of women who were treated during pregnancy increased from 78% in 1998 to 100% in 2007 ($p<0.001$).

Between 1998 and 2006, a regimen of zidovudine/lamivudin/nelfinavir (AZT/3TC+NFV) was most commonly used during the first pregnancy. In 2007, a regimen containing lopinavir/ritonavir (LOP/r) became the most prescribed regimen. During the second pregnancy, a wider range of regimens was used (Table 5.2).

The piecewise modelled HIV RNA plasma levels stratified by time of cART initiation (before versus during the pregnancy) are presented in Figure 5.2. Women who had initiated cART before pregnancy had significantly lower HIV RNA levels at the start of the pregnancy than those who commenced cART for the first time during their pregnancy. 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 commenced cART during their pregnancy ($p<0.0001$). This decline was significantly steeper relative to women who initiated cART before pregnancy ($p<0.0001$). After week 28, the decrease in HIV RNA levels became more gradual, but remained stronger amongst women who initiated cART during the pregnancy.

At the time of delivery, 75% of the women who were pregnant for the first time and for whom an HIV RNA test result was available had an undetectable load, and 70% of the women who were pregnant for a second time had an undetectable load at the time of delivery. This percentage was lower amongst women who initiated cART during their pregnancy; for 50% of the women, the last HIV RNA measurement before delivery showed a detectable load, and this difference was significant ($p<0.0001$).

Mode of delivery

Of the 754 first pregnancies, data on the mode of delivery was available for 610 pregnancies. Of those 610, 350 babies were born vaginally, and 260 (42%) by caesarean section. The proportion of caesarean deliveries did not significantly change over time (P=0.06). Of the 480 women who underwent a caesarean section in their first pregnancy, 165 (34%) had an undetectable load at the time of delivery (median HIV RNA levels: 1.6 log copies/ml [IQR: 1.6-1.7]) Forty of the 350 women who delivered vaginally had a detectable viral load at time of delivery (11%), and their median HIV RNA level was 3.7 log copies/ml (IQR: 3.0-4.4). Amongst women having a second pregnancy after HIV diagnosis, 37% of the babies were delivered by caesarean section, and this difference was not significant.

Discussion

Almost one quarter of the HIV infected women who were followed in ATHENA between 1998 and 2008 became pregnant. Overall, the number of pregnancies increased until 2005 and then declined.

Although the number of pregnancies was highest amongst women originating from sub-Saharan Africa, the incidence decreased between 1998 and 2006. Women of Dutch origin were older at the time of pregnancy and more often aware of their HIV infection before pregnancy than were women of non-Dutch origin.

Since the inclusion of HIV in the national prenatal screening in 2004, the proportion of women unaware of their HIV infection has not increased, according to our data. This might be explained by the decrease in the number of pregnancies per 1000 py amongst women originating from sub-Saharan Africa and the increase in the number of pregnancies amongst Dutch women. Non-Dutch women were less likely to be diagnosed with HIV before their pregnancy, whereas Dutch women more often had a positive test result for HIV before becoming pregnant. In Dutch women, who were on average older than non-Dutch women, awareness of their HIV infection, combined with a better knowledge of cART's suppression of HIV, may have resulted in more carefully planned pregnancies [82].

Although almost all women included in these analyses received cART during pregnancy, 20% to 25% still had a detectable HIV RNA load during delivery. Except for the calendar year 2007, a regimen containing nelfinavir was most commonly used. The second most commonly used regimen was one that contained nevirapine. A recent study showed that a nevirapine-containing regimen was associated with a shorter time to undetectable HIV RNA load [83]. The risk of MTCT is very low amongst women who are effectively treated with cART [84]. A caesarean section is recommended when there is a detectable viral load. In this study, this recommendation was not always followed, since 11% of the women with a detectable load delivered vaginally and 34% of the women with an undetectable viral load underwent a caesarean section.

In conclusion, the overall increase in pregnancies is explained by a peak in pregnancies between 2003 and 2005. Although most pregnancies still occur amongst women originating from sub-Saharan Africa, the number of pregnancies in this group is decreasing. Dutch women are more often aware of their HIV infection, suggesting that effectively treated HIV-infected Dutch women are planning pregnancies with the knowledge that the MTCT risk is very low.

		Total	First pregnancy	Second pregnancy
Number(%)		936	754	150
Known HIV infection before pregnancy(%)			393 (52)	150 (100)
Age at start pregnancy	Years (Median [IQR])		29 (24-33)	30 (25-35)
Transmission route	- Heterosexual (%)		709 (94)	144 (96)
	- Other (%)		45 (6)	6 (4)
Region of origin	-Netherlands (%)		105 (14)	26 (17)
	-Sub-Saharan Africa (%)		456 (60)	102 (68)
	-Latin America/ Caribbean (%)		111 (15)	15 (10)
	- Other (%)		82 (11)	7 (5)
Start cART	- Before pregnancy (%)		272 (36)	124 (83)
	- During pregnancy (%)		471 (62)	23 (15)
	- No cART during treatment (%)		11 (1)	3 (2)
Pregnancy outcome	- Partus (%)		619 (82)	104 (69)
	- Abortion (%)		135 (18)	46 (31)
	- Unknown (%)			
Mode of delivery	- Vaginal delivery (%)		350 (46)	64 (43)
	- Caesarean delivery (%)		260 (34)	39 (26)
	- unknown (%)		144 (19)	47 (31)
Undetectable load at delivery	Yes		480 (64)	90 (60)
	No		156 (21)	38 (25)
	Unknown		118 (16)	22 (15)

IQR: Interquartile range; cART: combination antiretroviral therapy

Table 5.1: Demographic and clinical characteristics of HIV-infected pregnant women.

Total number of pregnant women included in this analysis	First pregnancy		Second pregnancy
	Most common regime:	n/known regimes (%)	n/known regimes (%)
1998	AZT/3TC + NFV	10/28(36)	
	AZT/3TC +NVP	2/28 (7)	
1999	AZT/3TC + NFV	15/38(39)	2/6(33)
	AZT/3TC + NVP	4/38(11)	
2000	AZT/3TC + NFV	35/71(49)	1/8(13)
	AZT/3TC + NVP	10/71(14)	2/8(25)
2001	AZT/3TC + NFV	30/77(39)	4/13(31)
	AZT/3TC + NVP	18/77(23)	1/13(8)
	AZT/3TC + LOP/r		4/13(31)
2002	AZT/3TC + NFV	32/85(38)	2/14(14)
	AZT/3TC + NVP	26/85(31)	1/14(7)
2003	AZT/3TC + NFV	51/121(42)	4/21(19)
	AZT/3TC + NVP	35/121(29)	5/21(24)
	AZT/3TC + LOP/r	8/121(7)	3/21(14)
2004	AZT/3TC + NFV	42/93(45)	6/29(21)
	AZT/3TC + NVP	16/93(17)	8/29(38)
	AZT/3TC + LOP/r	8/93(9)	3/29(10)
2005	AZT/3TC + NFV	29/6(42)	7/27(26)
	AZT/3TC + NVP	6/69(9)	6/27(22)
	AZT/3TC+ LOP/r	3/69(4)	1/27(4)
2006	AZT/3TC + NFV	22/69(32)	3/16(19)
	AZT/3TC +NVP	8/69(12)	2/16(13)
	AZT/3TC+ LOP/r	14/69(20)	3/16(19)
	AZT/3TC + SAQ+RTV	8/69(12)	3/16(19)
	SAQ+RTV		
2007	AZT/3TC + NFV	1/18(6)	
	AZT/3TC +NVP	3/18(17)	
	AZT/3TC+ LOP/r	10/18(56)	1/5(20)
	AZT/3TC + SAQ+RTV	1/5(20)	

AZT: Zidovudine, 3TC: Lamivudine, NVP: Nevirapine, Lop/r: Lopinavir/Ritonavir, NFV: Nelfinavir, IDV: Indinavir, SAQ: Saquinavir, RTV: Ritonavir

Table 5.2: Most commonly used treatment regimens during first pregnancy after HIV diagnosis between 1998 and 2007

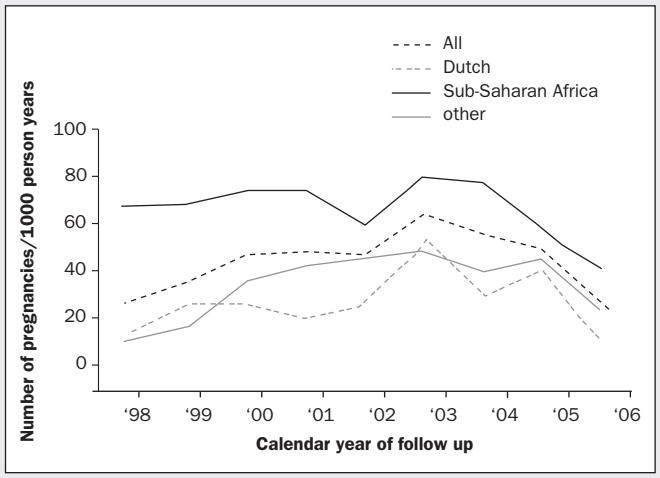


Figure 5.1: Number of pregnancies per 1000 person years amongst HIV-infected women, overall and according to region of origin

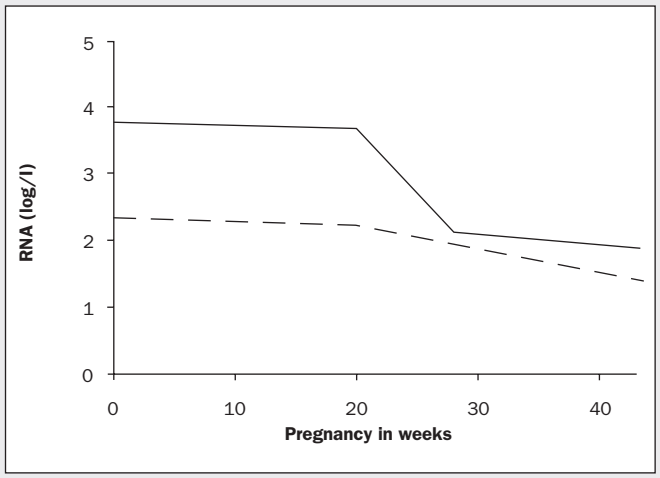


Figure 5.2: HIV RNA levels during pregnancy amongst women who initiated combination antiretroviral therapy (cART) before they became pregnant (dashed line) and amongst women who initiated cART during their pregnancy (solid line)

6. HIV-infected children in the Netherlands

Colette Smit

Introduction

In the Netherlands, most HIV-infected children are infected by mother-to-child transmission (MTCT)[85]. To prevent MTCT in the Netherlands during pregnancy and delivery, the national HIV pregnancy screening was implemented on 1 January 2004 [80, 81]. However, a large proportion of the HIV-infected children in the Netherlands were not born in the Netherlands[86] and were infected with HIV in their country of origin.

Although several studies have shown an improved prognosis for HIV-infected children who are treated with cART,a few studies on the immunologic and virologic responses to treatment have been conducted in HIV-infected children[87-89] [90].

Since 2004, HIV-infected children in the Netherlands have been registered and monitored by the HIV Monitoring Foundation. In this chapter, we report on the changes in demographic and clinical characteristics over time and on the immune and virologic response of HIV-infected children who are followed and treated in the Netherlands.

Study population and methods

All HIV-infected children in the Netherlands are followed and treated in one of the four specially designated paediatric HIV treatment centres. For this chapter we divided the population of HIV-infected children into two groups: those who were in follow-up at any time between 1 January 1997 and 1 June 2008, and those who are currently being followed and treated in one of these centres.

The term "children" in this chapter refers to all individuals younger than 18 years of age, unless otherwise noted in the text.

Total population of HIV-infected children and adolescents in follow-up between 1997 and 2008

All patients in the ATHENA observational database infected by MTCT or blood contact who were less than 18 years of age at the time of an HIV diagnosis that was made between 1 January 1997 and 1 June 2008 were included in these analyses. In patients where the mode of transmission was missing, we assumed that MTCT was most likely. Patients aged less than 18 years and infected by homosexual or heterosexual contact or injecting drug use (n=113) were not included.

In this analysis, patients diagnosed with HIV from ages 0 through 12 years are referred to as children and those from the age of 13 to the age of 18 years as adolescents.

Children currently in follow up

For this analysis, we selected all HIV-infected children who were younger than 18 years of age and alive and in follow-up as of 1 June 2008. Patients were considered to be in follow-up if data had been collected for them in the preceding year. Patients aged 0 through 12 years of age are referred to as children, and those aged from 13 to 18 years as adolescents.

Statistical analysis

In addition to the routinely collected data, information on the region of origin of the parents was available. Countries of origin were divided into six categories: the Netherlands, North America/Europe excluding the Netherlands, Latin America/the Caribbean, sub-Saharan Africa, South/Southeast Asia, and other. Lost to follow-up was defined as a last visit before 1 June 2007.

We described the demographic and clinical characteristics of the HIV-infected children and adolescents. The first combination antiretroviral therapy (cART) regimen for

children and adolescents ever in follow up is reported, as are the current regimens for those currently in follow up. Since CD4 cell counts are age-related, we subdivided the children into two groups; children who were 2 years of age or less and those who were 3 years up to 13 years [91].

Changes in the absolute CD4 cell counts and percentage and in HIV RNA levels after initiation of cART were assessed with a random effects model, which allowed for a random intercept. The slope was allowed to change 12 weeks after cART initiation. Immunologic and virologic responses were compared between young children (aged ≤2 years) and older children (aged 3 to 13 years). Adolescents were not included in the model, since numbers were too small.

To measure the impact of the national HIV pregnancy screening, changes over time in the number of HIV-infected children who were infected by MTCT and born in the Netherlands were reported and stratified by calendar year.

Results

Demographic characteristics of the total population of HIV-infected children and adolescents

The demographic and clinical characteristics of those diagnosed with HIV as children (0 to 13 years) or adolescents (13 to 18 years) participating in the ATHENA cohort are presented in Table 6.1a. Between 1 January 1997 and 1 June 2008, 139 children and 17 adolescents were diagnosed with HIV. The main route of infection was MTCT for children, and for adolescents it was blood contact or unknown. Most of the children with an unknown route of transmission originated from sub-Saharan Africa. The majority of the children were born in the Netherlands, and most of the adolescents originated from sub-Saharan Africa. Of those born in the Netherlands, both parents of only 7 (5%) children were born in the Netherlands; 93 (67%) of this group of children had at least one parent originating from sub-Saharan Africa. Most children and adolescents were diagnosed in 2000 or later. None of the children died between 1 January 1997 and 1 June 2008. However, 2 adolescents died in this time period. All other children and adolescents who reached the age of 18 years were still alive on 1 June 2008.

Changes in the number of HIV-infected children who were infected by MTCT and born in the Netherlands are shown in Figure 6.1. In the year 2000, 15 children were born with HIV in the Netherlands; from that year on, vertical transmission decreased, reaching 0 in 2006 and 2007. In 2004, 2 children were born infected with HIV, and in 2005, 1 HIV-infected child was born.

Clinical characteristics of the total population of HIV infected children and adolescents

cART was administered to 88% of the children and 71% of the adolescents (Table 6.1b). The four most common first regimens amongst children were: abacavir, lamivudine and efavirenz (ABC+3TC+EFV), abacavir, lamuvidine and lopanivir, ritonavir-boosted (ABC+3TC+LOP/r), zidovudine, lamivudine, efavirenz (AZT+3TC+EFV), and didanosine, lamuvidine, efavirenz (ddi+3TC+EFV). The two most frequently used first regimens amongst adolescents were: zidovudine, lamuvidine and lopanivir, ritonavir-boosted (AZT+3TC+LOP/r) and zidovudine, lamuvidine and nevirapine (AZT+3TC+NVP).

The median CD4 cell counts at the start of cART were 1074 x 10^6 cells/L (interquartile range [IQR]:461-1715) for young children aged 2 years or less, and the counts increased to 1745 x 10^6 cells/L (IQR:1090-2515) at 24 weeks after the start of cART. Older children (aged 3 through 13 years) had lower CD4 cell counts (341 x 10^6 cells/L (IQR: 120-600), and CD4 cell counts increased to 580 x 10^6 cells/L (IQR: 395-800) 24 weeks after cART initiation. Adolescents had lower CD4 cell counts than both young and older children (Table 6.1b).

Amongst young children, HIV RNA levels decreased from 5.8 $\log_{10}$/ml (IQR: 5.3-6.1) at baseline to 2.6 $\log_{10}$/ml

(IQR: 2.0-2.9) 24 weeks after cART initiation. Amongst the older children, HIV RNA levels were somewhat lower and decreased from 4.9 log_{10}/ml (IQR: 4.5-5.6) from baseline to 1.7 log_{10}/ml (IQR:1.7-2.6) at 24 weeks of treatment. HIV RNA levels amongst adolescents decreased from 5 log_{10}/ml (IQR: 4.8-5.3) at baseline to 1.7 log_{10}/ml (IQR: 1.7-1.9) 24 weeks after treatment initiation (Table 6.1b).

Immune response amongst total population of HIV-infected children

The changes in absolute CD4 cell counts after cART initiation among children are shown in Figure 6.2a. The immune response is stratified by age at cART initiation. Young children (aged <2 years) had significantly higher absolute CD4 cell counts compared to the older children (aged 2 through 13 years) ($p<0.0001$). In the first 12 weeks of cART, a significant increase in CD4 cell counts was observed in both young and older children ($p<0.0001$). This increase was significantly more rapid amongst the young children ($p<0.0001$). In both groups, CD4 cell counts continued to increase significantly more than 12 weeks after cART initiation.

The changes in CD4 cell percentages among young and older children from the time they commenced cART were also modelled piecewise and presented in Figure 6.2b. Older children had significantly higher CD4 cell percentages at baseline ($p<0.0001$). In the first 12 weeks after cART initiation, the CD4 cell percentages increased in both groups, but the increase was significantly more rapid amongst the older children. From 12 weeks onward, CD4 cell percentages continued to increase amongst only the older children. During the first year on cART, CD4 cell percentages remained higher amongst the older children compared to those in the young children.

Virologic response amongst total population of HIV-infected children

The virologic response after cART initiation was modelled for the young and older children (Figure 6.2c). The young children (aged <2 years) had significantly higher HIV RNA levels at the time of cART initiation compared to older children (aged from 3 up to 13 years) ($p<0.0001$). During the first 12 weeks of treatment a significant decrease in viral load was observed in both groups. More than 12 weeks after cART initiation, the decrease in viral load continued in the group of older children ($p<0.0001$), but stabilised amongst the young children.

Children and adolescents currently in follow up

We described the demographic and clinical characteristics of HIV-infected children and adolescents who were in follow-up as of 1 June 2008. As of 1 June 2008, 84 children and 30 adolescents were alive and in follow-up in the Netherlands. The majority of children and adolescents currently in follow-up were infected through MTCT (Table 6.2a).

The median CD4 cell counts for young children were 1230 x 10^6 cells/L(IQR: 890-1660), and it was lower amongst older children 740 x 10^6 cells/L (IQR: 585-950) and adolescents (Table 6.2b).

As of 1 June 2008, the two most frequently used regimens amongst children and adolescents were: abacavir, lamivudine and efavirenz (ABC+3TC+EFV) and abacavir, lamuvidine and lopanivir, ritonavir-boosted (ABC+ 3TC+LOP/r).

Discussion

Most HIV-infected children in the Netherlands were infected by MTCT. Whilst a majority were born in the Netherlands, only a few had both parents originating from the Netherlands, and most had at least one parent from sub-Saharan Africa. Most children and adolescents received cART treatment. Although young children had higher absolute CD4 cell counts at treatment initiation, older children had higher CD4 cell percentages and a more rapid increase in CD4 cell percentages.

Age-related variation in the absolute number of CD4 cell counts has been described previously in non-HIV-

infected children [92], and CD4 cell counts decline with increasing age [92], which explains the higher CD4 cell counts amongst the young HIV-infected children. The CD4 cell percentages are probably a better marker for immune response. Also, the virologic response was stronger amongst the older children, which might be explained by a better adherence. Suppression of HIV RNA levels is needed for the recovery of thymic function and, thus, for the return of CD4 cells [93]. A higher CD4 percentage at treatment initiation and during the first year of treatment is probably a result of the higher virologic suppression observed in the older children.

The rate of MTCT in the Netherlands has strongly declined over time. Since 2004, 3 HIV-infected children were born in the Netherlands. This decline is likely to be a result of the HIV testing scheme for pregnant women, which was introduced in 2004. The mothers of the 2 children who were born with HIV in 2004 were not included in the national HIV screening of pregnant women, since they became pregnant before 1 January 2004. The mother of the HIV-positive child born in 2005 had a negative test in the national HIV screening and was probably infected during her pregnancy.

It is to be expected that the number of children infected with HIV in the Netherlands by MTCT will stay close to zero as a result of the ongoing HIV testing policy of pregnant women. With the improved formulation, children can be effectively treated with cART, and most of the children will reach the age of 18 years. However, 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.

Demographic Characteristics at diagnosis	Children N (%)	Adolescents N (%)
Total	139	17
Gender		
- boy	78 (56)	13(76)
- girl	61(44)	4(24)
Route of transmission:		
- MTCT	125(90)	1(6)
- Blood contact	4(3)	6(35)
- Unknown	9(6)	9(53)
Region of origin:		
- the Netherlands	77(55)	
- Europe	3(2)	1(6)
- Latin America/Caribbean	6(4)	1(6)
- Sub-Saharan Africa	48(34)	15(88)
- South/Southeast Asia	2(1)	
- -Other	3(2)	-
Region of parents:		-
- both the Netherlands	7(5)	
- one or both sub-Saharan Africa	93(67)	
- one or both other region	39(28)	17(100)
Year at HIV diagnosis		
- <1998	13(9)	1(6)
- 1998-2000	22(16)	4(24)
- 2000-2003	49(35)	9(53)
- >2003	54(39)	3(18)
- missing	1(1)	-
Age at diagnosis		
≤ 2 years of age	63(45)	
> 2 years of age	76(55)	17(100)
Lost to follow up	35(25)	8(47)
Deaths	0(0)	2(12)

IQR, interquartile range; MTCT, mother-to-child transmission.

Table 6.1a: Demographic characteristics of HIV-1-infected children (age 0- to 13 years at time of HIV diagnosis) and adolescents (age 13 to 18 years at time of HIV diagnosis) ever in follow-up between 1 January 1997 and 1 June 2008 in the ATHENA observational cohort

Clinical Characteristics at cART initiation	Children N (%)	Adolescents N (%)
cART use	122(88)	12(71)
Baseline CD4 cell counts		
($x10^6$ cells/l) (median, IQR)		
≤ 2 years of age	1074 (461-1715)	
> 2 years of age	341 (120-600)	170 (11-232)
Baseline HIV RNA (log_{10}/ml)		
(median, IQR)		
≤ 2 years of age	5.8(5.3-6.1)	
> 2 years of age	4.9 (4.5-5.6)	5 (4.8-5.3)
Clinical characteristics at 24 weeks after cART initiation		
CD4 cell counts at T1		
($x10^6$ cells/l) (median, IQR)		
≤ 2 years of age	1745 (1090-2515)	
> 2 years of age	580 (395-800)	330 (201-449)
HIV RNA at T1 (log_{10}/ml)		
(median, IQR)		
≤ 2 years of age	2.6 (2.0-2.9)	1.7 (1.7-1.9)
> 2 years of age	1.7 (1.7-2.6)	
Undetectable HIV RNA levels at T1		
≤ 2 years of age	19(30)	
> 2 years of age	47(62)	8(47)

Baseline: start of combination antiretroviral therapy (cART);
t1, 24 weeks after start cART

Table 6.1b: Clinical characteristics of HIV-1-infected children (age 0 to 13 years at time of HIV diagnosis) and adolescents (age 13 to 18 years at time of HIV diagnosis) ever in follow-up between 1 January 1997 and 1 June 2008 in the ATHENA observational cohort

Demographic Characteristics	Children	Adolescents
	N (%)	N (%)
Total	84	30
Gender		
- boy	45(54)	14(47)
- girl	39(46)	16(53)
Route of transmission:		
- MTCT	80(95)	25(83)
- Blood contact	0(0)	1(3)
- Unknown	4(5)	4(13)
Region of origin:		
- the Netherlands	50(59)	14(47)
- Europe	3(4)	1(3)
- Latin America/Caribbean	2(2)	2(7)
- Sub-Saharan Africa	27(32)	12(40)
- South/Southeast Asia	2(2)	1(3)
- -Other	0(0)	0(0)
Region of parents:		
- both the Netherlands	5(6)	1(3)
- one or both sub-Saharan Africa	56(67)	20(67)
- one or both other region		
Year at HIV diagnosis	23(27)	9(30)
- <1998	7(8)	18(60)
- 1998-2000	10(12)	3(10)
- 2000-2003	30(36)	3(10)
- >2003	36(	5(17)
- missing	43)	1(3)
Age at diagnosis		
≤ 2 years of age	47(56)	10(33)
> 2 years of age	37(44)	20(67)

IQR, interquartile range; MTCT, mother-to-child transmission.

Table 6.2a: Demographic characteristics of HIV-1-infected children (age 0 to 13 years) and adolescents (age 13 to 18 years) in follow-up as of 1 June 2008

Clinical Characteristics at 1 June 2008	Children N (%)	Adolescents N (%)
cART use	73(87)	28(93)
Current CD4 cell counts		
($x10^6$ cells/l) (median, IQR)**		
≤ 2 years of age	1230 (890-1660)	
> 2 years of age	740 (585-950)	620 (471-930)
Current undetectable viral load		
≤ 2 years of age	40(85)	
> 2 years of age	25(57)	26(87)
Current HIV RNA		
(log_{10}/ml) (median, IQR)**		
≤ 2 years of age	1.4 (1.3-1.4)	
> 2 years of age	1.4 (1.3-3.8)	1.4 (1.3-1.4)

IQR, interquartile range.

Table 6.2b: Clinical characteristics of HIV-1-infected children (age 0 to 13 years) and adolescents (age 13 to 18 years) in follow-up as of 1 June 2008

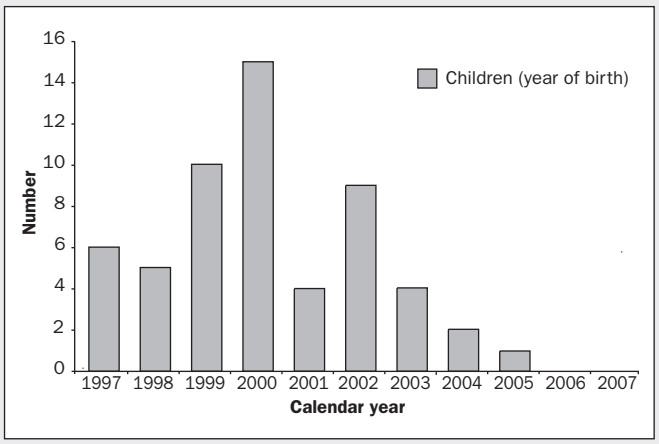


Figure 6.1: Number of HIV-infected children born in the Netherlands, according to year of birth.

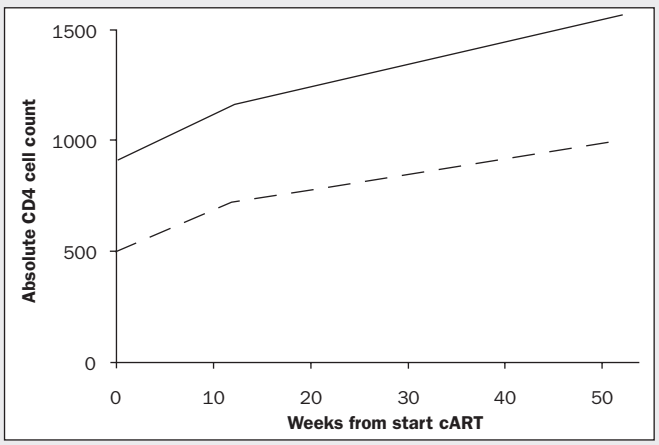


Figure 6.2a: Absolute CD4 cell counts amongst HIV-infected children, since the start of combination antiretroviral therapy (cART). (Solid line: young children (≤2 years of age) at time of cART initiation. Dashed line: Older children (>2 years to 13 years of age) at time of cART initiation)

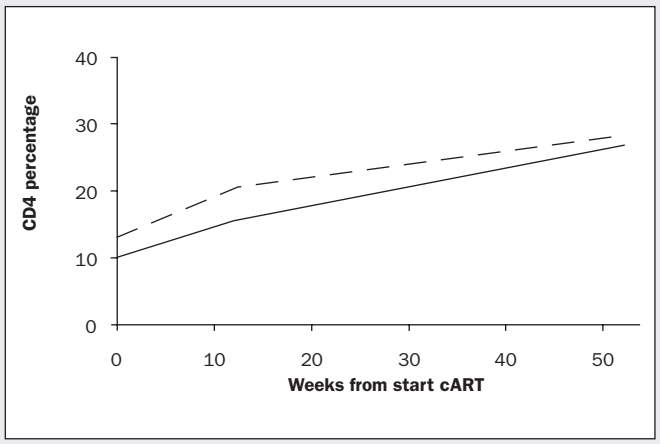


Figure 6.2b: CD4 cell percentages amongst HIV-infected children, since the start of combination antiretroviral therapy (cART). (Solid line: young children (≤2 years of age) at time of cART initiation. Dashed line: Older children (>2 years to 13 years of age) at time of cART initiation)

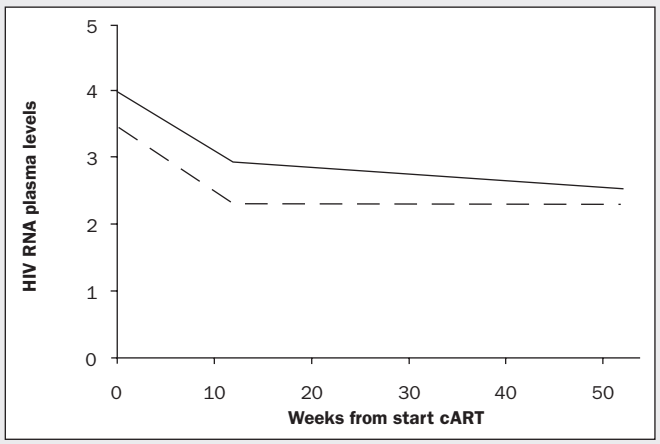


Figure 6.2c: HIV RNA levels amongst HIV-infected children, since the start of combination antiretroviral therapy (cART). (Solid line: young children (≤2 years of age) at time of cART initiation. Dashed line: Older children (>2 years to 13 years of age) at time of cART initiation)

7. Response to cART

Luuk Gras

Introduction

Progression to AIDS and death amongst HIV-infected patients has substantially slowed since the introduction of combination antiretroviral therapy (cART)[12-14], and a large proportion of patients is currently older than 50 years of age. However, even though the life expectancy of HIV-infected patients has dramatically improved, it is still lower than that of the general population. Life expectancy further improves when cART is started in a timely manner[15], and the short-term response to first-line cART is strongly prognostic for disease progression[16].

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[94]. Patients may suffer from adverse events and clinical manifestations owing to the toxic effect of antiviral drugs on cells and cell metabolism[95, 96]. Adverse events and toxicity may result in poorer patient adherence or even discontinuation of treatment, causing suboptimal drug levels and possibly treatment failure[97, 98] and resistance[99]. Serious adverse events in the aging 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[32, 34-36, 100, 101]. 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[102].

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, as well as changes in the incidence of several serious adverse events with older age.

Methods

HIV-1-infected patients who started cART between July 1996 and December 2007, were older than 16 years, and were not pregnant at the start of cART were selected from the ATHENA observational cohort. cART was defined as a combination of at least three antiretroviral drugs from at least two drug classes, or a combination of three nucleoside reverse transcriptase inhibitors (NRTIs) including abacavir or tenofovir.

For each patient, the CD4 count and plasma viral load at every 24 weeks (+/- 12 weeks) after the first start of cART was selected. The proportion of patients with a plasma viral load <50, 50-500, 500-1000, and ≥1000 copies/ml was calculated and compared by the Mann-Whitney U test according to year of starting cART, time after starting cART, age at the start of cART, continuous use of cART (a therapy interruption of <2 weeks was allowed), speed of initial suppression of plasma HIV RNA concentration <50 copies/ml, and region of origin. Median CD4 count and interquartile ranges (IQR) were calculated at every time point and separately for patients <50 and ≥50 years of age at the start of cART, for those from Western Europe or North America and those originating from other regions, and for those who had a suppressed plasma viral load of <50 copies/ml within 9 months after first starting cART (first of 2 consecutive measurements). In the last subgroup, plasma viral load was censored at the first of

2 consecutive measurements of HIV RNA >50 copies/ml after the initial suppression of <50 copies/ml.

We calculated the incidence of toxicity-related changes in the regimen during the first 3 years after the first start of cART according to age during follow-up (<30, 30-40, 40-50, 50-60 and ≥60 years), calendar year of starting cART (1996-97, 98-99, 2000-01, 02-03, 04-05 and 06-07) and time after starting cART (0-3, 3-6, 6-12, 12-24, and 24-36 months). For each period, the number of toxicity-driven changes in the cART regimen and the person-years on cART (PYcART) were calculated. Thus, more than one toxicity-driven regimen per patient per period 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 last. The incidence of toxicity-driven changes in regimen was calculated as the total number of these changes divided by the total PYcART in a time period, calendar year, or age group. In addition to adverse events leading to a change in regimen, certain serious adverse events or co-morbidities are routinely collected, regardless of whether an occurrence of one of these events leads to a cessation of one of the drugs in the regimen (Chapter 1). The incidence of each first adverse event after baseline (hepatic steatosis, lipodistrophy [since 2002 fat accumulation and fat loss have been collected separately], myocardial infarction, osteoporosis, diabetes mellitus, cerebrovascular accident [CVA], rash, non-AIDS malignancy, hypertension, peripheral neuropathy, renal insufficiency, and sexual problems [loss of libido and erectile dysfunction]) was calculated according to age and calendar year. Baseline was defined as the date of first cART initiation or the date of start of routine collection of the adverse event under question, whichever came last. Patients who had the adverse event in question prior to baseline were excluded from analysis. Reported 95% confidence intervals (CI) are based on the Poisson distribution.

Results

Between 1 July 1996 and 31 December 2007, 10,135 patients started cART. Of those, 1976 patients were pre-treated, and 8159 were antiretroviral therapy naïve at the first start of cART. Amongst the naïve patients, 4366 started cART prior to 2003, 2949 between 2003 and 2006 and 844 in 2007 (Table 7.1). 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 patients starting cART in 2007 compared to those starting between 2003 and 2006. Also, the median CD4 count at the start of cART was higher in patients starting cART in 2007 (210 vs. 180 cells/mm^3, p<0.0001). Of patients starting cART in 2007, 45.4% did so with a CD4 count of less than 200 cells/mm^3. Amongst patients aged 50 years or more, 55.5% had <200 CD4 cells/mm^3 at the start of cART compared to 42.8% of those <50 years (p=0.006). Of patients from the Netherlands, 43.2% started cART with a level below 200 CD4 cells/mm^3 compared to 49.4% of patients from sub-Saharan Africa (p=0.26).

Virological response

The short-term virological response (36 weeks) after first starting cART is shown in Figure 7.1. 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. The percentage of naïve patients with a plasma viral load less than 1000 copies/ml 36 weeks after starting cART increased from 80% in 1996 to 95% in 2007 (p<0.0001). Since 2002, when assays with a lower detection limit of 50 copies/ml were routinely used, the percentage of patients with less than 50 copies/ml has remained similar, with 80% in 2002 and 83% in 2007 (p=0.20). 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).

Figure 7.2 and Table 7.2 show the viral load of naïve patients starting cART in or after 2000 for every 24 weeks of follow-up. Only results of assays with a lower detection limit of 50 copies/ml are shown. From week 36 on, there was a stable percentage of patients with a plasma viral load <50 copies/ml of about 85% (left plot). This percentage was 94% for those continuously on cART (right plot). The percentage of patients with plasma viral load >500 copies/ml fluctuated between 2.7% at week 48 and 1.7% at week 192.

A higher percentage of patients starting between 2004 and 2007 had <50 copies/ml after 48 weeks than those who started in 2000-2003 (Table 7.2). The difference in the percentage of patients with a plasma HIV RNA concentration of <50 copies/ml fluctuated between 6% after 48 weeks and 2% after 192 weeks. The number of patients with follow-up after week 192 was too small to show. The percentage of patients with <50 copies/ml did not depend on time from start of cART to initial suppression of plasma HIV RNA concentration to <50 copies/ml as Table 7.2 shows. The percentage of patients with HIV RNA <50 copies/ml after starting cART fluctuated in the range of 88 to 89% for those with an initial suppression within 24 weeks as well as in those with a suppression between 24 and 48 weeks.

At week 48, a higher percentage of patients aged ≥50 years at the start of cART (86%) reached a level <50 HIV RNA copies/ml than did those <50 years (83%, p=0.02). The percentage of patients ≥50 years with <50 copies/ml increased further to 94% at week 240. The percentage of patients <50 years with <50 copies/ml between weeks 48 and 240 fluctuated between 83% and 86%.

Finally, at week 36, the percentage of patients from Western Europe or North America with <50 copies/ml was 85% compared with 81% for those originating elsewhere (p=0.003).

Immunologic response

Out of 10,135 patients, a CD4 count at the start of cART was unavailable for 1139 (11.2%), and they were excluded from further analyses. Overall, in antiretroviral therapy-naïve patients the median CD4 count after starting cART increased from 190 cells/mm^3 (IQR 80-290) to 320 (130-460) after 24 weeks, 360 (230-520) at 48 weeks, 460 (310-640) at 144 weeks, and 510 (360-710) at 240 weeks. Pre-treated patients started cART at a higher median CD4 count of 200 cells/mm^3 (90-340), but in comparison, counts in naïve patients were lower thereafter: 320 CD4 cells/mm^3 (190-490) at 48 weeks; 400 (240-600) at 144 weeks; and 450 (280-650) at 240 weeks. Figure 7.3 shows the increase in median CD4 count for pre-treated and naïve patients after starting cART, according to the count at the start of cART (<50, 50-200, 200-350, 350-500 and ≥500 cells/mm^3). Median increases in CD4 counts after 240 weeks of cART varied between 350 and 270 cells/mm^3 for the four pre-cART CD4 cell count strata below 500 cells/mm^3, whilst increases were smaller (160 cells/mm^3) for patients in the ≥500 cells/mm^3 stratum (Wilcoxon test, p=0.0001). Median increases in CD4 count in pre-treated patients were lower than those in naïve patients in all baseline CD4 count strata.

Figure 7.4 shows CD4 count changes for all naïve patients after starting cART compared to the changes for only those with a continuous suppression of viral load <50 copies/ml. After 240 weeks of continuous suppression, the median CD4 count in patients with a baseline CD4 count of <50, 50-200, 200-350, 350-500 and ≥500 cells/mm^3 was 360 (IQR 280-500), 460 (350-620), 610 (460-750), 700 (550-860), and 910 (730-1160) cells/mm^3. Amongst 1254 patients with viral suppression <50 copies/ml within 24 weeks of starting cART and continuous suppression <50 copies/ml thereafter for whom at least 3 CD4 cell counts were available, 168 patients (13%) never had a CD4 count ≥200 cells/mm^3 during the first year after starting cART. Amongst 406 of the 1254 patients with at least 3 years of follow-up available, 82 patients (20%) never had a CD4 count ≥350 cells/mm^3 during 3 years of virologically successful cART.

The median CD4 count increased less after 5 years of successful cART in naïve patients aged ≥50 than in those <50 years (300 cells/mm^3, (IQR 180-430) vs. 360 (240-550), p<0.0001). The difference in the increase of CD4 count between patients <50 and ≥50 years after 240 weeks on cART was greatest for those with a CD4 count at the start of cART <50 cells/mm^3 (400 [300-550] vs. 260 [200-350] cells/mm^3, respectively) (p<0.0001, Figure 7.5). Because of small numbers, patients with 350-500 and ≥500 CD4 cells/mm^3 at the start of cART were grouped together.

Incidence of toxicity-driven regimen change during the first 3 years after starting cART

During the first 3 years after starting cART, patients were followed for a total of 25,421 person-years; of that number, 23,564 person-years (93.8%) included cART. The overall incidence of toxicity-driven regimen changes was 23.6 (95% CI, 22.9-24.2) per 100 PYcART. Patients could change the regimen more than once in a period. During follow-up, 6511 of the patients (64.1%) 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 (27.2, 95% CI, 25.7-28.7) per 100 PYcART compared to that in naïve patients (22.6, 21.9-23.3, difference p<0.0001); in men, it was 22.4 (21.8-23.1) per 100 PYcART, and 28.1 (26.6-29.7) in women (p<0.0001). Overall, the incidence was highest (58.5 per 100 PYcART) during the first 3 months after starting cART; it declined to 27.0 per 100 PYcART between 3 and 6 months, 20.7 per 100 PYcART between 6 and 12 months, and 14.9 per 100 PYcART between 24 and 36 months (p<0.0001).

Table 7.3 shows the incidence of toxicity-related therapy changes for men and women according to age and for pre-treated and naïve patients at the start of cART. The incidence of such changes was higher for naïve female patients aged <40 years and ≥50 years (27.5 and 37.9 per 100 PYcART, respectively) compared to 22.8 per 100 PYcART for female patients aged 40 to 50 years. In contrast, the incidence among naïve male patients did not seem to increase with age (linear trend p=0.13).
Since the incidence of toxicity-driven therapy changes strongly depends on the timing after starting cART, we restricted the follow-up to 1 year in the comparison of different calendar years of starting cART. Figure 7.6 shows a decreasing trend in the incidence of toxicity-driven therapy changes among naïve women starting cART in a later calendar year (p=0.002). The trend among naïve men is less clear cut, but the incidence in those starting prior to 2002 was 34.3 per 100 PYcART (95% CI 32.2-36.5) compared to 29.2 (27.3-31.2) in males starting between 2002 and 2006 (p=0.0007).

Incidence of routinely collected co-morbidity and adverse events

Table 7.3 shows the incidence of routinely collected adverse events and co-morbidity for male and female patients and for pre-treated and naïve patients. All routinely collected adverse events, except rash, clearly showed an increasing incidence with older age. In men, the incidence of rash was higher in younger patients compared to older ones (for male patients <30 years 17.1 per 1000 PY compared to 8.2 for those 50-60 years, p=0.0001). The incidence of rash in women was increased only in the group aged 50 to 60 years. The incidence of rash and peripheral neuropathy declined over the years, and by 2006-2008, the incidence of rash was 8.9 (7.5-10.5) per 100 PY and peripheral neuropathy 6.4 (5.3-7.8) (Figure 7.7). The incidence of peripheral neuropathy increased with age in both men and women.

Of all routinely collected adverse events, lipodistrophy was by far the most frequently recorded. The distinction between peripheral fat loss and central fat accumulation

has been made in the data collection only since 2000. Figure 7.8 shows the trend in lipodistrophy (either central fat accumulation or peripheral fat loss). After a high peak in 1998-2001, the incidence of lipodistrophy has declined to 18.5/1000 PY (95% CI 16.3-20.8) for peripheral fat loss and 12.4 (10.8-14.3) for central fat accumulation in 2006-2008 and was lowest in patients <30 years of age (Table 7.4). After lipodistrophy, the most frequent adverse events were hypertension (23.5, 95% CI 17.9-30.4 per 1000 PY) and non-AIDS malignancies (18.1, 95% CI 13.3-24.0 in male patients aged ≥60 years). Amongst female patients, the most frequent adverse events besides lipodistrophy were hypertension and diabetes mellitus. However, because the number of female patients ≥60 years was small, the 95% CI's were wide.

There was also an increase over calendar time in the incidence of hypertension and non-AIDS malignancies after starting cART. The incidence of hypertension in all patients increased from 8.2 in 2000-2001 to 14.9 in 2006-2008 ($p<0.0001$) whilst the incidence of non-AIDS malignancies increased from 2.0 in 2000-2001 to 6.7 per 1000 PY in 2004-2008 ($p<0.0001$). The incidence of osteoporosis, renal insufficiency, and hepatic steatosis has also showed an increasing trend in more recent calendar years (Figure 7.9).

Discussion

In this chapter, we studied plasma viral load, CD4 count recovery and incidence of toxicity-driven therapy changes, and certain serious adverse events after the first start of cART. Over time, cART regimens were less often changed because of toxicity, and a higher percentage of patients managed to suppress plasma HIV RNA concentration to <50 copies/ml. These results indicate improved HIV care in more recent calendar years, e.g., the introduction of new more virologically effective and less toxic drugs with a low pill burden[103], therapeutic drug monitoring[104], and genotypic resistance-guided HIV treatment decisions for patients with >1000 copies/ml[105]. If patients stayed continuously on cART, the percentage of patients with a plasma viral load <50 copies/ml was high (approximately 93%), whilst the percentage of patients with a load ≥500 copies/ml after more than 48 weeks of cART was low and fluctuated between 1% and 2% of patients on cART. Keeping HIV RNA levels at low levels is important, since levels higher than 1000 copies/ml are strongly associated with less restoration of CD4 cells in patients on uninterrupted cART[66, 106], selection of resistant virus strains[107, 108], and progression of disease[109, 110]. The evidence from other studies that patients with lower viral loads are less likely to transmit HIV infection to others[3, 111], together with the low percentage of patients on cART with high level viraemia in this chapter, may partly explain the low level of resistant transmitted virus as reported in Chapter 8. Furthermore, there did not seem to be an effect of the speed of initial HIV RNA suppression <50 copies/ml on subsequent plasma HIV RNA levels. The percentage of patients ≥50 years who maintained viral suppression <50 copies/ml was higher compared to patients <50 years, indicating that older patients are more adherent to cART, as has been shown by other studies[112].

Toxicity is the most frequently registered reason for interrupting or stopping treatment with certain antiretroviral drugs in a cART regimen[6]. The incidence of toxicity-driven changes was highest in the first 3 months after the start of cART and was significantly less amongst patients starting cART between 2002 and 2007 compared to those starting before 2002. As in other studies[17, 18, 113], women were more likely to discontinue antiretroviral drugs because of toxicity than were men. Although the incidence of toxicity-driven therapy changes did not seem to strongly depend on age in naïve male and female patients, the incidence of all routinely collected co-morbidities and adverse events, except rash, increased with older age.

The increasing number of older patients living with HIV-1 might explain the increasing trend with more recent calendar years of co-morbidities such as non-AIDS malignancy, osteoporosis, renal insufficiency, hepatic steatosis, and the fatal non-AIDS events described in Chapter 3. 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 when adjusted for age and other risk factors[32, 34-36, 100, 101]. The incidence of myocardial infaction in this chapter is also higher in comparison to that found in the general population living in the Netherlands[114]. This has led to the hypothesis that HIV is associated with an accelerated aging process, further supported by a study showing an increased frailty amongst HIV-infected patients compared to uninfected individuals[115]. Frailty has not been clearly defined, but it describes a state of increased functional impairment (such as exhaustion, low activity level, weakness, slowed walking speed and weight loss)[116] associated with an increased risk of morbidity and mortality. Chronic activation of inflammatory pathways through HIV infection and drug toxicities may lead to increased levels of D-dimer (anti-coagulant marker) and IL-6 (inflammation marker), which are associated with frailty in older HIV-negative people[117, 118] and with cardiovascular disease[119]. Finally, the incidence of serious fatal and some non-fatal non-AIDS events is higher when CD4 cell counts are lower. 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.

In cases where cART was started when CD4 counts were still high (≥350 cells/mm^3), CD4 counts after 5 years of continuous cART approximated the levels seen in an uninfected population. Normal CD4 levels were reported to be 1050, 840, and 800 cells/mm^3 for women, heterosexual men, and MSM, respectively[120], with likely geographic variation in normal CD4 ranges[121]. Patients ≥50 years of age experienced smaller increases in CD4 count, as shown previously and by other studies[66, 122]. This could not be attributed to differences in adherence. A new finding, to our knowledge, that needs further investigation is that the difference in improvement in CD4 cell count between patients ≥50 years and <50 years with <50 CD4 cells/mm^3 at the start of cART was much greater than at higher CD4 cell counts. Normal CD4 ranges in older individuals are reported to decrease with older age[123-125], possibly due to reduced thymic output[93]. Therefore, older individuals might benefit most from the recent change in treatment guidelines that recommends starting antiretroviral therapy before CD4 cell numbers have dropped below 350 cells/mm^3. To achieve this, it is necessary to diagnose HIV infection at an earlier stage of infection.

In conclusion, cART is virologically more effective, and the incidence of toxicity-driven therapy changes has decreased in more recent calendar years. Older patients (≥50 years) showed a smaller increase in CD4 count on cART and were more likely to experience serious adverse events than patients aged <50 years. Unless patients start cART in an earlier stage of HIV infection, an increase in the number of serious non-AIDS events in the aging HIV-infected population is to be expected.

	Pre-treated		Naïve <2003		Naïve 2003-2006		Naïve 2007	
	N	%	N	%	N	%	N	%
Total	1976	100	4366	100	2949	100	844	100
Gender								
Male	1612	81.6	3523	80.7	2294	77.8	671	79.5
Transmission risk group								
MSM	1154	58.4	2380	54.5	1442	48.9	476	56.4
IDU	241	12.2	275	6.3	103	3.5	21	2.5
Heterosexual contact	435	22.0	1404	32.2	1134	38.5	282	33.4
Blood-blood contact	62	3.1	84	1.9	38	1.3	7	0.8
Other	84	4.3	223	5.1	232	7.9	58	6.9
Region of origin								
Netherlands	1248	63.2	2512	57.5	1495	50.7	509	60.3
W-Europe/N-America/Australia	245	12.4	389	8.9	203	6.9	50	5.9
Caribbean/Latin America	186	9.4	451	10.3	361	12.2	89	10.5
Sub-Saharan Africa	183	9.3	713	16.3	653	22.1	122	14.5
Other	114	5.8	301	6.9	237	8.0	74	8.8
Clinical stage								
CDC-C	2892	63.7	468	90.3	1063	95.0	4423	71.6
	median	**IQR**	**median**	**IQR**	**median**	**IQR**	**median**	**IQR**
Age at starting cART	38.6	33.2-45.5	37.4	31.8-44.4	38.9	32.8-46.2	41.3	33.9-47.5
CD4 cell count at starting cART (cells/mm^3)	200	90-340	200	71-330	180	73-260	210	110-280
HIV RNA at starting cART (log_{10} cps/ml)	4.37	3.32-5.00	5.00	4.53-5.43	5.00	4.64-5.40	5.00	4.51-5.45

Table 7.1: Baseline characteristics of 10135 patients starting cART between 1 July 1996 and 31 December 2007

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

		Weeks after starting cART					
	Plasma HIV RNA	0	48	96	144	192	240
	(copies/ml)	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**	**N (%)**
All	<50	32 (0.8)	3578 (83.2)	3053 (85.1)	2557 (86.3)	2060 (86.3)	1623 (87.4)
	50-500	43 (1.0)	359 (8.3)	214 (6.0)	146 (4.9)	125 (5.2)	102 (5.5)
	>500	4154 (98.2)	364 (8.5)	321 (8.9)	261 (8.8)	201 (8.4)	132 (7.1)
On cART	<50	32 (0.8)	3295 (90.0)	2691 (93.0)	2150 (93.7)	1655 (94.0)	1241 (94.7)
	50-500	43 (1.0)	268 (7.3)	146 (5.0)	85 (3.7)	75 (4.3)	46 (3.5)
	>500	4154 (98.2)	98 (2.7)	57 (2.0)	59 (2.6)	30 (1.7)	23 (1.8)
Calendar year of starting cART							
2000-2003	<50	9 (0.5)	1665 (80.2)	1735 (83.3)	1767 (85.5)	1729 (86.1)	1618 (87.5)
	50-500	18 (1.0)	183 (8.8)	125 (6.0)	99 (4.8)	99 (4.9)	101 (5.5)
	>500	1705 (98.4)	227 (10.9)	223 (10.7)	200 (9.7)	181 (9.0)	131 (7.1)
2004-2007	<50	23 (0.9)	1913 (85.9)	1318 (87.6)	790 (88.0)	331 (87.8)	
	50-500	25 (1.0)	176 (7.9)	89 (5.9)	47 (5.2)	26 (6.9)	
	>500	2449 (98.1)	137 (6.1)	98 (6.5)	61 (6.8)	20 (5.3)	
Time from start of cART to ini-tial suppression <50 copies/ml							
0-24 weeks	<50	32 (1.2)	2419 (88.8)	1954 (88.5)	1533 (88.5)	1189 (87.6)	902 (89.4)
	50-500	35 (1.4)	158 (5.8)	110 (5.0)	71 4.1	61 (4.5)	43 (4.3)
	>500	2492 (97.4)	148 (5.4)	145 (6.6)	129 7.4	108 (7.9)	64 (6.3)
24-48 weeks	<50	0 (0.0)	986 (90.6)	787 (89.3)	647 (88.3)	497 (89.2)	381 (89.0)
	50-500	4 (0.4)	69 (6.3)	44 (5.0)	41 (5.6)	28 (5.0)	25 (5.8)
	>500	866 (99.5)	33 (3.0)	50 (5.7)	45 (6.1)	32 (5.7)	22 (5.1)
Age at the start of cART							
<50 years	<50	30 (0.8)	2998 (82.7)	2566 (84.5)	2160 (85.6)	1748 (85.8)	1367 (86.2)
	50-500	36 (1.0)	302 (8.3)	183 (6.0)	125 (4.9)	104 (5.1)	94 (5.9)
	>500	3488 (98.1)	323 (8.9)	286 (9.4)	239 (9.5)	186 (9.1)	124 (7.8)
≥50 years	<50	2 (0.3)	580 (85.5)	487 (88.1)	397 (90.2)	312 (89.7)	256 (94.1)
	50-500	7 (1.0)	57 (8.4)	31 (5.6)	21 (4.8)	21 (6.0)	8 (2.9)
	>500	666 (98.7)	41 (6.0)	35 (6.3)	22 (5.0)	15 (4.3)	8 (2.9)

Table 7.2: Number of patients (%) with plasma HIV RNA concentration (copies/ml) longitudinally measured with an ultra-sensitive assay after starting cART

	Naïve				Pretreated			
	Male		Female		Male		Female	
Months after starting cART								
0-3	56.6	(53.2-60.2)	79.6	(71.6-88.3)	45.7	(39.6-52.5)	54.9	(41.3-71.7)
3-6	25.2	(22.7-27.9)	30.8	(25.4-37.0)	30.2	(24.8-36.4)	28.4	(17.8-43.0)
6-12	19.0	(17.4-20.7)	22.7	(19.2-26.5)	23.2	(19.8-27.0)	31.0	(22.8-41.2)
12-24	16.4	(15.3-17.5)	18.5	(16.2-21.1)	25.2	(22.6-28.0)	29.7	(23.7-36.7)
24-36	11.9	(10.9-13.0)	16.7	(14.3-19.5)	21.7	(19.2-24.5)	23.2	(17.6-29.9)
Age at the start of cART (years)								
<30	21.6	(19.3-24.1)	29.1	(25.8-32.7)	25.1	(19.3-32.2)	26.4	(19.8-34.6)
30-40	20.1	(18.9-21.3)	26.5	(24.1-29.1)	25.9	(23.4-28.5)	29.1	(24.4-34.6)
40-50	22.0	(20.7-23.4)	22.8	(19.6-26.4)	28.9	(26.2-31.7)	37.7	(29.3-47.7)
50-60	23.0	(21.0-25.1)	36.2	(28.7-45.0)	21.9	(18.3-26.0)		
≥60	22.0	(18.4-26.0)	41.0	(30.6-53.7)	29.7	(21.0-40.8)		

Table 7.3: Incidence of toxicity-driven therapy changes per 100 PYcART (95% 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

95% CI: 95% confidence interval, PYcART: person-years on combination antiretroviral therapy

		Male				Female			
	Age during follow-up (yrs)	Diagnoses	PY	Incidence /1000 PY	95% CI	Diagnoses	PY	Incidence /1000 PY	95% CI
Diabetes mellitus	<30	2	2658	0.75	(0.09-2.71)	5	2798	1.79	(0.58-4.17))
	30-40	37	14955	2.47	(1.74-3.41)	20	5707	3.50	(2.14-5.41)
	40-50	79	18187	4.34	(3.44-5.41)	18	3211	5.61	(3.32-8.86)
	50-60	75	8842	8.48	(6.67-10.63)	3	747	4.02	(0.83-11.74)
	≥60	32	2607	12.27	(8.39-17.33)	7	352	19.90	(8.00-41.00)
Myocardial infarction	<30	0	2662	0.00	(0.00-1.39)	0	2811	0.00	(0.00-1.31)
	30-40	11	15033	0.73	(0.37-1.31)	2	5760	0.35	(0.04-1.25)
	40-50	61	18398	3.32	(2.54-4.26)	2	3292	0.61	(0.07-2.19)
	50-60	57	9023	6.32	(4.78-8.18	0	761	0.00	(0.00-4.85)
	≥60	30	2672	11.23	(7.58-16.03)	3	368	8.15	1.68-23.82
Osteoporosis	<30	1	2662	0.38	(0.01-2.09)	2	2808	0.71	(0.09-2.57)
	30-40	3	15056	0.20	(0.04-0.58)	0	5758	0.00	(0.00-0.64)
	40-50	25	18515	1.35	(0.87-1.99)	9	3286	2.74	(1.25-5.20)
	50-60	16	9183	1.74	(1.00-2.83)	3	752	3.99	(0.82-11.66)
	≥60	6	2773	2.16	(0.79-4.71)	5	370	13.51	(4.39-31.53)
Rash	<30	44	2570	17.12	(12.44-22.98)	38	2715	14.00	(9.91-19.21)
	30-40	195	14269	13.67	(11.81-15.72)	73	5422	13.46	(10.55-16.93)
	40-50	199	17373	11.45	(9.92-13.16)	44	3046	14.45	(10.50-19.39)
	50-60	72	8737	8.24	(6.45-10.38)	21	650	32.31	(20.00-49.39)
	≥60	21	2653	7.92	(4.90-12.10)	4	350	11.43	(3.11-29.26)
Non-AIDS malignancies	<30	1	2496	0.40	(0.01-2.23)	0	2706	0.00	(0.00-1.36)
	30-40	34	14123	2.41	(1.67-3.36)	6	5589	1.07	(0.39-2.34)
	40-50	95	17709	5.36	(4.34-6.56)	20	3219	6.21	(3.80-9.60)
	50-60	89	8814	10.10	(8.11-12.43)	4	742	5.39	(1.47-13.80)
	≥60	47	2603	18.06	(13.27-24.01)	1	368	2.72	(0.07-15.15)
Hypertension	<30	8	2648	3.02	(1.30-5.95)	6	2805	2.14	(0.79-4.66)
	30-40	61	14912	4.09	(3.13-5.25)	44	5645	7.80	(5.66-10.46)
	40-50	199	17934	11.10	(9.61-12.75)	55	3097	17.76	(13.38-23.12)
	50-60	187	8604	21.74	(18.73-25.08)	12	710	16.91	(8.74-29.54)
	≥60	59	2507	23.54	(17.92-30.36)	7	361	19.41	(7.80-40.00)
Neuropathy	<30	8	1422	5.63	(2.43-11.08)	12	1881	6.38	(3.30-11.14)
	30-40	47	8302	5.66	(4.16-7.53)	25	3889	6.43	(4.16-9.49)
	40-50	103	12452	8.27	(6.75-10.03)	22	2502	8.79	(5.51-13.31)
	50-60	71	6300	11.27	(8.80-14.22)	5	601	8.31	(2.70-19.40)
	≥60	31	2087	14.85	(10.09-21.08)	4	285	14.03	(3.82-35.92)

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
Renal insufficiency	<30	3	1428	2.10	(0.43-6.14)	5	1897	2.64	(0.86-6.15)
	30-40	27	8389	3.22	(2.12-4.68)	7	3956	1.77	(0.71-3.65)
	40-50	54	12723	4.24	(3.19-5.54)	18	2550	7.06	(4.18-11.15)
	50-60	47	6480	7.25	(5.33-9.65)	4	595	6.73	(1.83-17.23)
	≥60	26	2191	11.87	(7.75-17.39)	3	294	10.21	(2.11-29.83)
Lipodystrophy – central	<30	19	1937	9.8	(5.9-15.3)	35	2255	15.5	(10.8-21.6)
fat accumulation	30-40	242	10591	22.8	(20.1-25.9)	130	4396	29.6	(24.7-35.1)
	40-50	345	13908	24.8	(22.3-27.6)	75	2560	29.3	(23.0-36.7)
	50-60	201	6848	29.3	(25.4-33.7)	14	585	23.9	(13.1-40.1)
	≥60	47	2147	21.9	(16.1-29.1)	13	283	46.0	(24.5-78.6)
Lipodystrophy – peripheral	<30	40	1879	21.3	(15.2-29.0)	30	2292	13.1	(8.8-18.7)
fat loss	30-40	380	10174	37.3	(33.7-41.3)	120	4431	27.1	(22.5-32.4)
	40-50	584	12707	46.0	(42.349.8)	92	2524	36.4	(29.4-44.7
	50-60	324	6088	53.2	(47.6-59.3)	18	559	32.2	(19.1-50.9)
	≥60	80	1922	41.6	(33.0-51.8)	13	264	49.2	(26.2-84.1)
Hepatic steatosis	<30	4	2659	1.50	(0.41-3.85)	2	2809	0.71	(0.09-2.57)
	30-40	59	14909	3.96	(3.01-5.10)	14	5712	2.45	(1.34-4.11)
	40-50	90	18195	4.95	(3.98-6.08)	10	3248	3.08	(1.48-5.66)
	50-60	66	8949	7.38	(5.70-9.38)	3	758	3.96	(0.82-11.56)
	≥60	20	2669	7.49	(4.58-11.57)	2	374	5.34	(0.65-19.31)
Sexual problems	<30	12	1417	8.47	(4.38-14.79)	0	1907	0.00	0.00-1.93)
	30-40	102	8219	12.41	(10.12-15.06)	1	3969	0.25	(0.01-1.40)
	40-50	186	12252	15.18	(13.08-17.53)	6	2563	2.34	(0.86-5.09)
	50-60	91	6270	14.51	(11.69-17.82)	0	607	0.00	(0.00-6.07)
	≥60	23	2122	10.84	(6.87-16.27)	0	297	0.00	(0.00-12.41)

Table 7.4: Incidence per 1000 person years (PY) of newly diagnosed routinely collected adverse events for male and female patients after starting cART per age group

CVA: cerebrovascular accident

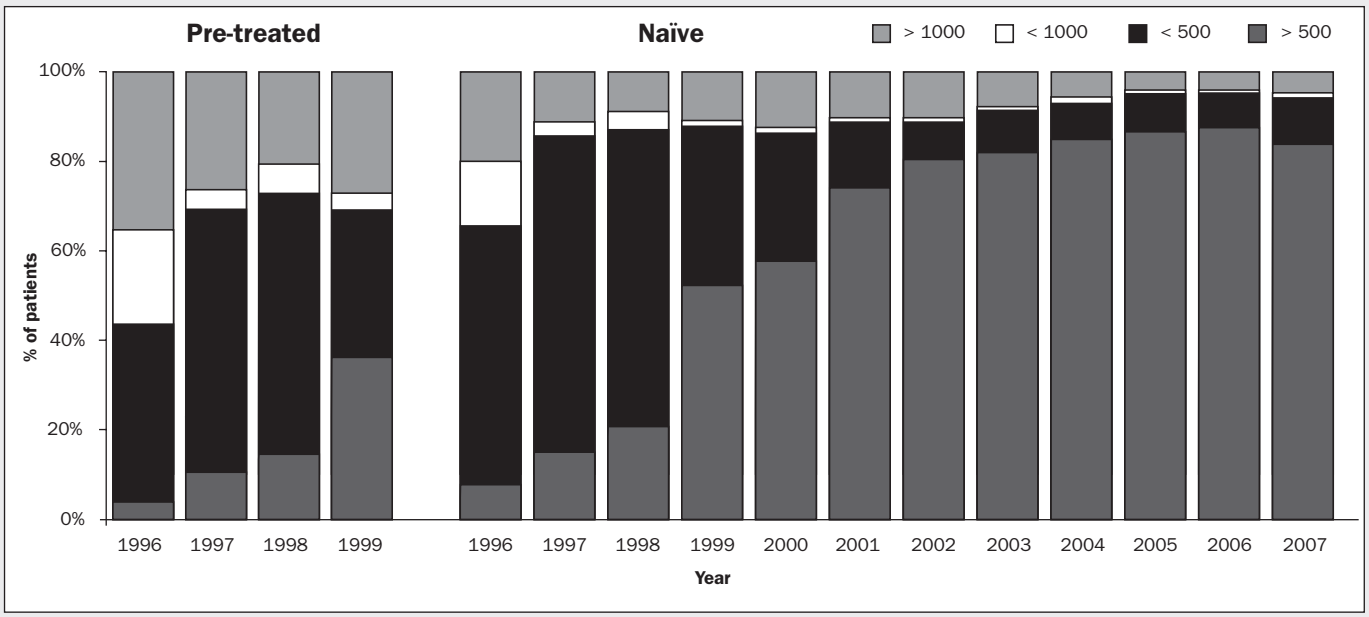


Figure 7.1: Plasma HIV-RNA (copies/ml) at week 36 for pre-treated and naïve patients at the start of cART according to calendar year of starting cART

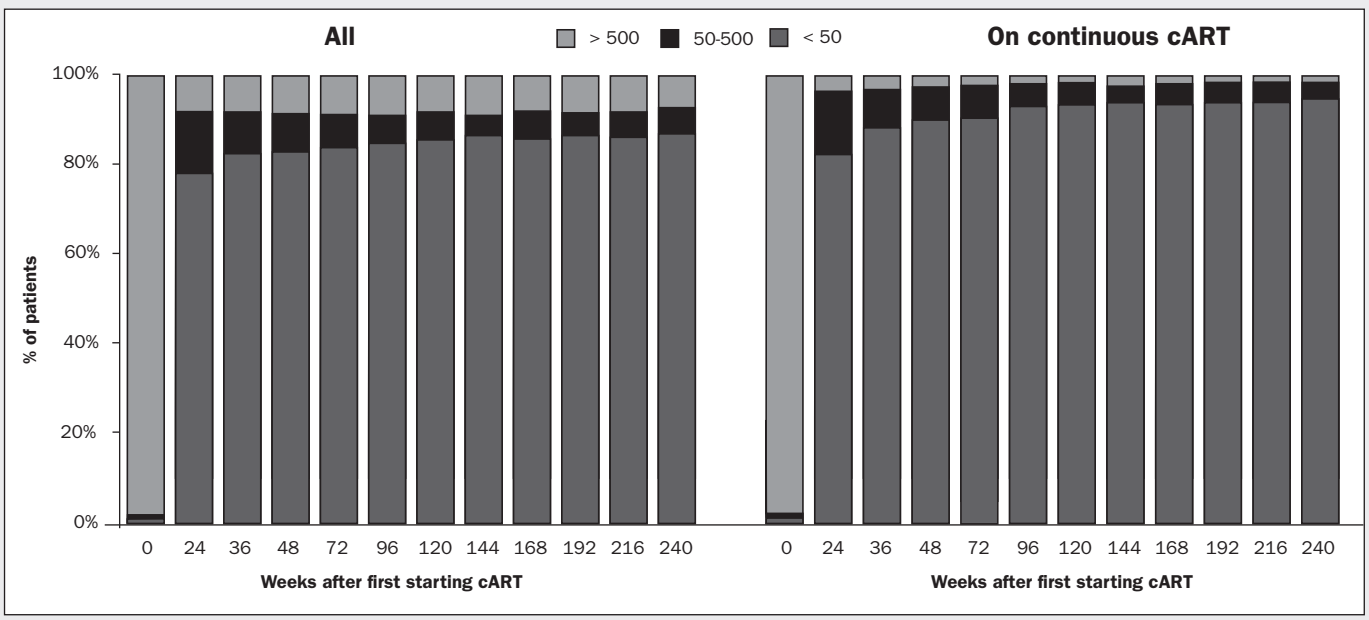


Figure 7.2: Plasma HIV RNA concentration (copies/ml) measured with assays with a lower detection limit of 50 copies/ml or less, in naïve patients after starting cART in or after 2000 and in a subgroup of patients continuously on cART

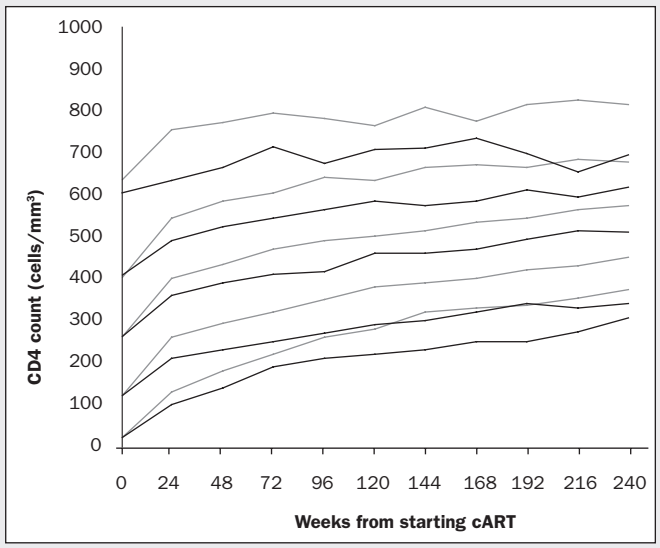


Figure 7.3: Median CD4 count and IQR of 8159 naïve patients (grey lines) starting cART and 1976 pre-treated patients (black lines) according to CD4 count at the start of cART (<50, 50-200, 200-350, 350-500 and ≥500 cells/mm^3)

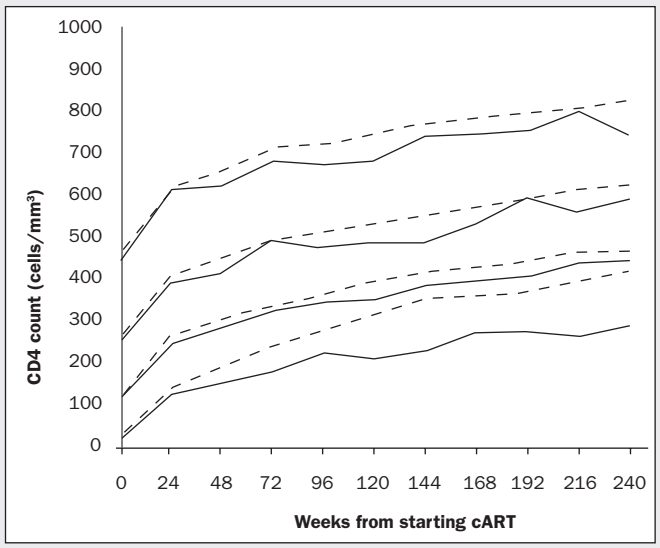


Figure 7.5: Median CD4 count according to CD4 count at start of cART in naïve patients aged <50 years (dashed lines) and ≥50 years (solid lines) at the start of cART with viral suppression

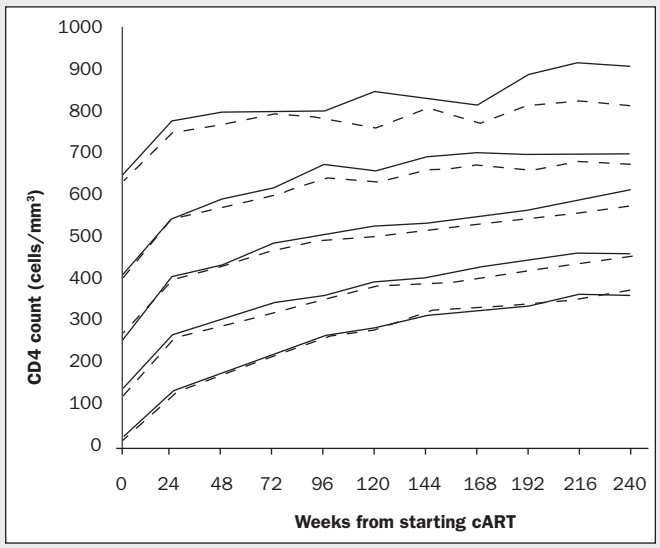


Figure 7.4: Median CD4 count according to CD4 count at start of cART in all naïve patients (dashed lines) and naïve patients with viral suppression (solid lines)

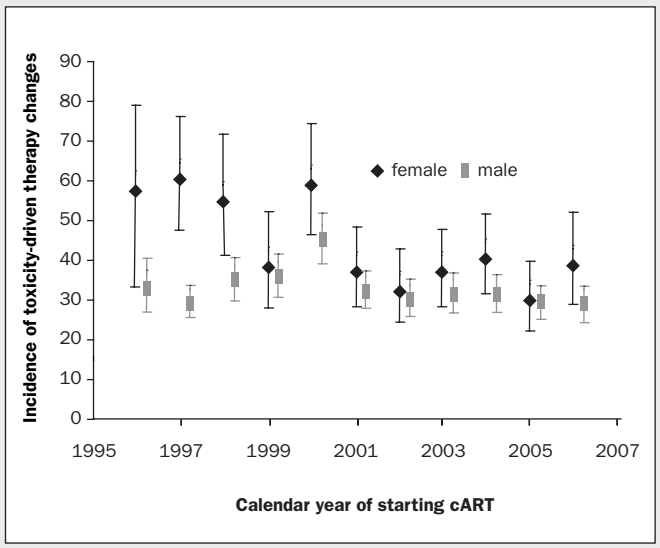


Figure 7.6: Incidence of toxicity-driven regimen changes during the first year after starting cART per 100 person-years of cART use according to calendar year of starting cART

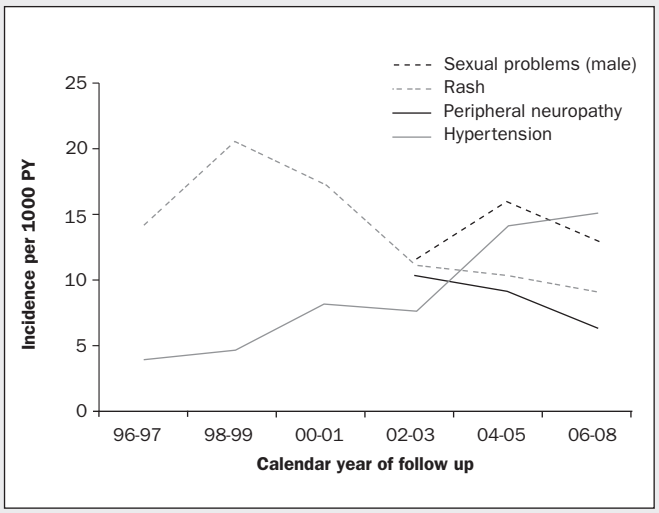


Figure 7.7: Incidence per 1000 PY (95% CI) after start of cART of rash (circles), peripheral neuropathy (diamonds), sexual problems among men (triangles) and hypertension (squares) by calendar year of follow-up

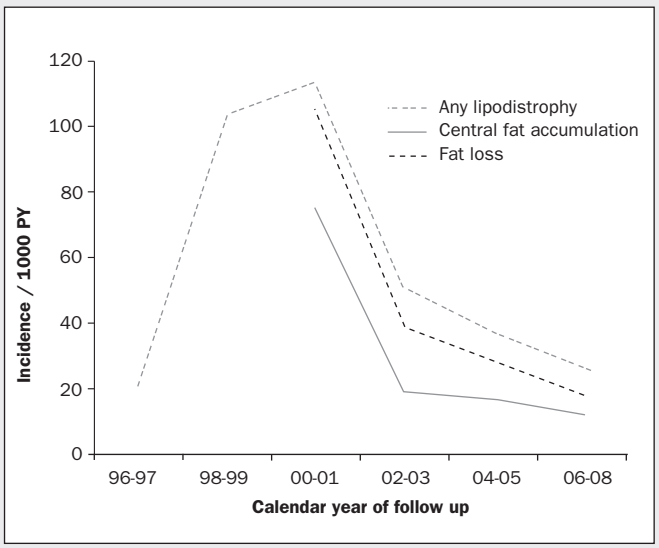


Figure 7.8: Incidence per 1000 PY (95% CI) after start cART by calendar year of follow-up of lipodistrophy (any) and further subdivided into central fat accumulation and peripheral fat loss

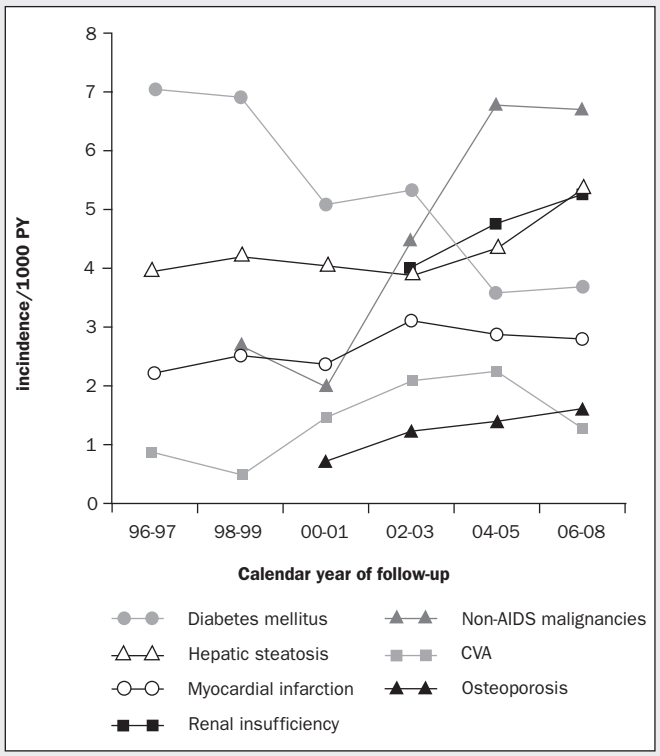


Figure 7.9: Incidence per 1000 PY after start of cART of myocardial infarction (white circles), osteoporosis (black triangles), non-AIDS malignancies (grey triangles), renal insufficiency (white squares), hepatic steatosis (white triangles), diabetes mellitus (grey circles) and cerebrovascular accident (CVA) (grey squares) by calendar year of follow-up

8. Resistance

Ard van Sighem

Introduction

When adherence to combination antiretroviral treatment (cART) is not optimal, suppression of HIV replication may be incomplete. This, in turn, may lead to selection of HIV-1 viruses that are resistant to one or more of the drugs in the cART regimen. The presence of resistant strains of the virus limits future therapy options and may lead to a worsened prognosis. In addition, resistant strains can be transmitted to uninfected patients. This chapter presents an update on the prevalence and the transmission of resistant strains of the virus in the Netherlands.

Methods

Resistance measurements were based on isolation of HIV-1 RNA in plasma of patients and amplification of the protease gene and part of the reverse transcriptase (RT) gene of the virus. HIV-1 RT and protease were genotyped with the use of the amplified genes in a sequencing procedure. Sequences were scanned for specific major mutations at codons known to be associated with resistance to the three major classes of anti-HIV drugs: nucleoside RT inhibitors (NRTI), non-nucleoside RT inhibitors (NNRTI), and protease inhibitors (PI)[126]. A genotypic resistance interpretation algorithm developed by Stanford University was used to assign a drug penalty score for each mutation associated with drug resistance[127]. The total score for a drug was determined by summing all individual mutation scores, and it was then translated into an inferred drug susceptibility, according to a 5-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance.

Transmission of drug-resistant strains was studied in two separate patient groups: patients with a recent infection and those with a new HIV diagnosis. Patients with a recent infection were diagnosed either during the acute phase of infection or had tested positive for HIV-1 less than 2 years after their last negative test. All other patients with a known positive test for HIV-1 were assigned to the group with newly diagnosed infections. For both groups, an available sequence within 1 year after diagnosis and before the initiation of antiretroviral treatment was required.

Data on viral load measurements were used to define the start and end point of failures that occurred after initiation of antiretroviral treatment. Failure was defined as at least one viral load measurement above 500 copies/ml. 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. It should be noted that this definition of failure did not take into account the use of therapy. The annual proportion of failing patients, which was corrected for therapy use, was calculated as the ratio of the number of patients failing to the number of patients being followed during the year.

The annual prevalence of high-level resistance was calculated as the prevalence amongst the patients who were tested for resistance after starting cART. The maximum resistance score for individual drugs from previous tests was carried forward. Only genotypic sequences were used that had been obtained during treatment or, at most, 2 weeks after cessation of therapy, thus allowing for uncertainties in the date on which therapy was stopped. Patients were considered resistant to a class of antiretroviral drugs if they had

high-level resistance to at least one drug from the class. Lamivudine and emtricitabine were considered as a separate class.

Exact confidence intervals were calculated to determine proportions; the intervals were compared by a chi-square test or, if sample sizes were small, by Fisher's exact test. For continuous variables, medians were reported with the interquartile range (IQR).

Results

Transmission of drug-resistant virus

In total, 2351 patients had a genotypic sequence available within one year after diagnosis and before the start of antiretroviral treatment. Of these patients, 704 (29.9%) were recently infected. The other 1647 (70.1%) patients with a known date of their first positive test for HIV were assigned to the group of newly diagnosed patients.

Table 8.1 shows the characteristics of both the 704 recently infected patients and the 1647 patients who were newly diagnosed and had had a resistance test within 1 year after diagnosis. Of the 704 recently infected patients, 464 (65.9%) were men of Dutch origin who were infected by homosexual contact, whereas only 686 (41.7%) of the 1647 newly diagnosed patients had the same characteristics. Heterosexually infected patients from sub-Saharan Africa accounted for 242 (14.6%) of the newly diagnosed patients and 10 (1.4%) of the recently infected patients. Between 2003 and 2007, 1807 sequences were obtained in the combined group of patients who were newly diagnosed (1289 sequences) and recently infected (518 sequences). During the same period, there were 5202 HIV diagnoses, as shown in Table 2.3. Hence, a sequence was obtained for 34.7% of the diagnosed patients.

Amongst the 704 recently infected patients, resistance-associated mutations were found in 41 (5.8%), of whom 5 were infected during or before 1996. The number of patients with recent infections with a sequence between 1994 and 2001 was limited, and as a result, the percentage with resistance fluctuated between 0% and 20% (Figure 8.1). After 2001, resistance was found in 33 of the 569 recently infected patients (5.8%, 95% confidence interval [CI] 4.0-8.0).

Of the 569 patients with a recent infection after 2001, 553 were fully susceptible to all protease inhibitors, 541 to all NRT inhibitors, and 555 to all NNRT inhibitors. Four patients (0.7%) had intermediate or high-level resistance to at least one protease inhibitor, 14 (2.5%) to at least one NRT inhibitor, and 5 (0.9%) to at least one NNRT inhibitor. Overall, 18 patients had intermediate or high-level resistance to at least one drug, corresponding to a prevalence of 3.2% (95% CI 1.9-5.0). Two patients had intermediate or high-level resistance to all three drug classes. One of these patients was infected at the end of 2004 or early 2005, whereas the other patient was infected at the end of 2007.

Resistance-associated mutations were found in 128 (7.8%) of 1674 newly diagnosed patients. The majority of the resistant sequences, which amounted to 114 (89%), were obtained from the 1416 patients diagnosed during or after 2002. The annual percentage of transmissions of resistant strains varied between 0% and 10% (Figure 8.1). After 2001, the proportion of patients with at least one mutation was 8.1% (95% CI 6.7-9.6), which was slightly, but not significantly, higher than in patients with a recent infection ($p=0.08$). Amongst the 789 patients infected via homosexual contact, 84 (10.6%) had at least 1 mutation, compared to 25 (5.1%) of the 492 patients infected via heterosexual contact ($p<0.001$). Resistance was also more common amongst patients infected with a B subtype virus (9.8%), compared to those with a non-B subtype (3.5%) ($p<0.001$).

In the group of 1416 patients who were diagnosed after 2001, intermediate or high-level resistance to

protease inhibitors was found in 7 (0.5%) patients, to NRT inhibitors in 34 (2.4%), and to non-nucleoside RT inhibitors in 32 (2.3%). These proportions for protease and NRT inhibitors did not differ from those observed in patients with a recent infection ($p>0.5$), but the proportion of patients with NNRTI resistance was marginally higher ($p=0.04$). Intermediate or high-level resistance to efavirenz was found in 22 (1.6%) newly diagnosed patients and in 5 (0.9%) recently infected patients ($p=0.2$), whereas resistance to nevirapine was found in 32 (2.3%) newly diagnosed patients and in 5 (0.9%) of those recently infected ($p=0.04$). In total, 61 (4.3%) patients had intermediate or high-level resistance to at least one antiretroviral drug, corresponding to a prevalence of 4.3% (95% CI 3.3-5.5), which was not significantly different from the prevalence amongst recently infected patients ($p=0.2$). Two patients had high-level resistance to drugs from all three classes.

Resistance during treatment

The annual proportion of pre-treated patients who failed on cART declined from 49% in 1997 to 14% in 2007 (10% in 2008). During the same period, the proportion of previously therapy-naïve patients who experienced failure remained between 6% and 9%. In the group of pre-treated patients, the fraction of failing patients from whom a sequence was obtained increased from 9% in 1997 to 30% in 2003; thereafter, the proportion declined to 19% in 2006, but increased to 27% in 2007. In the therapy-naïve group, the fraction of patients with a sequence was 34% in 2003, and it decreased to 18% in 2005 and beyond. Overall, 95% of the sequences obtained from pre-treated patients and 79% of those from therapy-naïve patients contained one or more resistance-associated mutations.

In the total population, 3023 sequences were obtained after the patients started cART. Of these sequences, 1365 (45.2%) were obtained from pre-treated patients and 1658 (54.8%) from previously therapy-naïve patients; 2220 (73.4%) contained at least one resistance-associated mutation, and the rest, 803 (26.6%), contained none. Resistance was found in 1203 (88.1%) sequences from pre-treated patients and in 1017 (61.3%) sequences from therapy-naïve patients. In total, 2512 (83.1%) sequences were obtained whilst the patients were on treatment.

The nature of drug resistance observed per calendar year changed over time (Figure 8.2). The proportion of patients with high-level resistance to zidovudine decreased from 50% (95% CI 32-68) in 1996 to 20% (18-23) in 2004 and beyond. A similar pattern was observed for resistance to stavudine. Meanwhile, the proportion of patients with resistance to lamivudine and emtricitabine decreased slightly from 76% (65-85) in 1996 to 59% (52-65) in 2007. Resistance to didanosine did not change over time ($p=0.04$), whereas resistance to abacavir declined. High-level resistance to tenofovir was rare and varied between 1% and 4% between 1996 and 2007. However, when intermediate and high levels of resistance to tenofovir were combined, the level of resistance was 53% (35-71) in 1996, with a decline to 26% (20-32) in 2007.

Resistance to NNRTIs increased after the introduction of nevirapine and efavirenz as part of the cART regimen in approximately 1998. High-level resistance to nevirapine increased from 43% (33-53) in 1999 to 51% (45-57) in 2007, whereas high-level resistance to efavirenz was less common and increased from 32% (24-42) in 1999 to 39% (33-45) in 2007. Resistance to the new NNRTI etravirine was less than 4%. When intermediate and high-level resistance to etravirine were combined, the level of resistance was 30% (28-32) from 2003 onwards.

Resistance to protease inhibitors also increased after the widespread introduction of PIs in approximately 1996. High-level resistance to the older generation of

PIs, including nelfinavir, saquinavir, and indinavir, peaked in roughly 1999 and became less prevalent thereafter. Less than 10% of the sequences were fully resistant to lopinavir, tipranavir, and darunavir. In 2007, intermediate or high levels of resistance to lopinavir were found in 23% of the sequences, to tipranavir in 22%, and to darunavir in 11%.

As of June 2008, a total of 11,349 HIV-1-infected adults were still being actively followed. In 1379 (12.2%) of those patients, at least one sequence with resistance-associated mutations had been obtained, and 1112 (80.6%, or 9.8% of the population in follow-up) had high-level resistance to at least one antiretroviral drug. The number of patients with high-level resistance to drugs from one class was 490 (35.5%). Resistance to drugs from two classes was found in 524 (38.0%) patients, whereas 180 (13.1%) were found to be resistant to drugs from all three classes. High-level resistance to at least one NRTI was found in 1039 (75.3%) of the patients; of those, 918 (88.4%) were resistant to lamivudine and emtricitabine and 473 (45.5%) to other NRTIs, whereas high-level resistance to at least one PI was found in 346 (25.1%) patients and to at least one NNRTI in 693 (50.3%). Table 8.2 shows the inferred resistance level for each antiretroviral drug in the group of 1379 patients.

Discussion

The rate of transmission of intermediate and high-level drug-resistant HIV-1 virus in the Netherlands remains low. In the current analysis, only 3.2% of recently infected patients and 4.3% of newly diagnosed patients after 2001 were infected with a strain that was resistant to at least one antiretroviral drug. These proportions tended to be lower than those observed in other Western countries[23-28]. Prevalences of major resistance-associated mutations were higher in both patient groups. Apparently, the presence of major resistance-associated mutations is not necessarily a sign of full resistance. As was found in Switzerland, we did not observe an increase in transmitted drug-resistant HIV-1 over time[27].

Characteristics of newly diagnosed patients were similar to those of the total diagnosed population. Hence, reported levels of resistance are probably a good estimate of the true levels in the total population. The stable and low level of transmission of resistant strains of the virus is somewhat surprising, given the increase in the number of treated patients since 1996. One explanation is that the number of patients failing therapy has decreased over time, and, as a consequence, the reservoir of possibly infectious patients is relatively small. On the other hand, the low level of transmitted resistance could also indicate that most HIV infections are transmitted by infected individuals who are untreated or who are not yet aware of their infection, which is more likely for the group of homosexual men in the Netherlands[4].

Transmitted resistance amongst patients infected with a non-B subtype, most of whom were of sub-Saharan origin, appeared to be limited. However, the roll-out of widely available antiretroviral treatment in Africa will undoubtedly increase the prevalence of drug resistance in that area. This increased prevalence could subsequently lead to an increase in transmitted resistance not only in Africa but also in the migrant population in the Netherlands.

As observed previously, the prevalence of resistance to specific antiretroviral drugs has changed over time in correlation with changes in antiretroviral drug use. Thus, the prevalence of resistance to NNRTIs has increased, whilst resistance to the first generation of protease inhibitors has declined. The prevalences of high-level resistance to NRTIs and NNRTIs matched those of a recent study in France, but prevalences of PI resistance were lower in our cohort[20]. Resistance to

newer drugs like tenofovir and lopinavir remained at a low level, despite increasingly frequent use of these drugs in recent years. Recently, a new NNRTI, etravirine, has become available for antiretroviral treatment in the Netherlands. This drug has antiretroviral activity even when the virus is highly resistant to the other NNRTIs efavirenz and nevirapine.

It was found that almost 10% of the patients who were failing on antiretroviral therapy and were still being followed in one of the HIV treatment centres in the country harboured strains with high-level resistance to at least one antiretroviral drug. This percentage is probably an underestimation, since a resistance test was performed in only 30% of the patients failing on therapy. Also, other cohorts with more frequent sampling for resistance have found prevalences between 20 and 30%[21, 22]. Compared to 2007, the proportion of patients with resistance slightly decreased, but the absolute number of patients harbouring resistant virus increased from 1064 to 1112[6].

	new diagnoses, N=1647		**recent infections, N=704**	
	N	%	N	%
male gender	1284	78.0	656	93.2
region of origin				
the Netherlands	937	56.9	540	76.7
sub-Saharan Africa	295	17.9	24	3.4
transmission category				
MSM	930	56.5	581	82.5
heterosexual contact	538	32.7	80	11.4
injection drug use	25	1.5	11	1.6
other/unknown	154	9.4	32	4.5
non-B subtype	455	27.6	96	13.6
≥ **1 RAMs**				
any drug	128	7.8	41	5.8
PIs	19	1.2	14	2.0
NRTIs	87	5.3	28	4.0
NNRTIs	39	2.4	4	0.6
intermediate/high-level resistance				
any drug	67	4.1	26	3.7
PIs	8	0.5	5	0.7
NRTIs	39	2.4	20	2.8
NNRTIs	33	2.0	6	0.9
	median	**IQR**	**median**	**IQR**
CD4 (cells/mm^3)	290	120–482	490	350-670
RNA (log_{10} copies/ml)	4.8	4.2–5.3	4.9	4.3–5.4
age (years)	37.7	30.9–44.8	36.1	30.1–43.1

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

Table 8.1: Characteristics of both newly diagnosed and recently infected patients at HIV diagnosis

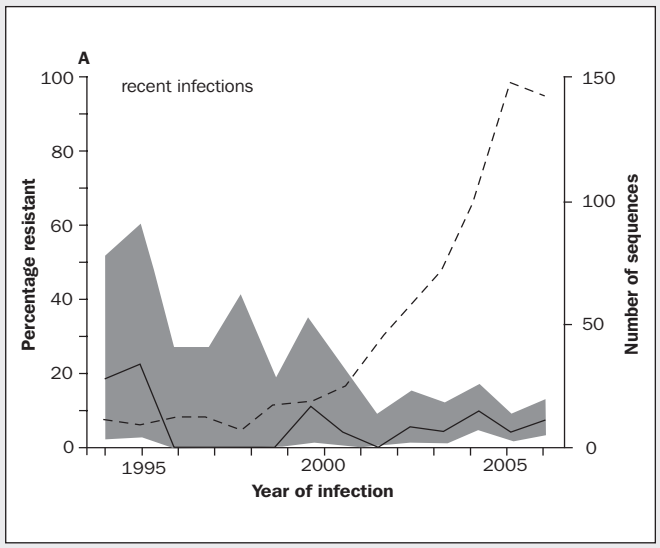
	susceptible		potential low-level		low-level		intermediate		high-level	
	N	%	N	%	N	%	N	%	N	%
protease inhibitors[a]										
fAPV	946	68.9	52	3.8	117	8.5	157	11.4	102	7.4
IDV	928	67.5	54	3.9	72	5.2	134	9.8	186	13.5
NFV	853	62.1	18	1.3	38	2.8	122	8.9	343	25.0
SQV	945	68.8	49	3.6	34	2.5	150	10.9	196	14.3
LOP	942	68.6	92	6.7	96	7.0	182	13.2	62	4.5
ATV	896	65.2	36	2.6	120	8.7	180	13.1	142	10.3
TPV	1014	73.8	57	4.1	105	7.6	170	12.4	28	2.0
DRV	1056	76.9	77	5.6	163	11.9	76	5.5	2	0.1
nucleoside RT inhibitors[b]										
3TC	346	25.1	36	2.6	48	3.5	34	2.5	914	66.3
FTC	346	25.1	36	2.6	48	3.5	34	2.5	914	66.3
ABC	184	13.4	378	27.4	151	11.0	416	30.2	249	18.1
AZT	576	41.8	30	2.2	135	9.8	267	19.4	370	26.9
d4T	493	35.8	80	5.8	198	14.4	306	22.2	301	21.8
ddI	476	34.5	124	9.0	150	10.9	377	27.4	251	18.2
TDF	598	43.4	133	9.7	229	16.6	394	28.6	24	1.7
non-nucleoside RT inhibitors[a]										
EFV	640	46.4	32	2.3	108	7.8	100	7.3	498	36.1
NVP	615	44.6	53	3.8	7	0.5	12	0.9	691	50.1
ETR	669	48.5	159	11.5	175	12.7	334	24.2	41	3.0

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 5 patients

[b] RT not available for 1 patient

Table 8.2: Number of patients in follow-up as of June 2008 with evidence of resistance to specific antiretroviral drugs, according to the Stanford algorithm for scoring mutations



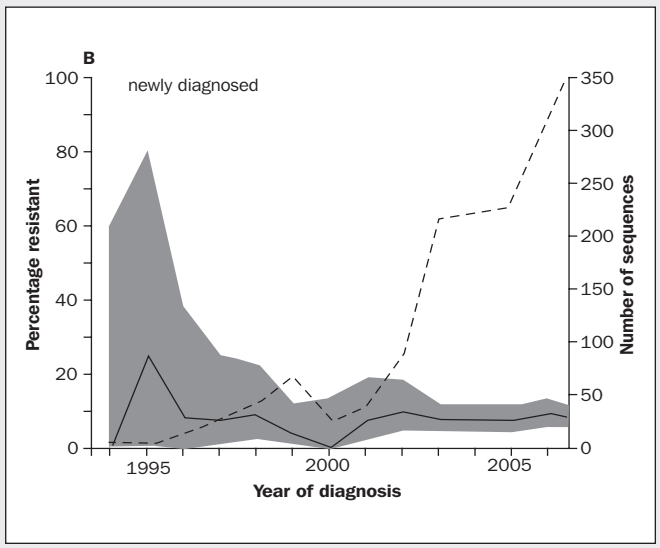
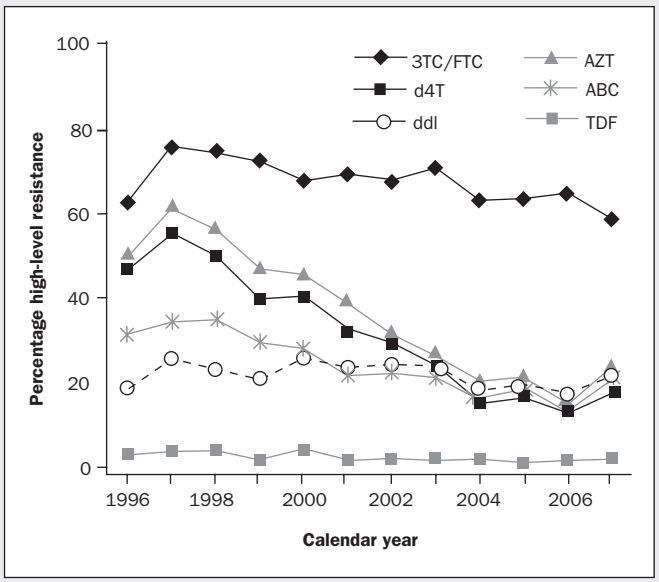
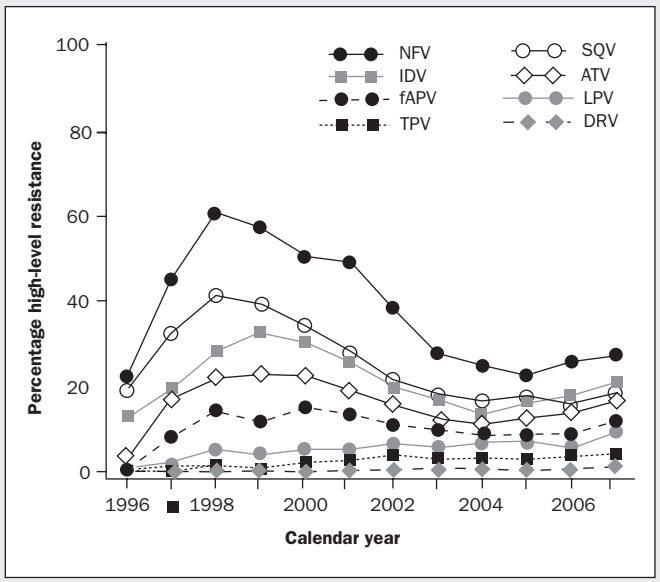


Figure 8.1: Percentage of transmissions of resistant virus as a function of calendar time amongst recently infected (A) and newly diagnosed (B) patients. The solid black line represents the percentage whilst the grey areas are the 95% confidence intervals. The dashed line is the number of sequences obtained in each year (right axis)





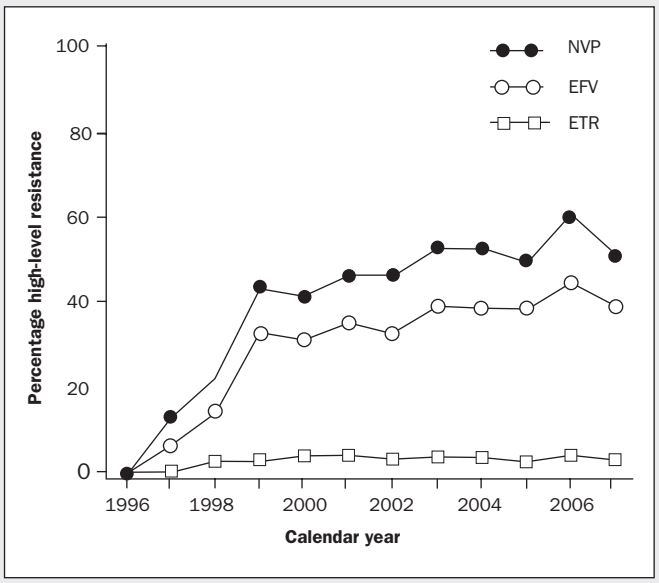


Figure 8.2: Percentage of patients with high-level resistance, according to the Stanford algorithm for scoring mutations

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

special reports

9. Curaçao

Ard van Sighem, Ashley Duits

Introduction

Since November 2005, the HIV Monitoring Foundation has collected data on HIV-infected patients living in Curaçao. The majority of these patients were followed prospectively after inclusion in the database. The rest of the patients were included after they died, and their data were entered retrospectively. In this report, demographic and clinical characteristics of the total HIV-infected population are described, as well as treatment outcomes in those patients who started combination antiretroviral treatment (cART).

Methods

The methods used in this chapter are largely identical to those described previously in the chapter on the characteristics and trends in the Dutch HIV-infected population. The frequency of measurements or clinical visits was calculated as the ratio of the number of visits or measurements to the total number of person-years in follow-up. Interval censoring methods were used to estimate the time from start of cART to a viral load level below 500 copies/ml or an increase in CD4 cells of more than 150 cells/mm^3.

Results

The total HIV-infected population recorded in Curaçao was 447 patients, including 379 (84.8%) patients who were still alive as of 1 June 2008, and 68 (15.2%) patients who had already died. Of the 379 patients who were still alive, 68 (17.9%) had no data recorded in the year preceding 1 June 2008. The total follow-up since HIV diagnosis was 2585 person-years for the entire population, 2334 person-years for those still alive, and 251 for those who already died. Of these 447 patients, a majority of 416 (93.1%) were infected with HIV-1. Two patients were infected with HIV-2, and in five patients, seroreactivity to both HIV-1 and HIV-2 was found. For 24 (5.4%) patients serologic results were inconclusive or not (yet) known or recorded in the HIV Monitoring Foundation database. In total, 72 patients (16.1%) were diagnosed in or before 1995; of those, 24 (35%) were in the group of deceased patients (Table 9.1). Between 1996 and 2008, 343 patients were diagnosed, 310 (90.4%) of whom were still alive, corresponding to an average of 26 diagnoses per year. According to Table 9.2, the majority of the patients were male (65.5%), infected via heterosexual contact (64.2%), and originated from the Netherlands Antilles and Aruba (79.0%).

For 196 (43.8%) patients, the most likely country of infection was known. Most patients, 171 (87.2%), were reported to have been infected in the Antilles, whereas 14 (7.1%) patients were infected in Haiti or the Dominican Republic. The HIV-1 subtype was known for 101 (22.6%) patients; all of them harboured a subtype B strain.

The median age at diagnosis was 38.0 (interquartile range [IQR], 31.0-46.4) years and did not differ between patients who were still alive and those who had died (p=0.1). Only 28 (6.3%) patients presented with an AIDS-defining event. However, at the start of cART, 58 (13.0%) had experienced an AIDS event in the previous year. In the population that was still alive, CD4 counts increased from 318 (101-502) cells/mm^3 at diagnosis to 374 (213-516) cells/mm^3 at present.

In total, 296 (66.2%) patients were tested for hepatitis B, and 245 (54.8%) were tested for hepatitis C. Of those tested, 28 (9.5%) patients were co-infected with hepatitis B, and 2 (0.8%) patients had hepatitis C.

Between 2001 and 2007, the frequency of RNA measurements was 1.88 (95% confidence interval [CI], 1.81-1.94) per year in the group of patients who were still alive,

whereas it was 0.97 (0.79-1.18) in the group of deceased patients. The frequencies of CD4 measurements were slightly higher: 2.02 (1.96-2.09) in the patients who were still alive and 1.26 (1.06-1.50) in the patients who had died. The overall visit frequencies were 2.37 (2.30-2.44) and 1.98 (1.71-2.28), respectively.

In total, 304 patients started cART, but the exact date of start was not known for 4 of those patients. The most frequently used initial regimens in the 300 patients who started cART in or after 1995 were lopinavir + zidovudine + lamivudine (130 patients, 43.3%), nelfinavir + stavudine + lamivudine (83 patients, 27.7%) and indinavir + zidovudine + lamivudine (24 patients, 8.0%). The prescription of antiretroviral regimens changed over calendar time (Figure 9.1). The proportion of patients using indinavir + zidovudine + lamivudine decreased from 58% in 1998 to 1% in 2007. This decrease was counterbalanced by an increase in the percentage of patients treated with nelfinavir + stavudine + lamivudine. From 2001 onwards, a combination of lopinavir + zidovudine + lamivudine was increasingly used, and 46% of the patients on cART were on this regimen at the beginning of 2008. At that time, 11% of the patients used a combination of nevirapine + zidovudine + lamivudine. After 2004, 10 to 20% of the patients who ever started cART were (temporarily) not being treated.

The median time to the first switch in therapy was 2.32 (0.86-5.08) years. Of the 83 patients who interrupted their first regimen and started a new regimen after a period without treatment, 41 (49%) repeated their initial regimen.

Prospective follow-up in Curaçao started in 2006. In total, as of 1 January 2006, 365 patients were still alive or were diagnosed with HIV after that date. Two years later, 14 of these patients had died, and 96% were still alive, according to a Kaplan-Meier estimate.

In total, 272 patients started cART whilst being antiretroviral therapy-naïve. Figure 9.2a and 9.2b show the proportion of patients whose CD4 cell counts increased by more than 150 cell/mm^3 and the proportion of patients who reached a viral load level below 500 copies/ml. After 6 months, CD4 cell counts had increased by more than 150 cells/mm^3 for 50% of the patients; after 2 years, this proportion had increased to 80%. A viral load level below 500 copies/ml was achieved within 6 months in 80% of the patients.

Figure 9.2c and 9.2d show the median CD4 cell count and the proportion of patients with a viral load below 500 copies/ml in the group of 226 patients who started cART whilst being antiretroviral therapy-naïve and who were still in follow-up. CD4 counts increased from 137 (50-245) cells/mm^3 at start of cART to 259 (149-398) cells/mm^3 after 24 weeks. After 2 years, CD4 counts stabilised at a level of approximately 400 cells/mm^3. The proportion of patients with a viral load below 500 copies/ml was 68% after 24 weeks and 73% after 48 weeks. Thereafter, the proportion gradually declined to a level between 50% and 60% after 5 years.

In total, 70 genotypic sequences were obtained after start of cART in 53 patients. Of these 53 patients, 22 had high-level resistance to nelfinavir, and 11 patients had resistance to saquinavir. Resistance to nevirapine was observed in 6 patients. High-level resistance to lamivudine and emtricitabine was found in 28 patients, whereas resistance to zidovudine and stavudine was found in 10 patients. In 31 (7%) patients with a sequence available within 1 year after diagnosis and before the start of antiretroviral treatment, no infections with resistant virus strains were observed.

Discussion

Since 2007, the HIV-infected population in Curaçao as registered by the HIV Monitoring Foundation has increased by 155 patients. Of the total registered

population, 15% have died, and the majority of these patients were already dead at inclusion in the database. In addition, almost 20% of the population of patients who were still alive were not in follow-up anymore as of 1 June 2008. As a result, our analyses were limited since the registered population was probably not representative of the total HIV-infected population on the island.

Also, the possibilities for survival analyses were limited, since patients who were lost to follow-up before the registration in Curaçao were generally not part of the registered population. The Kaplan-Meier estimate of 96% patients surviving after 2 years was obtained for a very heterogeneous population of patients who were already on treatment and those who were recently diagnosed with HIV. A similar analysis in the population of patients born in the Netherlands Antilles who were followed in the Netherlands gave an estimate of 98%.

Patients starting cART responded well to treatment and quickly reached viral load levels below 500 copies/ml, with a good immunologic response. However, after 1 year of therapy, the proportion of patients with a suppressed viral load started to decline. This decreasing ability to suppress viral load was probably a consequence of the limited number of treatment options available in Curaçao. Just three regimens accounted for the majority of all those administered in Curaçao. Ritonavir, which is used to achieve optimal blood levels of protease inhibitors, is not available in Curaçao, except in a fixed-dose combination with lopinavir. Hence, the number of boosted protease-containing regimens is limited. Non-nucleoside RT inhibitors were not available for years, but from 2007 on, approximately 10% of the treated patients were using nevirapine as part of their cART regimen.

So far, transmission of resistant strains has not been observed in Curaçao, but the number of patients in whom a genotypic sequence was obtained shortly after diagnosis was very limited. Also, the number of sequences obtained after start of cART was limited, given the large proportion of patients with a viral load above 500 copies/ml. It is, therefore, not yet feasible to ascertain whether the gradual loss of viral suppression leads to an increasing prevalence of resistance, as would be expected, and subsequent transmission of resistant virus to previously uninfected individuals.

	alive, in follow-up		alive, lost to follow-up		dead		total	
	men	women	men	women	men	women	men	women
≤1995	25	14	7	2	18	6	50	22
1996	9	9	1	1	0	1	10	11370
1997	5	9	2	1	6	2	13	12
1998	9	7	5	0	1	0	15	7
1999	10	7	3	0	0	0	13	7
2000	14	7	4	2	2	0	20	9
2001	6	7	3	1	2	2	11	10
2002	17	6	3	1	2	0	22	7
2003	18	11	6	4	5	0	29	15
2004	8	9	4	2	6	0	18	11
2005	17	8	1	3	2	1	20	12
2006	18	11	3	2	0	0	21	13
2007	21	7	-	-	1	0	22	7
2008	6	2	-	-	0	0	6	2
total	183	114	42	19	45	12	270	145
unknown	12	2	6	1	5	6	23	9

Table 9.1: Annual number of diagnoses in Curaçao stratified by gender and survival status as of 1 June 2008

		alive, N=379		dead, N=68		total, N=447	
		N / median	% / IQR	N / median	% / IQR	N / median	% / IQR
gender, male		243	64.1	50	74	293	65.5
transmission	MSM	74	19.5	9	13	83	18.6
	heterosexual	242	63.9	45	66	287	64.2
	other/unknown	63	16.6	14	21	77	17.2
country of birth	Antilles	292	77.0	61	90	353	79.0
	Haiti	41	10.8	4	6	45	10.1
	Dominican Republic	18	4.7	2	3	20	4.5
treated with cART		268	70.7	36	52.9	304	68.0
diagnosis	CD4 (cells/mm^3)	318	101-502	99	68-307	291	93-491
	RNA (log_{10} copies/ml)	4.5	3.7-5.2	4.0	3.5-5.6	4.4	3.7-5.2
	age (years)	38.0	31.0-46.4	38.8	31.4-45.9	38.0	31.0-46.4
	AIDS	18	4.7	10	15	28	6.3
	time to cART	1.6	0.4-4.7	1.6	0.2-4.2	1.6	0.3-4.7
	follow-up (years)	5.0	2.1-9.3	2.1	0.3-6.9	4.7	1.7-8.9
start of cART	CD4 (cells/mm^3)	137	49-244	57	6-110	123	45-225
	RNA (log_{10} copies/ml)	5.0	4.5-5.5	5.1	4.3-5.6	5.0	4.5-5.5
	age (years)	41.8	35.1-50.8	41.1	36.4-52.0	41.8	35.2-51.1
	AIDS	39	10.3	19	27.9	58	13.0
	follow-up (years)	3.6	1.5-7.3	1.9	0.6-4.3	3.4	1.4-7.1
present (1 June 2008)	CD4 (cells/mm^3)	374	213-516	50	6-89	365	201-511
	RNA <500 copies/ml[a]	152	40.1	3	4	155	34.7
	age (years)	44.8	39.2-53.3	47.6	43.4-58.0	45.5	39.8-54.1

IQR: interquartile range; MSM: men having sex with men; cART: combination antiretroviral therapy;

[a] available for 319 patients still alive and for 13 patients who died.

Table 9.2: Characteristics of the HIV-infected population in Curaçao

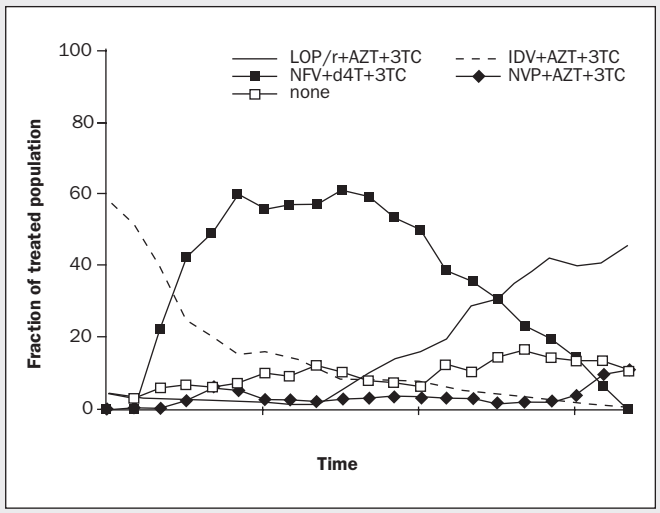


Figure 9.1: Percentage of patients treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. AZT: zidovudine; 3TC: lamivudine; IDV: indinavir; LOP/r: ritonavir boosted lopinavir; NFV: nelfinavir; NVP: nevirapine

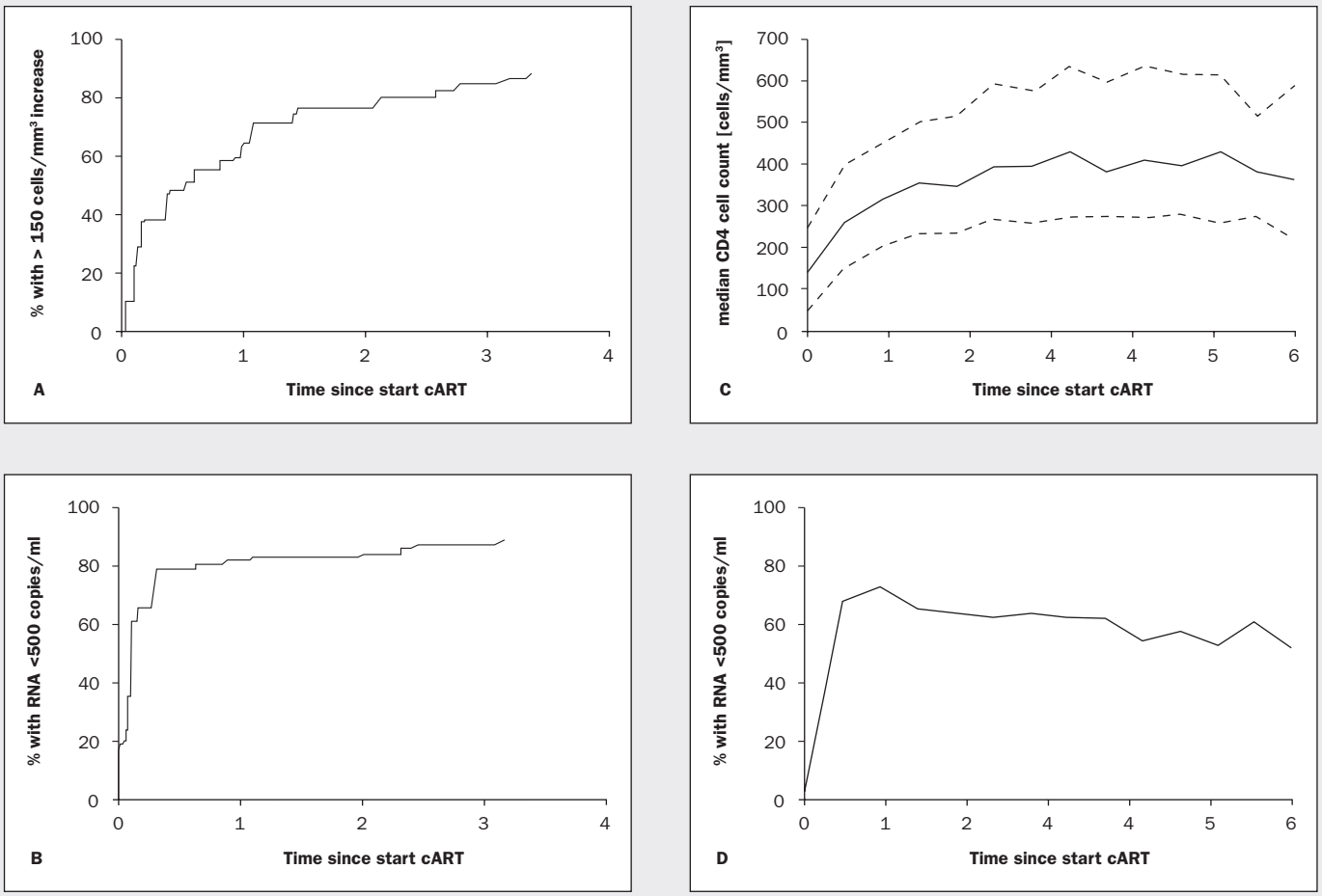


Figure 9.2: (a) Proportion of patients with a CD4 cell increase of more than 150 cells/mm^3 after start of combination antiretroviral therapy (cART), (b) proportion of patients reaching, but not necessarily maintaining, HIV RNA below 500 copies/ml after start of cART, (c) median CD4 cell count (solid line) and interquartile ranges (dotted lines) after start of cART, (d) proportion of patients with HIV RNA levels <500 copies/ml after start of cART. In all plots, only previously therapy-naïve patients are considered; (a) and (b) represent time to event analyses

10. The Amsterdam Cohort Studies on HIV infection

Annual Report 2007

Hanneke Schuitemaker

Introduction

The Amsterdam Cohort Study (ACS) on Human Immunodeficiency Virus (HIV) Infection and AIDS among homosexual men was initiated in 1984, followed shortly in 1985 by the Amsterdam Cohort Study among Drug Users. The ACS, a collaboration of the Public Health Service Amsterdam (PHSA), the Academic Medical Center of the University of Amsterdam, Sanquin Blood Supply Foundation, and the University Medical Center Utrecht (UMCU), is part of the Netherlands HIV Monitoring Foundation and financially supported by the Netherlands National Institute for Public Health and the Environment.

Until 31 December 2007, 2349 homosexual men (HM) and 1666 (injecting) drug users (DU) have been included in the ACS. Every 3 to 6 months, participants complete a standardized questionnaire designed to obtain information regarding medical history, sexual and/or drug use behaviour, underlying cognition, 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 biologic and immunologic tests and storage.

Of the 2349 HM, 571 were HIV-positive at study entry, and 198 seroconverted during follow-up. For the 1666 DU, 323 were HIV-positive at study entry, and 96 seroconverted during follow-up. By 31 December 2006, 331 HM and 405 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, homosexual men visited PHSA 46,910 times, and injecting drug users made 23,948 visits.

ACS Open*

The ACS data are very suitable for universities and research institutes to teach students in epidemiology, biomedicine, and social science 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, multi-level, and repeated measurement analyses. For this purpose, a data set that includes social-scientific, demographic, clinical, and biomedical information obtained from the participants of the ACS during the past 20 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 grant number 91104002 from MaGW and ZonMw.*

The cohorts in 2007

Homosexual men

In 2007, 551 HM were followed at the PHSA of Amsterdam. Forty-nine of them were newly recruited in 2007. 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 2007, 499 men were HIV-negative, and 52 men were HIV-positive. The HIV-positive men, of whom 36 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 the time of entry into the study in the cohort of young HM after 1999.

Another 7 HIV-positive men were included in the HOP, but were exclusively followed in an HIV treatment centre outside the PHSA. As of June 2006, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants were invited to participate in the ACS. By the end of 2007, 11 HIV discordant and 2 HIV-positive concordant couples had been included in this partner study.
In 2007, 226 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 25 other HIV treatment centres in the Netherlands. Sixty of them were HIV seroconverters. Plasma and cells from 54 of the 122 HIV-positive HM in active follow-up at the Jan van Goyen clinic in 2007 were stored. Of these, 33 were HIV seroconverters. The remaining 21 were defined as 1) a slow or non-progressor or matched fast progressor in 1996 and 2) HIV-positive for more than 10 years with a CD4 count greater than 400 cells/mm^3 after 10 years of follow-up after a HIV-positive result without effective therapy.

Drug users

In 2007, 432 drug users were followed at the PHSA of Amsterdam: 61 were young drug users (aged 30 years or less) and recruited after 2000. In 2007, six new drug users were included because of the possibility that they had received hepatitis C treatment within the cohort (see below Dutch-C study). The cohort remained open to drug users less than 30 years of age who had used cocaine, heroin, or amphetamines at least 3 times a week in the 2 months preceding enrolment. Of the 432 DU followed in 2007, 64 were HIV-positive, of whom 24 seroconverted 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), 15 HCV mono-infected DU in the cohort initiated HCV therapy in 2007, resulting in a total group of 35 DU on HCV therapy.

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 2006, 139 patients were already included as primary-infection patients. In 2007, 33 new patients with acute HIV-1 infection were enrolled in the study. Specimens of blood are collected from these patients for storage of plasma and peripheral blood mononuclear cells (PBMC). Sampling is more frequent early after entry into the study. For the ACS, follow-up of individuals randomized to the no-treatment arm is discontinued 1 year after the start of highly active antiretroviral therapy (HAART) caused by a CD4+ T cell decline to <350 cells/μl blood. Similarly, follow-up is discontinued 1 year after reinitiation of HAART for individuals who have to reinitiate therapy because of a CD4 decline to <350 cells/μl blood after scheduled interruption of the first HAART regimen begun during the primary infection phase.

HIV incidence

Nine homosexual men and one drug user had a first positive test for HIV in 2007 after a previous negative test. The drug user had a first positive test in 2007, but a last negative test in 2003, and therefore the HIV-seroconversion date is assigned to 2005 (midpoint between both dates). The incidence of HIV is approximately 1.2 per 100 person-years among HM and less than 1 per 100 person-years among DU. Figures 10.1 and 10.2 show the yearly HIV incidence rates for homosexual men and drug users since the start of the ACS through 2007.

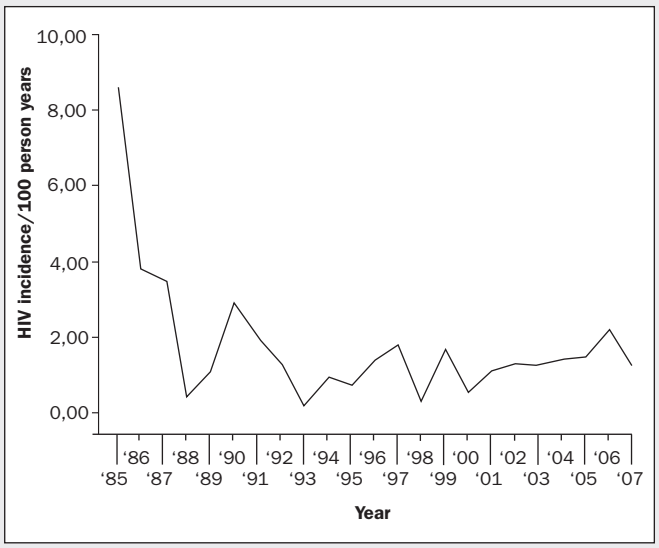


Figure 10.1: Yearly HIV incidence per calendar year in the ACS among homosexual men (HM)

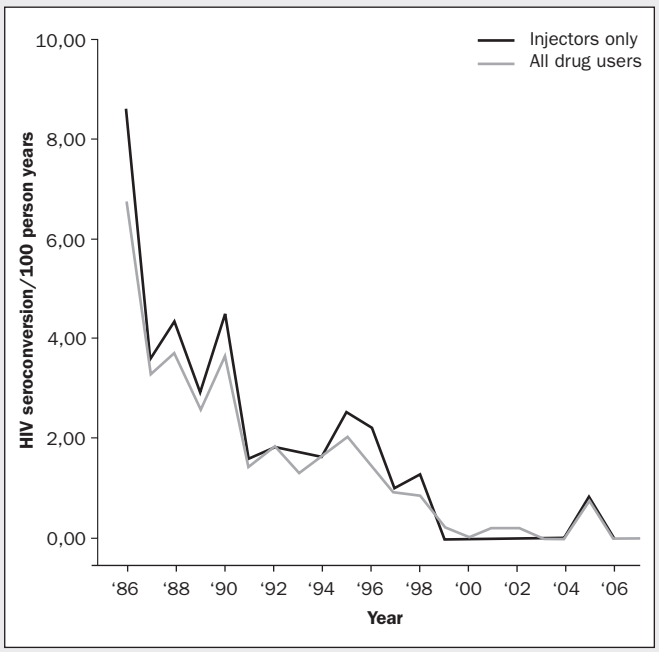


Figure 10.2: Yearly HIV incidence per calendar year in the ACS among drug users (DU)

Transmission of therapy resistant HIV strains

Of 10 HIV seroconverters with a first positive test result within the ACS in 2007 (9 HM, 1 DU), a sequence could be obtained for 8. Of these, no one was found to be infected with a drug-resistant strain.

HAART uptake

For the 243 HIV-positive HM (226 of whom were recruited before 1999 and 17 after 1999) who visited the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands in 2007, all received some form of antiretroviral therapy. Of 202 HM with a known viral load, it was less than 50 copies/ml (assays: bDNA, M2000rt) for 189 men (94%).

Of the 64 HIV-positive DU who visited the PHSA of Amsterdam in 2007, 40 (59%) received any combination of antiretroviral therapy. Of these, 33 (83%) had an undetectable viral load (less than 150 copies/ml (assay: m2000rt)) at their latest visit. Of 18 HIV-positive drug users not receiving HAART, 6 (33%) had an undetectable viral load.

In 2007, adherence was determined amongst 100 HIV-positive DU attending the ACS and reporting HAART use between January 1999 and August 2007. Full adherence (defined as taking more than 95% of medication in the past 6 months) was reported in 87.8% of visits. (Lambers et al., submitted).

Risk behaviour HM

In 2007, 558 HM (551 participants visiting the APHS and 7 HIV-positive men followed outside the APHS) filled in the behavioural questionnaire at least once. Of the 499 HIV-negative HM, 51.7% reported unprotected anal intercourse (UAI) in the past 6 months. Of the 59 HIV-positive HM, 23.3% reported UAI in the past 6 months.

Like the HIV incidence, trends in unprotected anal intercourse (UAI) amongst young (<36 years of age) HIV-negative HM participating in the ACS have remained relatively stable in recent years. See Figure 10.3.

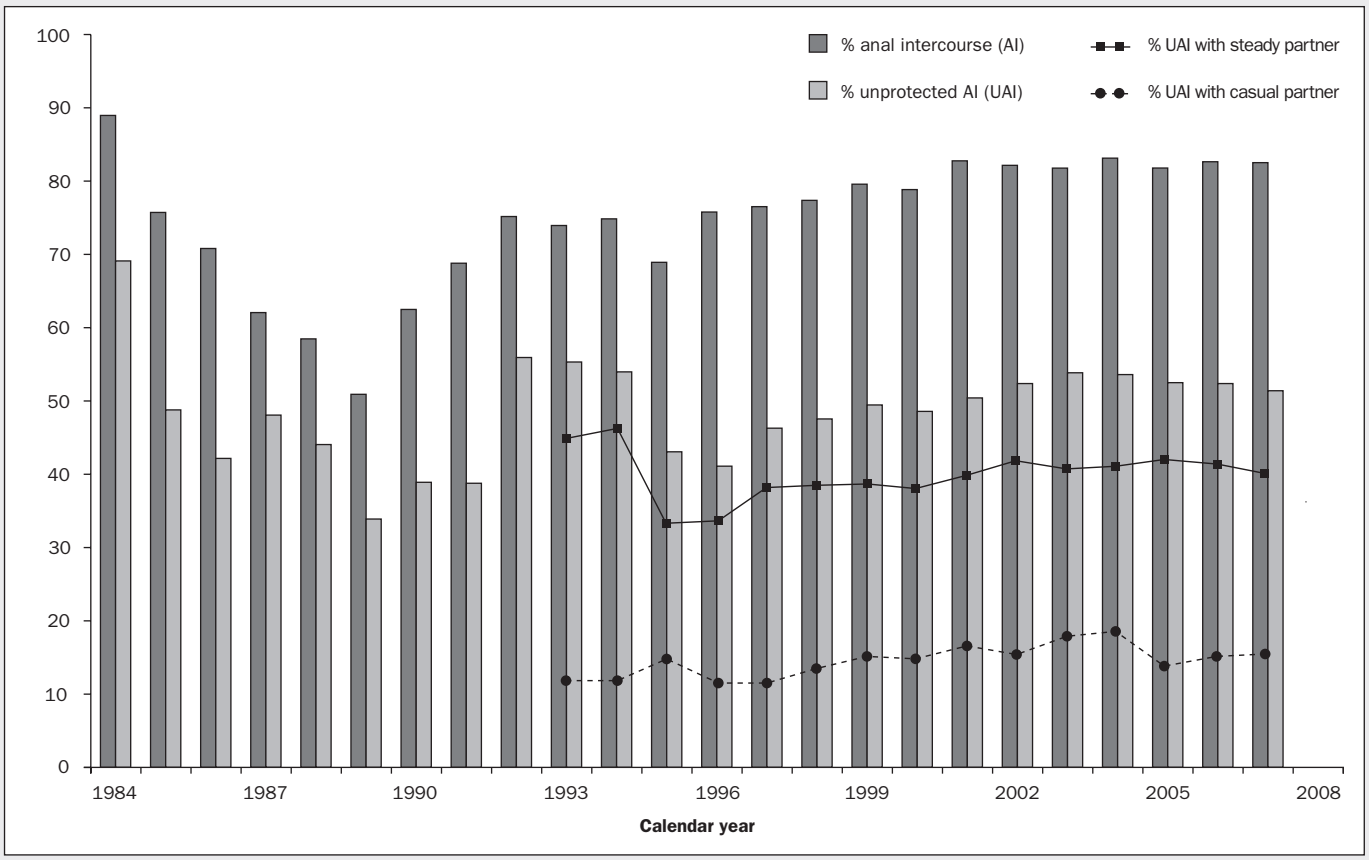


Figure 10.3: Trends in unprotected anal intercourse in the past six months amongst young HIV-negative HM (age at entry<30 and current age <36) from the Amsterdam Cohort Study 1984-2007

Risk behaviour DU

In the cohort of HIV-negative DU, reports of both injecting drugs and borrowing needles significantly declined over the period 1985-2007 (Lindenburg et al, 2006 + update 2007). Reports of sexual risk behaviour and sexually transmitted infections (STI) at follow-up visits decreased before 1996, but not after 1996 (see Figure 10.4). This trend has not changed in recent years.

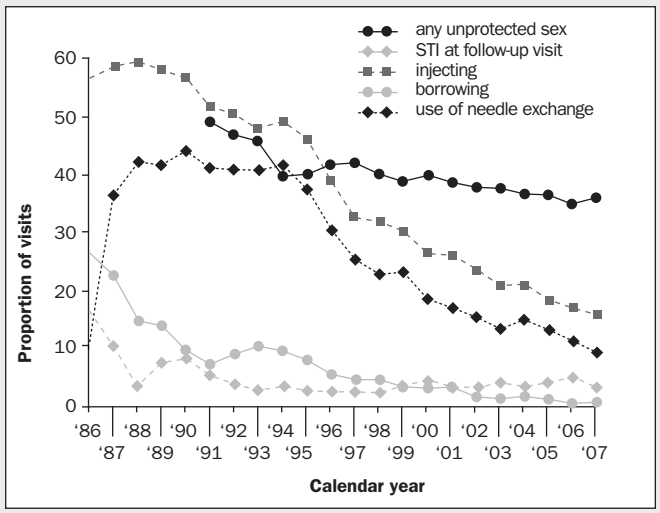


Figure 10.4: Proportion of visits per calendar year at which injecting drugs and sexual risk behaviour was reported among 1315 DU who were HIV-negative on ACS entry, 1986-2007

Herpes Simplex Virus (HSV)-1 and HSV-2 prevalence among homosexual men

Between 1984 and 2003 seroprevalence of HSV-1 and HSV-2 was determined amongst 1847 HIV-positive and HIV-negative HM. Of these men, 1207 (65%) were HSV-1 antibody positive, whilst 759 of the 1847 (41%) were HSV-2 antibody-positive. Of the total group, 558 (30%) were positive for both. HSV-1 and HSV-2 prevalence decreased over calendar time among HIV-negative HM, but remained stable in those who were HIV-positive. The association between HIV infection and HSV-2 became stronger over time. (Smit et al., 2007)

Incidence of hepatitis C (HCV), hepatitis B (HBV) and HIV among injecting drug users

HIV, HBV, and HCV incidences were determined among 960 ever-injecting DU (IDU) between 1985 and 2002. These data were used to model patterns of incidence for all three viruses with use of flexible curves. Differences between the three separate incidence curves over calendar time were calculated.

Figure 10.5 shows that there was a difference in the incidence of new infections each year for HIV, HBV, and HCV. The decline in incidence over time followed the same trend for all three viruses, probably due to a decline in injecting behavior. However, for HBV this decline started later, which might have been due to sexual transmission or a difference in transmissibility of HBV.

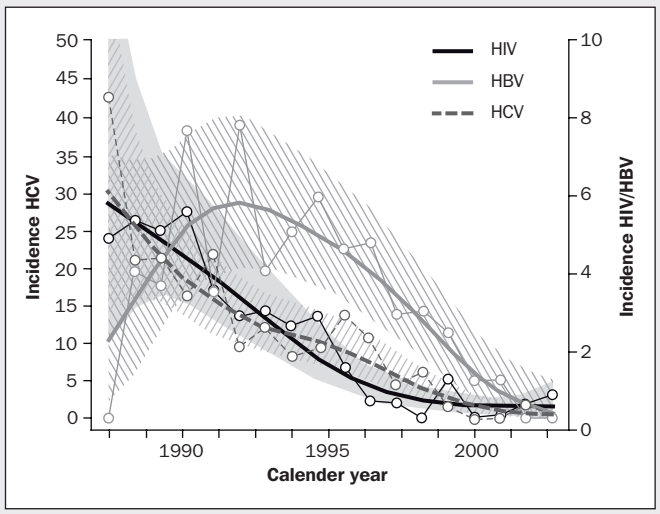


Figure 10.5: HIV (black), HBV (grey), HCV (dashed) incidence among IDU in Amsterdam, 1985 until 2002

Steering committee: The politburo

In the 2007, the politburo met several times to consider proposals submitted for use of data and/or samples (serum/PBMCs): 22 from Sanquin, 5 from the AMC, 2 from the PHSA, 7 from the UMCU, and 2 from researchers not affiliated with the ACS. All requests were approved, some after revision.

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Co-promotor: Nicole Dukers

Colette Smit
25 years of HIV: Trends in mortality, HIV co-infections, and HIV-related risk behaviour
10 april 2007
Promotor: Roel Coutinho
Co-promotor: Maria Prins

Marloes Naarding
Inhibition of mother to child transmission of HIV-1 during breastfeeding
9 March 2007
Promotor: Ben Berkhout
Co-promotor: Bill Paxton

Esther Quakkelaar
Antibody neutralization of HIV-1
March 23 2007
Promotor: Hanneke Schuitemaker

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Colophon

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Mission
The HIV Monitoring Foundation is appointed by the Dutch Minister of Health, Welfare and Sports (Ministerie van Volksgezondheid, Welzijn en Sport) as the national executive organization for the registration and monitoring of HIV-infected patients in follow-up in one of the Dutch Treatment Centres. Our mission is to further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection.

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