REPORT 2010

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

STICHTING HIV MONITORING

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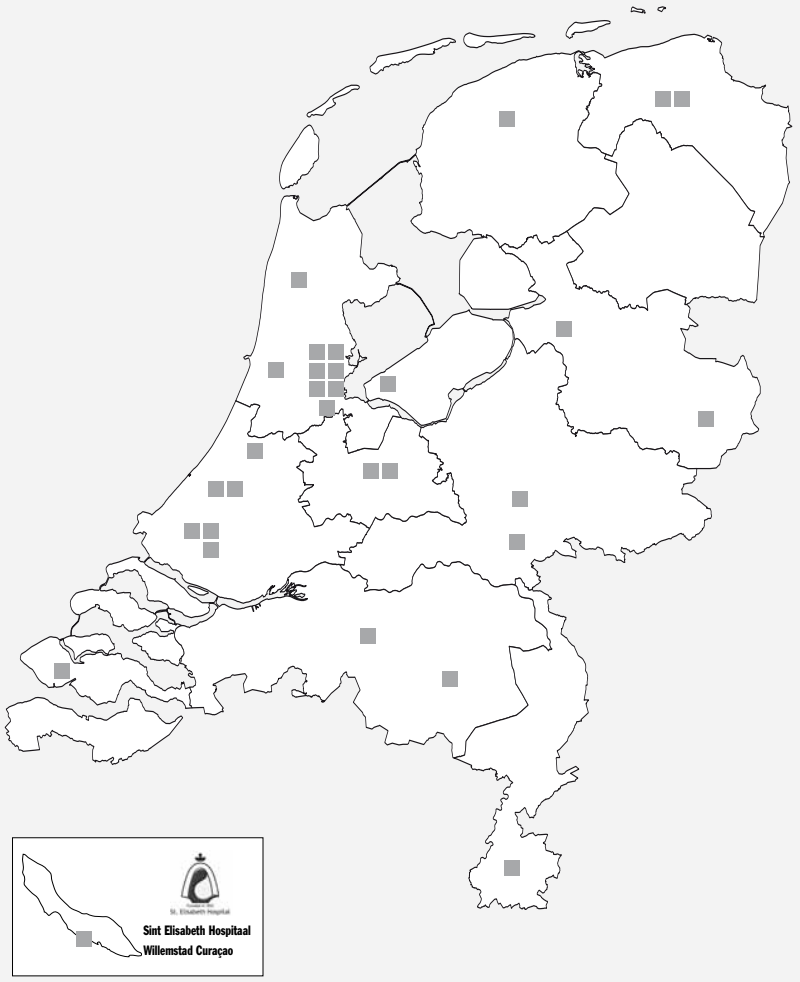

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table of

contents

introduction

In the annual report of Stichting HIV Monitoring (SHM, the Dutch HIV monitoring foundation) on the monitoring programme in the Netherlands, SHM provides information on trends over time in the epidemic and the effect of treatment on HIV. The main trends we report this year are the ongoing increase in the number of HIV diagnoses amongst men who have sex with men and the late start of combination antiretroviral therapy (cART). cART has effectively suppressed virus production in the monitored populations and the incidence of toxicity-driven treatment changes has declined over time. The increase in non-AIDS-related causes of death in the chronically HIV-infected population who receive lifelong treatment has continued. In addition, we report on the limit to which CD4 cell counts seem to recover, even when cART is initiated early in the infection.

Stichting HIV Monitoring 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 1 of the 25 hospitals throughout the country that are acknowledged as HIV treatment centres. Treating physicians have access to the data provided by each centre to SHM, and, when research proposals are approved, to all the data available from all the centres. Other HIV research groups have access under the same conditions.

The report, after the summary and recommendations, includes a section on the quality of data collected by SHM; one chapter in this section focuses on the prediction of missing data on liver fibrosis by use of the alanine aspartyl transferase-to-platelet ratio index (APRI) as an indicator for source data verification for liver fibrosis. A section on the HIV monitoring programme follows, with more detailed descriptions of the findings on the number of newly registered HIV diagnoses, the changes over time in the initial characteristics of the infected population at the time of diagnosis, the effects of cART, and the development of resistance to antiretroviral drugs. Also in this section are chapters on HIV infection amongst pregnant women and children and co-infection with hepatitis B and hepatitis C virus.

The Special Reports section includes a chapter on results from the Amsterdam Cohort Studies and one on HIV in Curaçao and the Netherlands Antilles. References can be found in a separate section after Special Reports. This year we have introduced a summary in English and Dutch at the beginning of each chapter. A web-based Appendix with supplementary tables and figures can be found on our website, www.hiv-monitoring.nl.

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

Professor Frank de Wolf, MD
Director, Stichting HIV Monitoring

summary & recommendations

Frank de Wolf

Treatment of HIV

In 1987, 18 asymptomatic men who had tested positive for HIV-1 antigen and were in the Amsterdam Cohort Study involving homosexual men took part in the first trial with azidothymidine, or AZT[1]. The result was remarkable, although short-lasting. The amount of virus, which was monitored by measuring the concentration of HIV-1 p24 antigen in serum, decreased, and CD4 cell counts increased. However, after 48 weeks of treatment, results began to deteriorate, i.e., the initial increase in CD4 cell counts was not sustained, and serum antigen levels rose in a number of the participants[2]. Also, although disease progression to AIDS was postponed, neither the initial development of the disease nor the progression to death was halted. Moreover, resistance to AZT developed in the participants in the trial within 2 years of treatment[3].

Ten years later, the era of combination antiretroviral therapy (cART) had just started and a large study to evaluate AIDS therapy in the Netherlands, the ATHENA study, was established, with the aim of monitoring the effect, side effects and development of resistance amongst the substantial number of infected people who were, and would be, treated with a combination of at least three drugs from two different drug classes. In 2001, the ATHENA report summarised the impressive results of cART in 3449 HIV-infected patients. The incidence of AIDS and AIDS-related mortality substantially declined, HIV production was substantially suppressed on both the individual and population level, and a substantial immune restoration was reflected by the increase in CD4 cell numbers over time[4].

Adverse events that frequently resulted in changing the combination of drugs used in the regimen were reported following the start of cART. Obviously, the long-term toxicity of the drugs in use at the time and development of resistance to antiretroviral drugs were subjects of debate. Those issues, together with the uncertainties regarding the long-term efficacy cART, were the primary reasons for converting ATHENA into a permanent facility, Stichting HIV Monitoring (SHM, the Dutch HIV monitoring foundation).

Currently, 23 years after the first trial in asymptomatic HIV-infected individuals, 17,327 patients are registered with SHM and 16,832 of them have a date of diagnosis. Of the latter group, 13,917, or 83%, were ever receiving cART. Antiretroviral drugs are exclusively prescribed to HIV-infected individuals by or under the supervision of HIV/AIDS-treating physicians in one of the 25 HIV treatment centres throughout the country. SHM monitors the infected population followed in these centres and collects data on the course of HIV infection in both treated and untreated patients.

Despite considerable success in suppressing viraemia and preventing progression of the disease and resulting death in HIV-infected individuals, it has not been possible to induce permanent remission of the disease in the absence of antiretroviral drugs. HIV appears to be able to shield itself from the human immune system and from cART in so-called cellular sanctuaries. These sanctuaries form persistent reservoirs of infection and are major obstacles in curing HIV infection. Because HIV infection cannot be cured, infected individuals on cART are at risk of the cumulative effects of drug toxicities. In addition, episodes of viraemia that occur due to variation in the level of adherence to the regimen may induce chronic inflammatory responses, as well as development of resistance and virologic failure.

The 2010 scientific report of SHM continues to provide an overview of the HIV epidemic in the Netherlands and the changes after the introduction of life-long antiretroviral treatment.

First, we report on the trends over time in mortality and morbidity in the HIV-infected population in the Netherlands (Chapter 3). Mortality rates and incidence of AIDS amongst HIV-infected individuals have been in a steady decline since the introduction of cART in 1996. The incidence of serious non-AIDS–defining events in the treated population is higher than the incidence of AIDS-defining events when CD4 cell counts are above 200 cells/mm^3, and since 2005 the annual incidence of serious non-AIDS–defining events has been higher than that of AIDS-related events. Interestingly, the incidence of death because of non-AIDS–defining malignancy, myocardial infarction and suicide in male patients with HIV infection appears to be higher than in the age-standardized general male population. Older age, longer exposure to HIV and higher levels of immune deficiency, as well as intravenous drug use as the mode of HIV transmission, were independently associated with a higher risk for serious non-AIDS–defining diseases. Studies will be needed to disentangle the effects of HIV infection itself, HIV treatment, and behavioural risk factors for each specific non-AIDS–defining disease.

But AIDS still exists, and the number of new AIDS diagnoses has remained stable at 120 to 140 diagnoses per year. This implies that testing rates in individuals at high risk for HIV infection must be improved to reduce the number of patients diagnosed at an advanced stage of the disease, to ensure a timely start of cART, and to contribute to a further decline in mortality.

The effect of cART on HIV production and the immune system is monitored through the longitudinal follow-up of two key laboratory measures: the concentration of HIV RNA in plasma and the number of CD4 lymphocytes in peripheral blood (Chapter 4). Both measures are clinically relevant predictors for progression to HIV-related disease and AIDS-related death.

cART should preferably commence when CD4 cell counts are still at or above the level of 350 cells/mm^3, according to treatment guidelines from 2008 onwards[5-7]. Previously, the threshold was 200 cells/mm^3. According to the prior guidelines, overall, 38% of the patients presented for HIV care late in the infection, which becomes 56% when the CD4 threshold in the current guidelines is used. Although late presentation over time declined to 40% in 2009 in homosexual men, there is still room for improvement. Improved testing policies are especially needed for the populations at risk for acquiring HIV through heterosexual contact, since late presentation ranges between 50% (women) and 70% (men).

The late start of cART, defined as a start when CD4 cell counts are below 200 cells/mm^3, occurred in 13% of the patients diagnosed with HIV between 1996 and 2009, whilst CD4 cell counts were well above 350 cells/mm^3 at the time of diagnosis. A late start of cART was associated only with intravenous drug use and HIV diagnosis between 2001 and 2003. So, although improvements have occurred in recent years, attention should still be given to preventing the late start of cART.

Most of the patients treated with cART achieve sustained suppression of HIV viral load, and HIV RNA plasma concentrations of <50 copies/ml are found in 50% of the patients within 4.8 months of treatment. The probability of maintenance after the initial suppression to <50 copies/ml has increased with a longer time on cART and with later calendar years. Seven years of successful cART-induced viral suppression has resulted in an increase of CD4 cell counts to a median of 750 cells/mm^3, provided that cART was started when counts were between 350 and 500 cells/mm^3. Interestingly, with a longer time on cART, older age and higher CD4 cell counts, an increasing proportion of patients have experienced periods of decreasing CD4 cell counts whilst maintaining virological suppression to <50

copies/ml. The question of why a CD4 cell count decreases after long-term viral suppression that has resulted in almost normal CD cell counts needs further analysis.

Finally, on the basis of the declining incidence of toxicity-driven therapy changes since 2000, it appears that less toxic drugs, together with better insights into the prevention of toxicity, have improved the clinical management of HIV infection in patients on cART.

Viral suppression was found to be incomplete in a small group of patients monitored in the SHM observational database (Chapter 5). Incomplete suppression may be a marker of inadequate adherence to therapy and may herald the presence of drug resistance. In the Netherlands, incomplete suppression, or virologic failure, is observed in 8% to 10% of the treated patients annually, and 39% of the patients have one or more episode of failure. Altogether, 9% of patients currently in follow-up are resistant to at least one antiretroviral drug, which is probably an underestimation, since a sequence is obtained in less than one third of patients with virologic failure.

Evidence of transmission of resistant virus is found in less than 5% of newly diagnosed patients. The relatively low annual percentage of incomplete suppression amongst treated patients and the low percentage of resistance amongst newly diagnosed patients indicate that the contribution of the population receiving cART to the transmission of HIV is limited.

Hepatitis B (HBV) and C (HCV) infection are highly prevalent amongst HIV-infected individuals and are associated with major liver diseases such as hepatic fibrosis, cirrhosis and hepatocellular carcinoma (Chapter 6). HIV seems to accelerate the progression of HBV- and HCV-related liver disease. The impact of HBV and HCV on the course of HIV infection is still unclear. To gain insight into the changes in the course of both HBV-HCV and HIV infections, we also monitor patients for HBV and HCV co-infection.

The prevalence of HBV co-infection up to 2009 appears to be 7%, for HCV this is a prevalence of 11%, and for co-infection with both HBV and HCV it is 1%. HBV co-infection is associated with male gender and younger age, and HCV co-infection is associated with injecting drug use and a European origin other than Dutch. However, the HCV prevalence significantly rose over time amongst homosexual men, and currently homosexual men form the largest group of patients with HCV co-infection. This increase also implies that HCV transmission is likely to be caused by sexual transmission.

When we adjusted for demographic and clinical differences, the risk of death in the co-infected population appears to not differ significantly from the population solely infected with HIV. This stresses the importance of successful treatment of these co-infections and the need to test for HBV and HCV infections.

In addition to HBV/HCV co-infection, we analysed available data on sexually transmitted infections (STIs), since STIs are relatively frequent amongst HIV-infected individuals and especially amongst young adults and homosexual men. The prospective collection of data regarding STIs such as chlamydia, lymphogranuloma venereum, gonorrhoea and syphilis started in 2008. Most patients were screened whilst having symptoms of an STI. A preliminary and descriptive analysis shows that STIs frequently occur in the HIV-infected population. Half of the patients tested for syphilis were reported to have an active syphilis infection, and a substantial number of patients were diagnosed with neurosyphilis between 2000 and 2010. Further study is needed to analyse associations between STIs and HIV disease progression and the HIV epidemic, including

studies of the prevalence and incidence of neurosyphillis among HIV-infected individuals.

Preventing new infections

In previous reports and studies we have signalled the growth of the HIV-infected population since the introduction of cART in 1996. In part, the increasing life expectancy of people infected with HIV explains the growth in the total number of those infected. However, over time there also has been an increase in the number of new and recent infections. That increase started a few years after 1996 and was seen especially amongst men who were reported to be infected by having sex with men; in this group the annual number of new infections since 2006 doubled to 850 in 2008. A doubling of the annual number of new infections was also found amongst men and women who heterosexually acquired HIV, but that number of new infections has declined since 2004, although it is still higher than in 1996. Together with the stable low number of new infections amongst intravenous drug users, the number of new infections have totalled about 1000 to 1200 annually since 2005.

The increase in the number of new infections a few years after the start of large-scale antiretroviral treatment[8] indicates that either cART does not suppress virus production sufficiently to prevent transmission or it does, thereby leading to the conclusion that the remaining group of untreated HIV-infected individuals are driving the epidemic. Since cART effectively lowers HIV viral load and low viral load limits transmission, only undetected episodes of high-level viraemia (episodes of non-adherence or virological failure) could explain sufficient transmission whilst patients are receiving therapy. However, the frequency of such episodes appeared to be low[9] and seemingly insufficient to maintain the epidemic. In addition, if the population with virological failure under cART were the source of transmission, an increase in transmission of drug-resistant HIV would be expected. So far, such an increase has not been observed in the SHM observational database.

So, if cART prevents transmission of HIV to a certain extent, then the people contributing most to the increase in the number of new infections over time are those who are infected but untreated, largely because they are not aware of their infection. It is estimated that approximately 8,000 to 10,000 individuals in the Netherlands do not know they are infected. Together with those who are aware of having been infected but who are not yet receiving cART, they will contribute most to the spread of HIV. To better understand the impact of cART on the epidemic, we mathematically modelled the HIV epidemic using data from the Amsterdam Cohort Studies and from the SHM observational database. We have shown that, along with preventive measures such as condom use, lowering population viral load by mass cART indeed brings the transmission of HIV down sufficiently to levels where the epidemic becomes unsustainable. However, to explain the observed increase in the number of new infections, the model predicted that 90% of new HIV infections will come from people unaware of their infection. Hence, increasing risk behaviour in that particular group will substantially impact the spread of HIV[8].

The HIV epidemic in the Netherlands

As of June 2010, 13,035 HIV-infected patients, including 12,946 adults and 89 children and adolescents, were still under clinical observation in one of the 25 HIV treatment centres in the Netherlands. Almost one third of the population in care was 50 years of age or older. More than 1100 new HIV infections are diagnosed each year, and the number of diagnoses is steadily increasing amongst men who have sex with men (MSM). In 2008, the annual number of new infections amongst MSM was 850, a number that has not been observed since the

peak of the HIV epidemic in the early 1980s. Although patients are being diagnosed earlier in their infection, as is manifest from increasing $CD4^+$ T cell counts at diagnosis, approximately 40% of MSM and more than half of heterosexual men and women are diagnosed with CD4 counts below 350 cells/mm^3, which currently is the CD4 threshold above which treatment should be started. Testing for HIV is becoming more frequent. As HIV-infected women currently in follow-up age, the number of pregnancies in this group decreases. It is to be expected that the number of children born with HIV infection in the Netherlands will stay close to zero as a result of the ongoing screening for HIV amongst pregnant women.

General conclusions and recommendations

HIV in the Netherlands is a concentrated epidemic that continues to grow amongst homosexual men more rapidly than it grew at the beginning of the epidemic. The sources that drive the epidemic are men who are most likely unaware of having been infected recently and are involved in high-risk sexual behaviour. Prevention measures should focus preferably on men in this phase of their infection. Although the 'test and treat' approach is still debated, SHM will direct a proportion of its capacity for analysis to simulation studies of the impact of HIV testing schemes and approaches to treatment on the spread of HIV.

AIDS still exists, with a stable number of 120 to 140 new diagnoses per year. Late presentation, defined as presentation for care with a CD4 cell count below 350 cell/mm^3 or presentation with an AIDS-defining disease, is frequent in the HIV-infected population. This is another reason to improve testing strategies, since according to current guidelines, cART should start when CD4 cell counts are at or above 350 cells/mm^3. Late presentation and presentation with advanced disease are further reasons to study the delay of entry into HIV care, which will be undertaken in collaboration with the National Institute for Health and the Environment (RIVM).

In 2009, half of the patients started cART with CD4 cell counts well below the recommended threshold of 350 cells/mm^3, and 13% of all patients diagnosed with HIV between 1996 and 2009 and with a CD4 cell counts equal or higher than 350 cells/mm^3 started cART with counts below 200 CD4 cells/mm^3. This indicates that, in addition to preventing transmission of HIV, improvement of HIV testing rates is needed to achieve higher proportions of infected people who have a timely start of cART.

Although the response to cART has improved over time, CD4 cell counts seem to decline in an increasing proportion of successfully treated patients with a longer time on cART, older age and higher CD4 cell counts during follow-up. This observation might reflect a decrease in thymic output with older age or might be the result of continuous low-level immune activation due to persistent low-level viral production. Further monitoring of these patients including follow-up of immune activation markers might provide better insight into the trend in CD4 cell counts over time after long-term continual cART.

From 2000 on, a decrease has been found in toxicity-induced changes in cART regimen, indicating improved clinical management of adverse events in patients on cART. SHM will continue to participate in international collaborations, such as the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, that aim to achieve insights into possible associations between certain drugs or drug combinations in cART regimens. Because of these collaborations, the collection of data on co-morbidity has grown substantially within the SHM observational database, and we are currently comparing co-morbidity rates prior to and after start of

cART. This work will also include studies of possible associations between HIV and certain co-morbidities and will contribute to research questions regarding HIV and aging.

In addition to our efforts in disentangling the association between HIV and co-infection with HBV or HCV, SHM will further study the impact of STIs on the course of HIV infection. Collection of data on STIs has started recently, and preliminary analyses reveal high numbers of active cases of syphilis and neurosyphilis.

During the last few years, virological failure amongst patients on therapy has been constant at 10% per year. However, for some time the frequency of measuring HIV RNA plasma levels has been in decline, and we reported earlier on the relationship between frequency of measurement and observation of episodes of viraemia. SHM will make an effort to further analyse this relationship and the occurrence of resistance.

Observed resistance-associated mutations amongst patients in whom therapy has failed is about 15%, with 9% having high-level resistance to at least one drug. The low level of measurement of drug resistance in patients in whom therapy has failed has resulted in a substantial underestimation of the true prevalence of resistance. This is of concern since, in those patients who were tested, one third had resistance to two of the three drug classes, nucleoside reverse transcriptase inhibitor (NRTI), non-nucleoside reverse transcriptase inhibitor (NNRTI), and protease inhibitor (PI), and one patient out of ten was resistant to all three of the classes. We recommend improving resistance measurement, so that all patients in whom cART fails are tested in order to discover resistance in time and avoid episodes where cART treatment is less than adequate.

The population of HIV-infected individuals who are being monitored through HIV care and who have access to cART is growing. By monitoring this population carefully and by predicting the outcomes, SHM is in a position to contribute substantially to the further development of both HIV health care and public health policies. For instance, important parameters, such as predicting time to entry into heath care, to the start and failure of therapy, to AIDS-related and non-AIDS–defining events, and to death, as well as predicting the distribution over time of CD4 cell counts, viral-load peaks, and risk groups including migrants, need to be analysed and used in modelling the progression of HIV, the effect of cART, and subsequently, the estimates of people living with HIV. SHM should further data analyses and model development and continue to contribute to the understanding and predictions of the changes in the HIV-infected population in the Netherlands[8, 10-12]. Together with our modelling partners at Imperial College (Chapter 7)[13] and in collaboration with groups such as the AntiRetroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), SHM can help reliably answer questions on prevention, diagnosis, and treatment of HIV in Europe.

data quality

1. Improvement of data on liver fibrosis

Sima Zaheri, Bianca Slieker, Colette Smit

In January 2006, Stichting HIV Monitoring (SHM implemented new customized procedures for continuous monitoring and improvement of the data quality[14, 15]. These procedures include selection and verification of data that have a marked influence on the data analyses. To select specific items for quality control, data-consistency checks are performed.
One clinical event often used as an endpoint in studies of non-AIDS related events in HIV-infected individuals is the diagnosis of liver fibrosis as a sign of progression to liver failure. The development of liver fibrosis in patients infected with hepatitis C virus (HCV) and those co-infected with HIV and HCV can be shown by the clinical marker alanine aspartyl transferase (AST)-to-platelet ratio index (APRI)[16]. In this study, we demonstrated that the APRI score can be used to select data for quality control in order to identify missing data on liver fibrosis in the SHM observational database.

Vanaf januari 2006 heeft Stichting HIV Monitoring (SHM) nieuwe op maat procedures geïmplementeerd voor de continue monitoring en verbetering van de kwaliteit van data[14, 15]. Deze procedures bestaan onder andere uit selectie en verificatie van data die een grote invloed hebben op de uitkomsten van de data-analyses. Daarvoor, worden dataconsistentie controles uitgevoerd om specifieke data-onderwerpen te selecteren voor kwaliteitscontroles.
De diagnose van leverfibrose is een teken van het ontwikkelen van leverfalen en wordt daarom vaak gebruikt als een 'endpoint' in studies van niet aan AIDS gerelateerde ziekten onder HIV besmette personen. Er is aangetoond dat de APRI (alanine aspartyl transferase (AST)-to-platelet ratio index) score een goede marker kan zijn voor het ontwikkelen van leverfibrose in HIV- en HIV-HCV- geïnfecteerde patiënten[16]. In deze studie hebben we aangetoond dat de APRI score ook gebruikt kan worden voor het selecteren van data voor kwaliteitscontroles om gemiste diagnose data van leverfibrose in de SHM database te kunnen identificeren.

Data (outlined in Web Appendix Table 1.1) on all HIV-infected patients who visit one of the 25 HIV treatment centres in the Netherlands and are registered at Stichting HIV Monitoring (SHM) is obtained directly from the patients' medical files and electronic data sources, according to the data collection protocols, and are entered on site in the SHM observational database.

Continuous monitoring of data quality is essential for all clinical research, and it is especially crucial for observational data like those of SHM[17-21]. The accuracy and completeness of SHM data sets is maintained by the data monitors at SHM by source data verification (SDV) and subsequently by resolving the identified discrepancies. Given the large population size of our cohort, it is not feasible to perform a 100% verification of the data sets. Therefore, the customized procedures implemented in 2006 are used to effectively select data for verification by the data monitors[14, 15]. Data-consistency checks are performed for quality control by selecting specific data areas that show discrepancies or include missing data. Clinical markers are used to identify missing data on clinical events. The aim of these customized procedures is to improve the quality of data that have a major impact on data analyses.

Data on hepatic fibrosis

Non-AIDS-related illnesses are becoming an increasingly important cause of death in HIV-infected patients receiving highly active antiretroviral therapy

(HAART)[22-28]. In particular, liver disease is shown to be a major contributor to mortality amongst HIV-infected patients due to the high prevalence of co-infection with hepatitis B virus (HBV) and hepatitis C virus (HCV)[29-32]. Also, the progression of liver disease associated with HBV, HCV, or both is known to be accelerated by HIV[33].

As combination antiretroviral therapy (cART) has led to significant increases in the life expectancy of HIV-infected patients, longitudinal and correct registration of progression of liver disease has become highly important.

Hepatic fibrosis is often used as an end point in studies on disease progression to liver failure amongst HIV-positive patients co-infected with HBV or HCV[34, 16, 35]. For the collection of data on liver fibrosis, SHM data collectors depend on a variety of sources for clinical information. Hence, registration of liver fibrosis is easily affected by missing data. For that reason, SHM investigated the possible predictive role of the alanine aspartyl transferase (AST)-to-platelet ratio index (APRI) in the quality of data collected on liver fibrosis.

Predictive value of the APRI score

The APRI has been shown to be a valuable predictor for the development of fibrosis in HCV-infected and HIV-HCV co-infected patients[16]. In this case-control study, we used the APRI score to investigate its predictive value for data on liver fibrosis missing from the SHM database. Since the APRI score >1.5 is found to be predictive for liver fibrosis[16], we hypothesized that data quality control of cases with APRI >1.5 could result in identification of missing data, and thus it could be an efficient procedure to improve the quality of data on liver fibrosis.

We were able to calculate the APRI scores for 6441 of 17540 patients with data in the SHM database. The APRI score was defined as [100 x (AST/upper limit of normal)/platelet count (10^9/L)]. The APRI score is calculated with laboratory results that were entered either manually or directly into the SHM database by means of an automated "lab link". The lab link data contain all the values for AST and platelets available in the hospital's computerized information system and the data are of good quality because errors caused by manual entry are prevented. For this study we used only data from the Academic Medical Centre (AMC) of the University of Amsterdam, which has the largest data set of cases with lab link data. Of 2319 cases with an available APRI score, 579 (25%) had an APRI score >1.5 and 1740 (75%) had an APRI score <1.5. We randomly selected patients from both groups for quality control by SDV. At the time of the analysis, data from 497 cases (APRI >1.5) and 529 controls (APRI <1.5) were verified (Table 1.1). During the SDV, the values on which the APRI scores are based were checked and subsequently all available data sources (physicians' notes and letters in the medical files, liver biopsy, and CT scan, MRI, and abdominal ultrasonography reports) were consulted for verifying data on liver fibroses. The numbers of missing and incorrect records were determined by the data monitors. The results of SDV were registered for further analysis.

SDV by data monitors revealed 42 missing diagnoses of fibrosis in the case group and no missing records in the control group. After SDV, the total number of records that included fibrosis was 84 (17%) in the case group (Table 1.1).

SDV of cases with an APRI score >1.5 seemed to result in a substantial improvement of the quality of data regarding fibrosis, because it identified all of the missing fibrosis diagnoses (50%) in this group. However, to evaluate this new quality control procedure before its implementation in all hospitals, we used a binary classification test to measure its sensitivity and specificity (Table 1.2). Assuming that SDV can be used

Table 1.1: Results of source data verification (SDV): APRI score as a predictor for missing data on a diagnosis of fibrosis.

	AMC N	Total N
Before SDV in the database		
Patients with data	2391	17540
Patients with APRI	2319	6441
Patients with APRI <1.5	1740	4926
Patients with APRI >1.5	579	1515
Patients with fibrosis diagnosis	74	414
Patients with APRI <1.5 and fibrosis diagnosis	17	44
Patients with APRI >1.5 and fibrosis diagnosis	56	214
Before SDV in the selection for SDV		
Patients in the selection	1026	
Patients with APRI <1.5	529	
Patients with APRI >1.5	497	
Patients with fibrosis diagnosis	47	
Patients with APRI <1.5 and fibrosis diagnosis	5	
Patients with APRI >1.5 and fibrosis diagnosis	42	
After SDV		
Patients with APRI <1.5	529	
Patients with APRI >1.5	497	
Patients with fibrosis diagnosis	89	
Patients with APRI <1.5 and fibrosis diagnosis	5	
Patients with APRI >1.5 and fibrosis diagnosis	84	
Identified missing record of fibrosis diagnosis in patients with APRI <1.5	*0*	
Identified missing record of fibrosis diagnosis in patients with APRI >1.5	*42*	

Legend: AMC=Academic Medical Centre, University of Amsterdam; APRI=alanine aspartyl transferase (AST)-to-platelet ratio index.

as the gold standard to identify a diagnosis of fibrosis, we defined true positive cases as patients with a diagnosis of fibrosis who had an APRI >1.5, and true negative cases as those without a diagnosis of fibrosis who had an APRI <1.5.

Table 1.2: Sensitivity and specificity of SDV in patients with APRI >1.5 and APRI <1.5.

		Fibrosis diagnosis: yes	Fibrosis diagnosis: no	
APRI	>1,5	84	413	Positive predictive value=17%
APRI	<1,5	5	524	Negative predictive value=99%
		Sensitivity =94%	Specificity =56%	

SDV of all 1029 patients with an APRI score in the AMC showed a high sensitivity (94%) and a low specificity (56%). An APRI score <1.5 seemed to have a high predictive value (99%) in identifying true negative cases (patients without a fibrosis diagnosis). The predictive value of an APRI score >1.5 was 17% for the true positive cases (patients with a fibrosis diagnosis).

Conclusion

Source data verification of data from patients with an APRI score >1.5 resulted in identification of a substantial number of diagnoses of liver fibrosis missing from the SHM observational database. In addition, the APRI score <1.5 seemed to be a very strong predictor for the absence of a diagnosis of liver fibrosis in patients registered in the SHM database. In conclusion, restricting SDV to a selection of patients with an APRI score >1.5 is an efficient way to identify missing data on liver fibrosis and subsequently to improve the quality of the SHM data. Finally, this approach should be included in our ongoing process of improving the data quality by introducing SDV targeted for specific end points.

monitoring programme report

2. The HIV epidemic in the Netherlands

Ard van Sighem, Colette Smit

As of June 2010, 13,035 HIV-infected patients, including 12,946 adults and 89 children and adolescents, were still under clinical observation in one of the 25 HIV treatment centres in the Netherlands. Almost one third of the population in care was 50 years of age or older. More than 1100 new HIV infections have been diagnosed each year, and the number of diagnoses is steadily increasing amongst men who have sex with men (MSM). In 2008, the annual number of new infections amongst MSM was 850, a number that has not been observed since the peak of the HIV epidemic in the early 1980s. Although the patients are diagnosed earlier in their infection, as has been shown by increasing $CD4^+$ T cell counts at diagnosis, approximately 40% of MSM and more than half of heterosexual men and women are diagnosed with CD4 counts below 350 cells/mm^3, which is the CD4 threshold above which treatment should be started. On a positive note, however, testing for HIV is becoming more frequent. As HIV-infected women who are currently in follow-up age, there is a decrease in the number of pregnancies in this group. Furthermore, the number of infants born in the Netherlands with HIV infection is expected to remain close to zero, as a result of the ongoing screening for HIV amongst pregnant women.

Medio 2010 waren er in Nederland 13.035 hiv-geïnfecteerde patiënten die regelmatig gezien werden in een van de 25 hiv-behandelcentra. Onder hen waren 12.946 volwassenen en 89 kinderen. Bijna een derde van de gevolgde groep was ouder dan 50 jaar. Per jaar wordt bij meer dan 1100 nieuwe patiënten de diagnose hiv gesteld en onder mannen die seks hebben met mannen (MSM) neemt het jaarlijks aantal nieuwe diagnoses al jaren onverminderd toe. In 2008 ware er 850 nieuwe infecties onder MSM, een aantal dat sinds het begin van de hiv-epidemie in de jaren 80 niet meer is waargenomen. Hoewel patiënten steeds eerder in hun infectie gediagnosticeerd worden, zoals blijkt uit het toenemen van het aantal $CD4^+$ T-cellen bij diagnose, wordt bij 40% van de MSM en bij meer dan de helft van de heteromannen en -vrouwen hiv pas vastgesteld, wanneer het CD4-aantal beneden 350 cellen/mm^3 is, de grenswaarde voor het starten van behandeling. Een positieve ontwikkeling is dat testen op hiv steeds frequenter wordt. De toenemende leeftijd van hiv-geïnfecteerde vrouwen heeft tot gevolg dat het aantal zwangerschappen in deze groep daalt. Daarnaast mag verwacht worden dat er hoogstwaarschijnlijk geen kinderen meer met hiv geboren worden in Nederland door de nationale hiv-screening onder zwangere vrouwen.

"Know your epidemic, know your response." With this paraphrase of the famous inscription, "Know thyself" on the temple of Apollo in Delphi, the Joint United Nations Programme on HIV/AIDS (UNAIDS) urges countries to identify the driving forces behind their national HIV epidemic[36]. Understanding the underlying dynamics of the epidemic is a prerequisite for formulating an effective response that targets each risk group with its own tailor-made prevention strategy.

Arguably, concentrated HIV epidemics like that in the Netherlands are more difficult to understand than the generalised epidemics that have so gravely affected many sub-Saharan African countries. Although the scale of the Dutch HIV epidemic is minute compared to that in Africa, it is much more difficult to quantify the size of the risk groups and the prevalence of HIV in each group in the Netherlands, let alone to develop the most effective prevention strategies.

In order to understand a country's HIV epidemic, a well-organised surveillance system is essential. The Netherlands is in a unique and privileged position in Europe because of its registration system, as implemented by Stichting HIV Monitoring (SHM), which follows everyone diagnosed with HIV and makes all information collected as part of routine clinical care available for public health purposes. In this chapter, we present an overview of the HIV-infected population in follow-up as of June 2010 and of the changes over time in the characteristics of the infected population. To further understand the underlying dynamics of the epidemic, mathematical modelling is a useful, if not indispensable, tool. Accordingly, we include two examples of how modelling provides invaluable insights into data that are hard to comprehend with only standard statistical tools.

Total population

As of June 2010, 18,000 HIV-infected patients were registered by SHM, 1285 more than in 2009. In this chapter, demographic and clinical characteristics of the 17,327 patients registered in one of the 25 HIV treatment centres in the Netherlands are presented. The remaining 673 patients are registered in the St. Elisabeth Hospital in Willemstad, Curaçao, and are discussed in more detail in Chapter 9 (Figure 2.1).

Of the 17,327 patients, the majority were infected with HIV-1 (16,888; 97%), whilst 84 patients were infected with HIV-2, and 53 patients had antibodies against both HIV-1 and HIV-2. For 302 patients, serologic results were not yet known. The total follow-up time since diagnosis was 133,290 person-years.

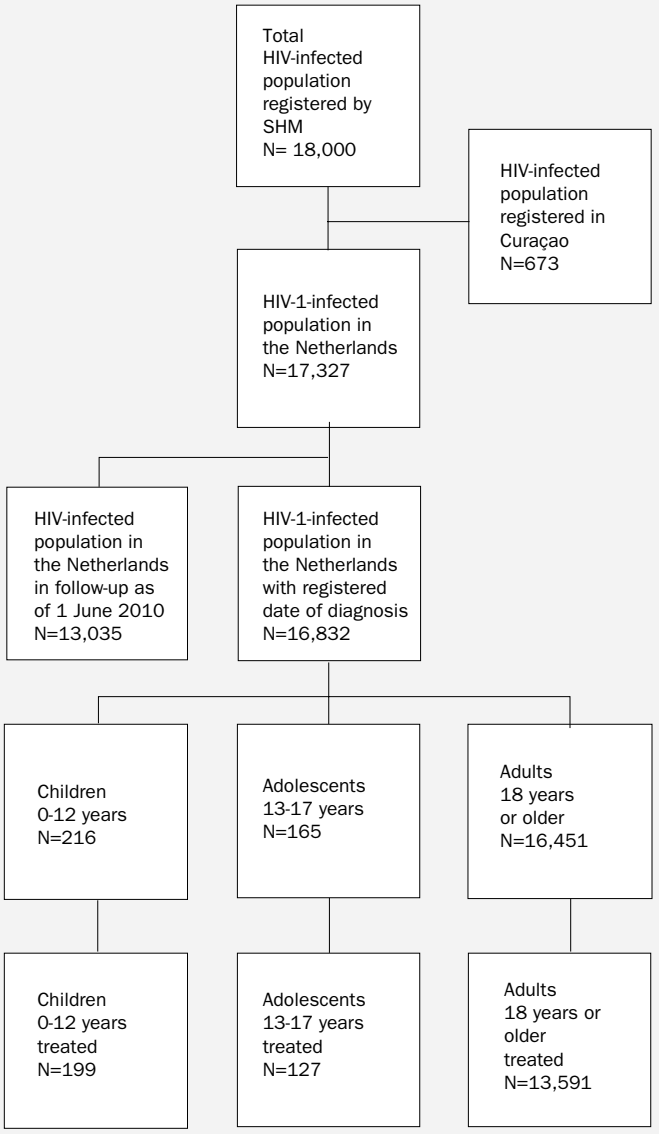


Figure 2.1: Overview of the HIV-infected population as registered by Stichting HIV Monitoring (SHM) as of June 2010.

Last year, we reported 16,129 patients registered in the Netherlands[37]. Hence, the registered population increased by 1198 patients, or 7.4%. Patients diagnosed with HIV in 2009 or 2010 accounted for 82% of the increase and patients diagnosed in 2008 for 9%, whilst the remaining 9% were diagnosed prior to 2008.

Population currently in follow-up

Patients in clinical care

As of June 2010, 13,035 of the 17,327 registered patients, including 12,946 adult patients and 89 children and adolescents, were still under clinical observation in one of the treatment centres in the Netherlands (Figure 2.1; Table 2.1; Web Appendix Table 2.1). The remaining 4292 patients had either died or were lost to follow-up. Patients were considered lost to follow-up if no data were available after June 2009. Most likely, the figure of 13,035 patients is an underestimation, because for some patients there was a backlog in data collection of more than one year.

Ageing population

The majority of the 13,035 patients were men who were infected via homosexual or heterosexual contact and originated from the Netherlands or sub-Saharan Africa. The median age of the population was 45 years (IQR, 38-52) and has been increasing over time since 1986 (Figure 2.2). In part, this increase can be attributed to an improved life expectancy of HIV-infected patients after the introduction of combination antiretroviral therapy (cART). In addition, patients are diagnosed at increasingly older ages. As a result, a large proportion of the patients currently in care, 3943 or 30%, are 50 years or older, including 33% of the men and 18% of the women (Web Appendix Table 2.1).

Table 2.1: Characteristics of the 13,035 patients in follow-up as of June 2010. An extended version of this table is available on the website (Web Appendix Table 2.1).

	Men (N=10,364, 80%)		Women (N=2671, 20%)		Total (N=13,035)	
	N	%	N	%	N	%
Transmission						
MSM	7532	73	-	-	7532	58
Heterosexual	1694	16	2338	88	4032	31
IDU	225	2	91	3	316	2
Blood (products)	104	1	69	3	173	1
Other/unknown	809	8	173	6	982	8
Age category (years)						
0-12	35	0	23	1	58	0
13-17	13	0	18	1	31	0
18-24	187	2	97	4	284	2
25-34	1308	13	661	25	1969	15
35-44	3258	31	996	37	4254	33
45-54	3564	34	622	23	4186	32
55-64	1541	15	188	7	1729	13
≥65	458	4	66	2	524	4
Region of origin						
The Netherlands	6925	67	773	29	7698	59
Sub-Saharan Africa	823	8	1155	43	1978	15
Western Europe	663	6	111	4	774	6
Latin America	714	7	228	9	942	7
Caribbean	349	3	143	5	492	4
Years aware of HIV infection						
<1	618	6	118	4	736	6
1-2	1676	16	311	12	1987	15
3-4	1470	14	349	13	1819	14
5-10	2777	27	954	36	3731	29
>10	3592	35	895	34	4487	34
Unknown	231	2	44	2	275	2

Legend: MSM=men who have sex with men; IDU=injecting drug user

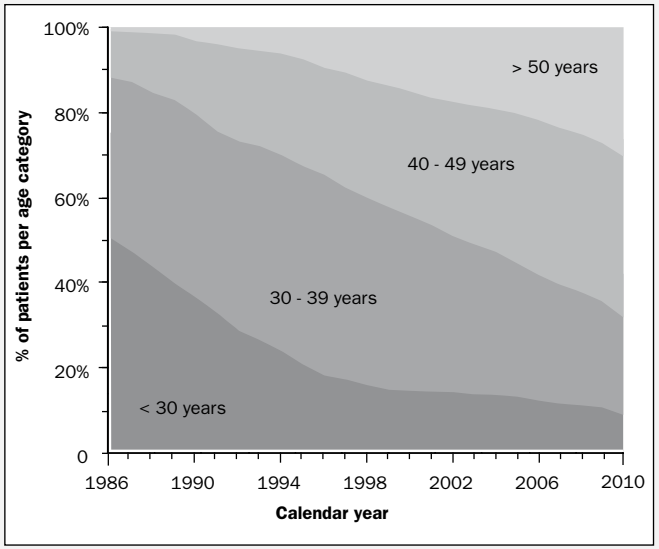


Figure 2.2: The age of the HIV-infected population in follow-up has increased over calendar time. In 1986, 50.4% of the patients in follow-up were younger than 30 years of age, whereas 0.9% were 50 years or older. As of 2010, these proportions were 8.9% and 30.2%, respectively. The Figure shows the proportion of patients in follow-up as of 1 June of each calendar year who were <30 years of age, 30 to 39 years, 40 to 49 years, and 50 years or older.

Duration of infection

On average, patients were diagnosed with HIV 8.5 years earlier. In total, 4473 (34%) patients were diagnosed more than 10 years previously, and 682 (5%) patients received their HIV diagnosis more than 20 years earlier. Approximately one-third (35%) of the homosexual men and 29% of the heterosexual men and women were diagnosed more than 10 years previously, whilst the same was true for three-quarters (75%) of the IDU population. The practice of injecting drugs has declined since the 1980s and, as a result, so has the number of infections amongst drug users[38]. Also, needle exchange programmes and easily accessible methadone dispensing has contributed greatly to a reduction in the number of new infections in this group.

Clinical condition

The immune system of the patients remained relatively intact: median CD4 counts were 510 (IQR, 380-690) cells/mm^3. Median CD8 counts were 885 (IQR, 640-1220) cells/mm^3, and 10,089 (77%) patients had HIV viral load levels below 500 copies/ml. One or more AIDS-defining events had been diagnosed in 23% of the patients; about half of these patients received both HIV and AIDS diagnoses at the same time.

Treatment combinations

cART was administered to 10,762 (83%) patients, whilst 54 patients received a non-cART regimen, and 2219 (17%) were not treated, probably because their CD4 counts were still above the threshold for starting treatment. The most frequently prescribed regimen was a combination of tenofovir and emtricitabine and either efavirenz or nevirapine, which accounted for 39% of all regimens. In 2009, these combinations accounted for 36% of all treatment regimens. Tenofovir was part of the treatment combination in 69% of the patients, whilst emtricitabine was given to 58%, efavirenz to 37%, and nevirapine to 26%.

Trends over time – diagnosis

Transmission route

Of the 17,327 HIV-infected patients registered at one of the 25 HIV treatment centres in the Netherlands, 16,451 were infected with HIV-1, had a registered date of their first positive test, and were diagnosed at 18 years of age or older. The majority of these patients were men who have sex with men (MSM) (9361, 57%), or they were men (2287, 14%) or women (2919, 18%) infected via heterosexual contact. For 676 (4%) patients, including 498 men and 178 women, the reported mode of transmission was injecting drug use, whilst 190 (1%) were infected by contact with infected blood or blood products. For 1018 (6%) patients, the mode of transmission was unknown.

Increasing number of diagnoses amongst homosexual men

Since 1996, the number of diagnoses amongst MSM has steadily increased to almost 800 in 2008 (Figure 2.3). A similar increase has been observed in other Western countries[39, 40]. So far, new HIV diagnoses have been recorded for 637 MSM in 2009. Due to the visit-based data collection by SHM, some of the HIV diagnoses in 2009 are still missing from the database, and the actual number of diagnoses in 2009 is expected to be 10% to 15% higher. Hence, approximately 720 diagnoses would be expected, which would suggest that the increasing trend in diagnoses has halted. However, no evidence for a changing trend was observed in the number of new HIV diagnoses made at sexually transmitted infection (STI) clinics. In 2009, 387 MSM were diagnosed with HIV in STI clinics, compared to 393 in 2008[41].

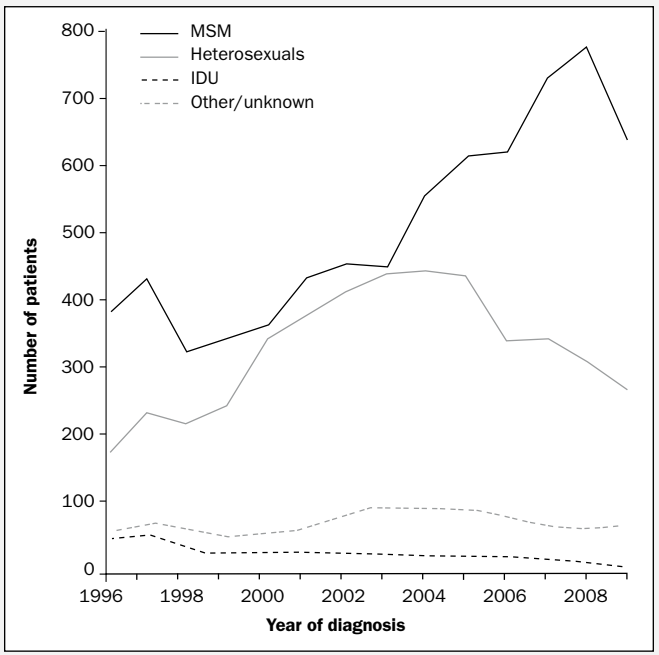


Figure 2.3: Annual number of HIV-1 diagnoses per transmission risk group. Legend: MSM=men who have sex with men; IDU=injecting drug users.

The annual number of diagnoses amongst heterosexuals reached a maximum around 2004 and then declined to 308 cases in 2008. Injecting drug use is rarely reported any longer as the most probable mode of transmission. In 2009, MSM accounted for 66% of the total number of HIV diagnoses, infections via heterosexual contact for 27%, and infections via other or unknown routes for 7% of the annual tally.

Region of origin

Amongst patients infected by homosexual contact, 73% originated from the Netherlands, 10% from other European countries and 7% from Latin America. In recent years, the number of MSM of non-Dutch origin has not changed; however, the number of MSM originating from the Netherlands increased to almost 600 in 2008, about three-quarters of all MSM diagnosed in that year (Figure 2.4).

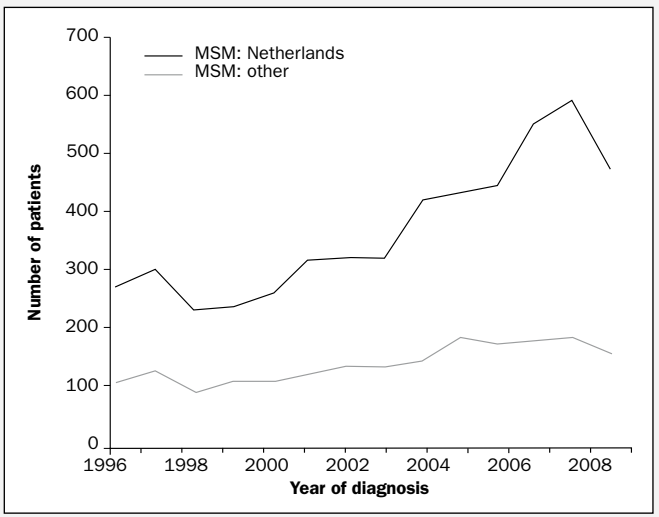


Figure 2.4: Annual number of diagnoses amongst men who have sex with men (MSM) stratified by country of birth. 6795 (73%) originated from the Netherlands, 913 (10%) from other European countries, and 611 (7%) from Latin America. In 2008, 598 of 780 MSM diagnosed in that year were of Dutch origin. Note: data collection for 2009 is not yet finalised.

Amongst heterosexual patients, 42% originated from sub-Saharan Africa, whilst 31% originated from the Netherlands (Figure 2.5). However, the number of diagnoses amongst sub-Saharan Africans dropped sharply after 2003, probably as a result of stricter immigration laws that came into effect in the Netherlands at approximately that time.

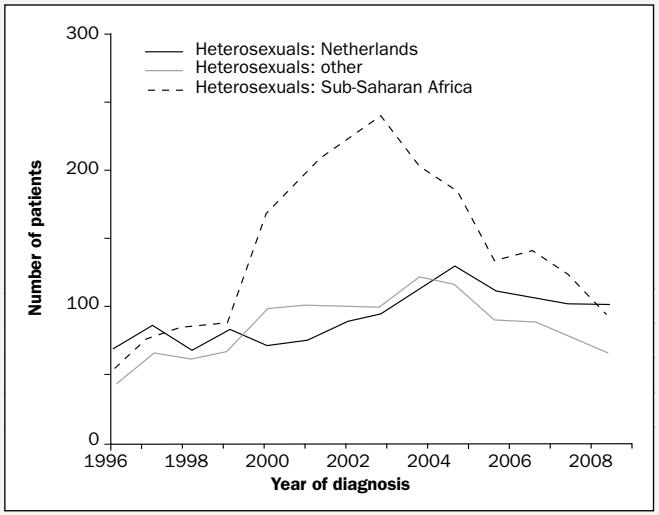


Figure 2.5: Annual number of diagnoses amongst patients infected via heterosexual contact stratified by country of birth. Amongst the 5206 heterosexual patients, 2189 (42%) originated from sub-Saharan Africa and 1616 (31%) from the Netherlands. Note: data collection for 2009 is not yet finalised.

Increasing number of infections amongst MSM

The increase in the annual number of diagnoses amongst MSM was mainly the result of an increase in the number of infections but, to a lesser extent, was also due to more frequent testing for HIV. According to a mathematical model describing HIV transmission amongst homosexual men in the Netherlands, the annual number of new infections increased to almost 850 in 2008, a number that has not been observed since the peak of the HIV epidemic in the early 1980s (Figure 2.6). The average time between infection and diagnosis was 2.4 years. Unfortunately, the same mathematical framework cannot be used to describe the HIV epidemic in the heterosexual population due to the population's heterogeneity and the relative importance of migrant populations.

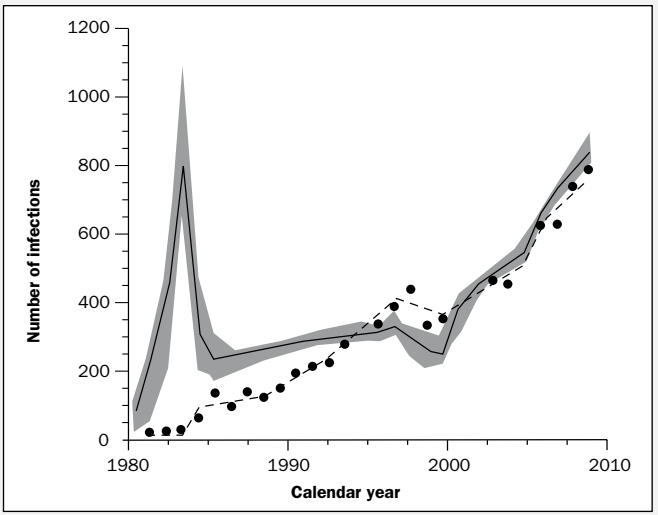


Figure 2.6: Annual number of HIV diagnoses and inferred number of infections from a transmission model amongst men who have sex with men in the Netherlands since the start of HIV. Solid line: number of infections with the results of an extensive sensitivity analysis as a gray band; dots: observed number of diagnoses; dotted line: predicted number of diagnoses obtained by fitting the transmission model to observed data on HIV and AIDS diagnoses.

Country of infection

For 12,719 (77%) of the diagnosed patients, the most likely country of infection was known. The majority of homosexual men, 88%, reported that they were infected in the Netherlands. Amongst heterosexuals, 45% were infected in the Netherlands and 38% in sub-Saharan Africa. Altogether, 79% of the Dutch patients were infected in the Netherlands, whilst 8% were infected in sub-Saharan Africa, and 7% in South and Southeast Asia, with those infected in Asia being almost all men. Patients originating from sub-Saharan

Africa were mostly infected in that region (85%), whereas 13% of them were infected in the Netherlands. Most of the injecting drug users were infected in the Netherlands (83%) or in other Western European countries (9%). Recent mathematical modelling has shown that about one-third of the HIV infections amongst migrants were already acquired before migration to the Netherlands, whilst a negligible number of infections was acquired during trips to their home country[42].

Increasing age at diagnosis

The age at which patients were diagnosed with HIV has been slowly increasing over time. In 1996, the average age at diagnosis was 37 years; in 2009, it was 39 years. During the same period, 13% of the diagnosed patients were 50 years of age or older. There are, however, considerable differences between MSM and men and women infected via heterosexual contact. For MSM, the mean age at diagnosis was 40 years for those born in the Netherlands and 35 years for those of foreign origin. Heterosexual men were generally older at diagnosis than heterosexual women, and patients of Dutch origin were older than patients born abroad. The mean age at diagnosis was 43 years for Dutch heterosexual men and 38 years for Dutch women. Amongst heterosexuals of sub-Saharan African origin, men were 34 years of age at diagnosis and women 30 years, approximately 8 years younger than their Dutch counterparts. Between 1996 and 2009, the average age at diagnosis of heterosexuals increased by 5 years.

Increasing CD4 cell counts

Between 1996 and 2009, median CD4 cell counts at the time of diagnosis for the total population increased from 250 to 370 cells/mm^3 (Figure 2.7). This overall increase was mainly the result of a rising number of CD4 counts in both homosexual and heterosexual men, whereas CD4 counts in women did not change over time.

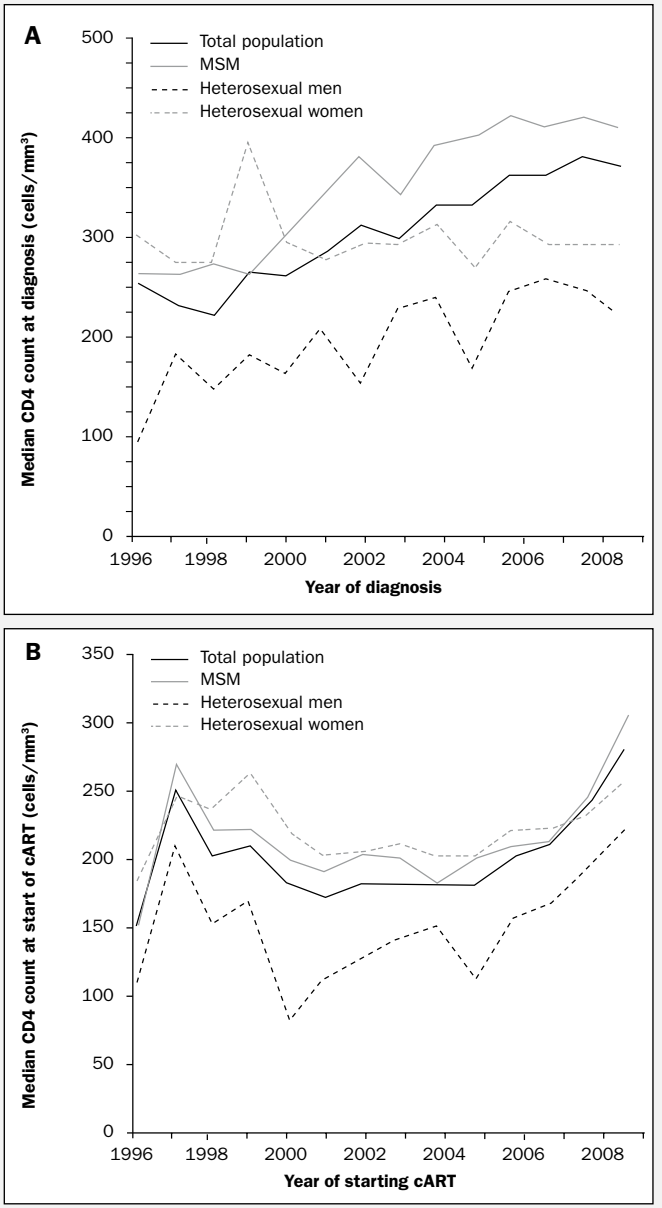
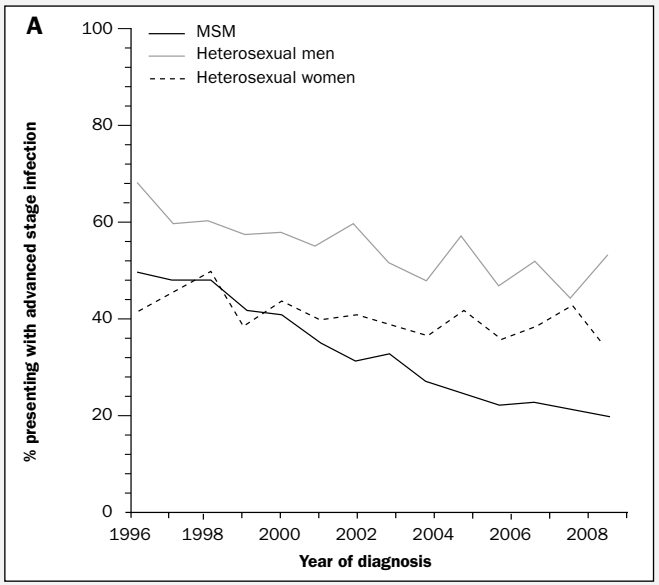


Figure 2.7: Changes over time in median CD4 T cell counts (A) at diagnosis and (B) at the start of combination antiretroviral therapy (cART). (A) Between 1996 and 2009, CD4 cell counts at diagnosis increased from 250 (interquartile range [IQR], 80-430) to 370 (IQR, 200-540) cells/mm^3 in the total diagnosed population. The increase was most apparent for men who have sex with men (MSM): 260 (IQR, 80-450) in 1996 and 410 (IQR, 270-

579) in 2009. During the same period, CD4 counts in heterosexual men increased from 90 (IQR, 21-380) to 220 (IQR, 68-370) cells/mm^3, whereas CD4 counts in heterosexual women were 300 (IQR, 129-500) cells/mm^3 and did not change over time. (B) In the total population, CD4 counts at the start of cART rose to 250 (IQR, 120-390) cells/mm^3 shortly after the introduction of cART in 1996, plateaued at levels around 180 cells/mm^3 between 2000 and 2005, and increased thereafter. In 2009, CD4 counts were 280 (IQR, 190-344) cells/mm^3 in the total population, 298 (IQR, 230-360) for MSM, 220 (IQR, 90-290) in heterosexual men, and 262 (IQR, 160-340) cells/mm^3 in heterosexual women.

Late presentation

Overall, 56% of the patients were late presenters, i.e., individuals presenting for care at the time of an AIDS-defining event regardless of the CD4 cell count or presenting with a CD4 count below 350 cells/mm^3 [43], which currently is the CD4 threshold above which treatment should be started. Between 10% and 15% of the patients already had AIDS at the time of HIV infection diagnosis. Although the proportion of late presenters decreased over time, in 2009 more than half of the heterosexual men and women and approximately 40% of the MSM were diagnosed late in their infection (Figure 2.8).



Amongst heterosexuals, patients of sub-Saharan African origin more often presented late for care (73%) compared to those of Dutch origin (53%). Late presentation was also more common amongst patients diagnosed at older age. Altogether, 65% of patients diagnosed at 50 years of age or older were late presenters as opposed to 54% of those diagnosed at younger ages. However, the declining trend in late presentation over time was observed for all ages, and in the past two years, 55% of the patients diagnosed at age 50 or older and 46% of those diagnosed at younger than 50 years were late presenters.

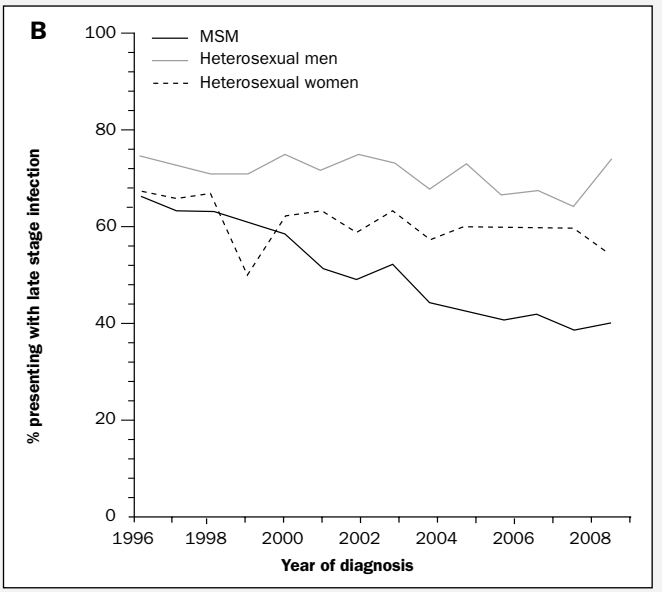


Figure 2.8: Proportion of patients classified as having an advanced (A) or late presentation (B). Between 1996 and 2009, 38% presented with advanced HIV disease: men who have sex with men (MSM) 29%, heterosexual men 54%, heterosexual women 39%, injecting drug users (IDU) 47%. Overall, 56% were late presenters: MSM 48%, heterosexual men 71%, heterosexual women 60%, and IDU 64%. Amongst heterosexuals, 73% of sub-Saharan Africans were late presenters compared to 53% of those of Dutch origin. Likewise, advanced HIV disease was more common in sub-Saharan Africans (50%) than in Dutch patients (39%). Advanced HIV disease: presenting for care with a CD4 cell count below 200 cells/mm^3 or presenting with an AIDS-defining event, regardless of CD4 count. Late presentation: presenting for care with a CD4 cell count below 350 cells/mm^3 or presenting with an AIDS-defining event, regardless of CD4 count[43].

Earlier diagnosis

The increase in CD4 cell count at the time of diagnosis and the decreasing proportion of patients presenting late amongst homosexual and heterosexual men indicates that these men were diagnosed earlier in their infection. This earlier diagnosis is also apparent from the observed increase (10% in 1996 to 36% in 2009) in the proportion of MSM who were diagnosed with a recent infection, defined as 1.5 years, at most, between the last negative and the first HIV-positive diagnostic test. For both heterosexual men and women, however, the proportion of patients diagnosed with a recent infection did not change over time and was well below 10%. Diagnosis of recent infections was less common in older patients. For instance, amongst homosexuals, 32% of the diagnoses were classified as recent infection amongst those aged 18 to 24 years, but this was true for only 16% amongst those aged 55 to 64 years.

Increasing frequency of testing

Apparently, since the proportion of recently infected MSM amongst all those diagnosed with HIV began to increase, testing for HIV has become more common. Whereas 23% of MSM diagnosed in 1996 had previously had at least one HIV-negative test, this proportion had risen to 66% by 2009. More modest increases were observed in heterosexuals, but nonetheless, 20% of the heterosexual men and 33% of the heterosexual women diagnosed in 2009 had a previous negative test.

Trends over time – start of cART

Treatment combinations

Amongst the 16,451 patients with an HIV-1 diagnosis, 13,591 patients started cART. The majority of these patients (83%) started cART whilst being antiretroviral therapy-naive. The most frequently prescribed first-line cART regimen in 2008 and 2009 was used by 69% of adult patients starting treatment and was a combination of a non-nucleoside reverse transcriptase (RT) inhibitor plus tenofovir and emtricitabine. In 84% of those starting this combination, efavirenz was used, whilst 16% of the patients started with nevirapine. Altogether, 92% of the patients used a tenofovir-containing first-line treatment regimen.

Earlier start of treatment

In the past few years, cART has been started increasingly earlier in the HIV infection (Figure 2.7B). CD4 counts at the time of start were similar for homosexual men and heterosexual women, and both were higher than in heterosexual men. In 2009, median CD4 counts at the start of cART were 280 (IQR, 190-344) cells/mm^3. Hence, approximately 25% of the HIV-infected population started treatment according to the current guidelines, which recommend starting treatment before CD4 counts decrease below 350 cells/mm^3. On the other hand, more than 25% of the patients still started treatment with CD4 counts below 200 cells/mm^3, which is considered late start of treatment.

Late presentation, late start of treatment

Late presentation was in part responsible for the late start of cART. In patients diagnosed in 2009 with CD4 counts below 350 cells/mm^3, there was no delay between diagnosis and start of treatment, as evidenced by almost identical CD4 counts at diagnosis and the start of cART. For those with more than 350 CD4 cells/mm^3 at diagnosis, CD4 cells were 550 (IQR, 420-690) cells/mm^3 at diagnosis and 320 (IQR, 270-390) at the start of treatment, and thus, approximately half of the patients who could have started treatment according to the guidelines did so.

Short-term treatment outcome

In the entire group, median CD4 counts increased from 210 cells/mm^3 at the start of cART to 340 cells/mm^3 after 24 weeks. At that time, RNA levels were below 500 copies/ml in 85% of the patients with a viral load measurement. A more exhaustive overview of treatment outcome is presented in Chapter 4.

HIV-infected children and adolescents

HIV-infected children in care in the Netherlands are seen in one of the specially designated paediatric HIV treatment centres. Demographic and clinical data on these children are registered and monitored by the SHM. In this report, the HIV-infected population aged below 18 years at time of HIV diagnosis is divided into children and adolescents. The term "children" refers to all individuals younger than 13 years of age at time of HIV diagnosis, whilst "adolescents" refers to individuals aged 13 to 18 years when diagnosed with HIV. As of June 2010, 216 children and 165 adolescents had been diagnosed with HIV (Table 2.2).

Table 2.2: Demographic characteristics of HIV-1 infected children (age 0-12 years at time of HIV diagnosis) and adolescents (age 13-18 years at time of HIV diagnosis) registered up to 1 June 2010 in the SHM observational database.

	Children		Adolescents	
	N	%	N	%
Total	**216**		**165**	
Gender				
Boy	124	57	54	33
Girl	92	43	111	67
Route of transmission				
MTCT	179	82	4	2
Blood contact	22	10	14	8
Unknown	13	6	11	7
Heterosexual contact	1	0.5	114	69
Homosexual contact	1	0.5	16	10
Region of origin				
Netherlands	112	52	38	23
Sub-Saharan Africa	79	37	104	63
Caribbean/Latin America	11	5	10	6
Other	14	6	13	8
Region of the parents				
Both the Netherlands	11	5	2	1
One or both sub-Saharan Africa	135	63	24	15
One or two other region or unknown	70	32	139	84
Median age at diagnosis (IQR)				
Years	3	(0.7-6)	17	(16-18)
Deaths	3	1	9	5

Legend: MTCT=mother to child transmission; IQR=interquartile range

Children

Most HIV-infected children in care in the Netherlands were infected by mother-to-child-transmission (MTCT). The median age at HIV diagnosis was 3 years. Although the majority of the children were born in the Netherlands, only 5% had parents who both originated from the Netherlands, and for most of the children at least one parent originated from sub-Saharan Africa. Figure 2.9 shows the number of children and adolescents according to their year of HIV diagnosis. Most children and adolescents have been diagnosed with HIV since 2000. However, the majority of vertically infected children were born before 1 January 2004, the date when the national HIV screening amongst pregnant women was implemented. The rate of MTCT in the Netherlands has strongly declined over time (Figure 2.9). This decline is probably the result of the HIV screening programme amongst pregnant women. Despite the effectiveness of this screening, 4 children born with HIV in the Netherlands after 1 January 2004 were reported to the SHM. The mothers of the 2 children born in 2004 were not included in the national HIV pregnancy screening because they became pregnant before 1 January 2004. The mother of the HIV-infected child born in 2005 had a negative result on the pregnancy screening and was probably infected with HIV during her pregnancy. For the child born with HIV in the Netherlands in 2006, it is not known if the mother was screened for HIV during her pregnancy. The number of HIV-infected children born with HIV in the Netherlands is expected to remain close to zero as a result of the ongoing testing policy amongst pregnant women. However, despite the high uptake of the pregnancy screening, a risk of MTCT will always remain amongst women who become infected during the last two trimesters of their pregnancy.

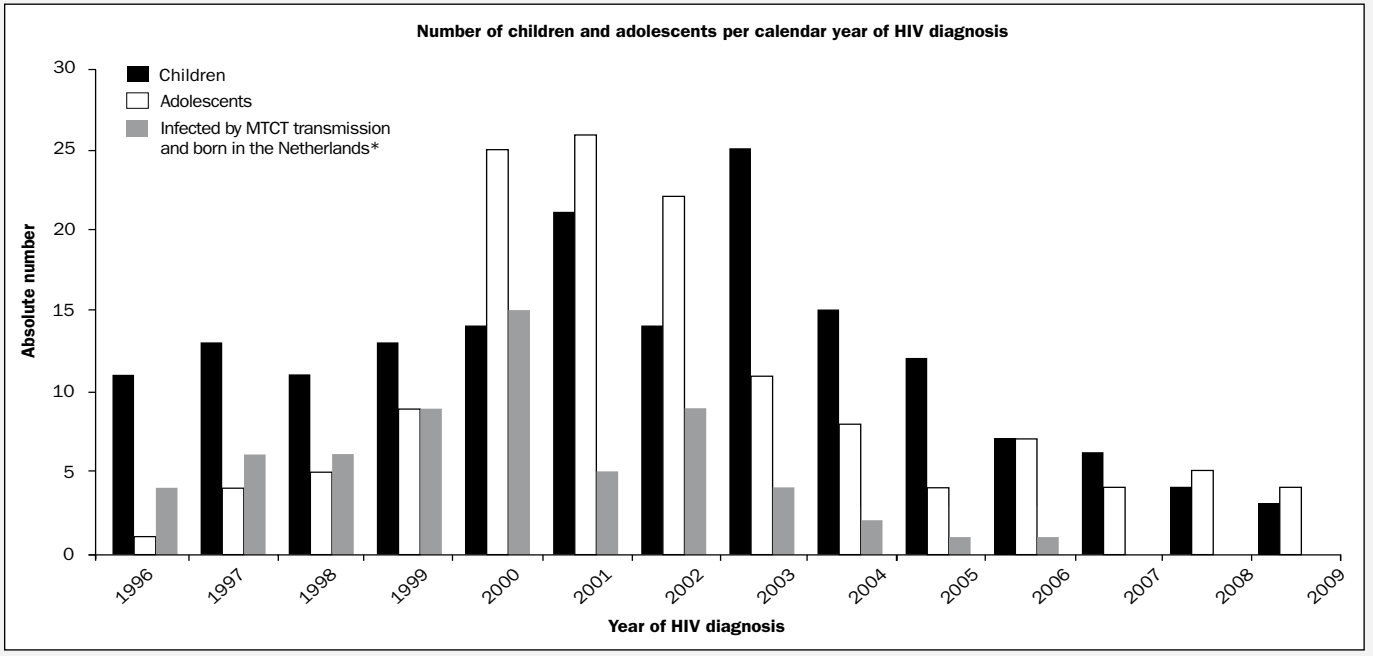


Figure 2.9: Number of HIV-infected children (0-12 years of age) and adolescents (13-18 years of age), according to their year of HIV diagnosis and the number of children infected with HIV by MTCT and born in the Netherlands. None of the adolescents born in the Netherlands was vertically infected with HIV.

Legend: MTCT=mother to child transmission * according to year of birth

Adolescents

Demographic characteristics differ for adolescents in comparison to children. By definition, adolescents were much older than children when diagnosed with HIV (Table 2.2), and this group was also older when they contracted HIV infection, since the route of transmission was sexual contact in most cases. None of the adolescents infected through MTCT was born in the Netherlands. The majority of the adolescents were female and born in sub-Saharan Africa. These figures typically reflect the HIV epidemic in sub-Saharan Africa, in particular, where 76% of the young HIV–infected individuals are women.

Mortality

Of the patients who were diagnosed with HIV as children, 3 patients died. Two of them were more than 18 years of age at time of death, and one patient died at the age of 12 years from an HIV-related cause. Among the adolescents, 9 died during follow-up, the median age at time of death was 29 years (IQR, 19-30 years). One patient died at the age of 17 years, and 6 out of 9 deaths were HIV-related. Treatment and treatment response amongst the HIV-infected children and adolescents are described in Chapter 4.

Pregnant women

MTCT is the most important route of HIV transmission amongst children[44]. As a result of improved prevention in Western countries, MTCT has been reduced dramatically in these countries[45]. In January 2004, voluntary HIV-antibody testing that allowed persons to

opt out was introduced in the Netherlands[46, 47]. Since then, a substantial proportion of cases of HIV in women unaware of their infection has been diagnosed.

Total number of pregnancies

By June 2010, data from 1184 pregnancies amongst HIV-infected women registered in the SHM observational database were available. Out of the 3334 women who are followed in the SHM database, 887 became pregnant, with a total number of 1184 pregnancies. After being diagnosed with HIV, 213 women became pregnant for a second time. Data from only 10 pregnancies were collected in 2009 (Table 2.3). However, for the 2009 calendar year, the data collection is not yet complete as the term date of these pregnancies is after 31 December 2009.

Demographics

The demographics of the HIV-infected women with a registered pregnancy are presented in Table 2.3. The median age at first pregnancy did not change over time. Dutch women were significantly older when they became pregnant compared to non-Dutch women. Heterosexual contact was the most important route of HIV transmission, and most women originated from sub-Saharan Africa, with a minority born in the Netherlands.

Of the 1184 pregnancies, 20% of pregnancies ended in an abortion (induced or spontaneous). Before the availability of cART, the proportion of induced abortions amongst HIV-infected women was much higher[48]. Awareness of the HIV infection, in combination with improved MTCT prevention, has resulted in a reduced proportion of induced abortions[49], which has remained stable in recent calendar years and varies between 19% and 22%.

The mode of delivery was available for 906 pregnancies with more than half of the babies delivered vaginally. Elective caesarean delivery is known to reduce the risk of MTCT in cases of a detectable maternal viral load, but the benefit of this type of delivery has been questioned[50, 51] when an undetectable maternal viral load is achieved as a result of successful treatment with cART.

Table 2.3: Demographic characteristics of HIV-infected pregnant women, 1 January 1988 to 1 June 2010.

	Women, N=887	Pregnancies, N=1184
	N (%)	N (%)
HIV diagnosis before pregnancy (%)	457 (51%)	
Number of pregnancies after HIV diagnosis		
1		887 (75%)
2		213 (18%)
3		57 (5%)
4		16 (1%)
5		7 (0.6%)
6		3 (0.3%)
7		1 (0.1%)
Age at start of first pregnancy occurring in HIV infection		
Years (Median [IQR*])	29 (24-33)	
HIV transmission route		
Heterosexual (%)	829 (93%)	
Other (%)	48 (7%)	
Region of origin		
Netherlands (%)	*129 (15%)*	
Sub-Saharan Africa (%)	*539 (61%)*	
Latin America/ Caribbean (%)	*127 (14%)*	
Other (%)	*92 (10%)*	
Pregnancy outcome		
Partus (%)		924 (78%)
Abortion (%)		242 (20%)
Unknown (%)		18 (2%)
Mode of delivery		
Vaginal delivery (%)		530 (45%)
Caesarean delivery (%)		376 (32%)
Unknown (%)		276 (23%)
Number of pregnancies per calendar year		
<1997 or unknown		99 (8%)
1997-1999		118 (10%)
2000-2001		187 (16%)
2002-2003		270 (23%)
2004-2005		265 (22%)
2006-2007		175 (15%)
2008-2009		70** (6%)

* IQR=Interqartile range ** Data collection for calendar year 2009 is not yet completed, as the term date is after 31 January 2009

Incidence of pregnancy amongst HIV-infected women and geographic origin of the mothers

Overall, the incidence of pregnancy amongst women aged 16 to 45 years was 40 pregnancies per 1000 person-years (PY) (95% confidence interval [CI] 37-43). The incidence in the total group of women and those according to geographic origin are presented in Figure 2.10.

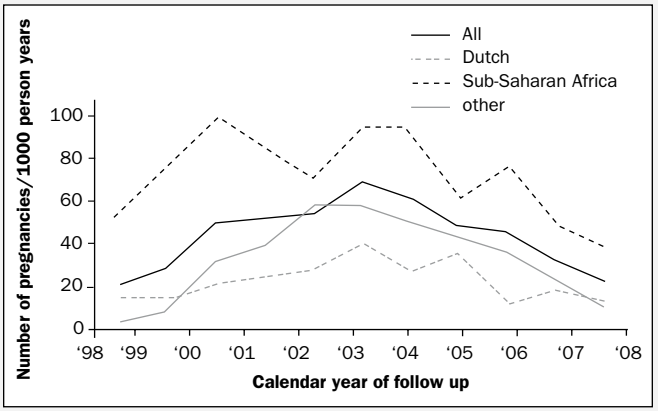


Figure 2.10: Incidence of pregnancies per 1000 person-years (PY) amongst HIV-infected women, overall and according to region of origin. The incidence of pregnancy in the HIV infected women in the Netherlands per calendar year of follow-up was calculated per 1000 PY. All women aged between 16 and 45 years were considered to be "at risk" for pregnancy. PY were calculated from the time of HIV diagnosis to either 1 January 2009 or the time of the patient's last visit, death, becoming lost to follow-up, or reaching the age of 45 years, whichever occurred first.

In the total group, the incidence increased from 21 (95% CI 12-34) in 1998 to 67 (95% CI 55-83) in 2003 and then declined to 22 (95% CI 16-31) in 2008. The highest incidence was found amongst women originating from sub-Saharan Africa, but also in this group of women the incidence of pregnancy has declined over time. Differences in the incidence of pregnancies amongst women of different geographic origins have been found previously, and incidence rates of pregnancy have been reported to be highest in women originating from sub-Saharan Africa[52]. An HIV-infected woman's decision to become pregnant has been found to be socially and culturally related[48]. Higher pregnancy incidence rates among women originating from sub-Saharan Africa can be largely explained by the characteristics of the HIV epidemic in the Netherlands. A substantial proportion of the heterosexually infected individuals are women from sub-Saharan African countries in whom HIV is diagnosed for the first time as part of the prenatal screening program in the Netherlands.

In conclusion, although most pregnancies occur amongst women originating from sub-Saharan Africa, the number of pregnancies in this group is decreasing. This decrease may be a result of the drop in newly diagnosed heterosexually infected patients from sub-Saharan Africa since 2003. Also, the women from sub-Saharan countries currently in follow-up are growing older, resulting in fewer pregnancies.

Conclusion

With the advent of cART, the life expectancy of HIV-infected patients has increased considerably. As a result, the HIV-infected population in clinical care grew to more than 13,000 patients by June 2010. Despite treatment, the annual number of new infections amongst homosexual men continues to rise. In fact, in 2008, the annual number of infections was as high as in the early days of the HIV epidemic.

Although HIV testing and treatment is easily accessible in the Netherlands, almost half of HIV-infected individuals are diagnosed in a late stage of infection. In other words, for half of the patients, CD4 counts at diagnosis are already below the threshold at which treatment should be started. Even more worrisome is that many patients are only diagnosed with HIV when they already have AIDS. To maximise the beneficial effect of treatment, it is of the utmost importance that HIV-infected individuals be tested more frequently to allow treatment in earlier stages of the infection.

3. Death, AIDS, and serious non-AIDS–related diseases

Luuk Gras, Ard van Sighem

Since the introduction of combination antiretroviral treatment (cART), mortality rates and the incidence of AIDS amongst HIV-infected individuals have been in a steady decline. An increasing proportion of the treated HIV-1 infected population have reached CD4 cell counts that indicate a low risk of AIDS. The incidence of serious non-AIDS–defining diseases such as hepatic, renal, or cardiovascular disease; diabetes mellitus; osteoporosis; and non-AIDS–defining cancer in the treated population is higher than the incidence of AIDS when CD4 cell counts are above 200 cells/mm^3. In addition, since 2005, the annual incidence of serious non-AIDS–defining diseases has been higher than that of AIDS. Still, the absolute number of registered new AIDS diagnoses was stable between 1997 and 2008, with an average of 130 diagnoses per year. Patients who were ART-experienced when they first started cART remained at high risk of death from AIDS, even after a longer time on cART. The incidence of loss to follow-up was especially high in immigrants with advanced disease from sub-Saharan Africa, suggesting that many of them may have returned to their native country before death.
The incidence of death in male HIV patients from non-AIDS–defining malignancy, myocardial infarction and suicide was higher than in the age-standardized general male population. Lower CD4 cell counts and older age at the start of cART, together with a history of mono- or dual antiretroviral therapy prior to cART and intravenous drug use as the mode of transmission, were independently associated with a higher risk for serious non-AIDS–defining diseases. Specific risk factors have been associated with each of the serious non-AIDS-defining diseases and causes of death. To further lower mortality and morbidity rates, it will be necessary to address these risk factors. In addition, improving testing rates in individuals at high risk for HIV infection will not only reduce the number of patients with advanced disease but will also increase the number of patients who initiate cART in a timely manner and contribute to a further decline in mortality.

De mortaliteit en incidentie van AIDS in HIV-1 geïnfecteerde patiënten zijn na de invoering van combinatie antiretrovirale therapie (cART) sterk gedaald. Door behandeling nemen CD4 cel aantallen toe en zijn bij een toenemend deel van patiënten op een dusdanig nivo dat het risico op AIDS minimaal is. De incidentie van ernstige comorbiditeit anders dan AIDS in de behandelde populatie is hoger dan dat van AIDS bij CD4 cel aantallen van meer dan 200 cellen/mm^3. De jaarlijkse incidentie van ernstige comorbiditeit is sinds 2005 hoger dan die van AIDS. Toch is er, met gemiddeld 130 per jaar, weinig verandering in het absolute aantal patiënten met een eerste nieuwe AIDS diagnose na het starten van behandeling. Patiënten die voor de start van cART al eerder werden behandeld met mono- of duotherapie hadden een grotere kans op overlijden door AIDS, zelfs na langere tijd op cART. Patiënten uit sub-Sahara Afrika met een vergevorderd ziektestadium raakten vaker lost to follow-up. Een aantal van deze patiënten is voor overlijden waarschijnlijk teruggekeerd naar het land van herkomst.
De incidentie van overlijden door niet AIDS gerelateerde maligniteiten, myocard infarct en zelfmoord in mannelijke HIV patiënten was hoger dan in de algemene mannelijke bevolking. Lage CD4 cel aantallen en hogere leeftijd bij de start van behandeling, naast intraveneus drugs gebruik als de meest waarschijnlijke transmissieroute en een

geschiedenis van mono- of duotherapie voordat met cART werd gestart, waren onafhankelijk geassocieerd met een grotere kans op ernstige comorbiditeit. Om mortaliteit en morbiditeit verder omlaag te krijgen is het noodzakelijk om deze risicofactoren in het HIV behandelingsbeleid te betrekken. Een hogere frequentie van testen op HIV infectie in groepen met verhoogd risico op HIV zal leiden tot een kleiner aantal patiënten met vergevorderd ziektestadium bij diagnose, een groter aantal patiënten dat op tijd met behandeling begint en zal een bijdrage leveren tot een verdere daling van de mortaliteit.

Provided combination antiretroviral therapy (cART) is effective and begun early in the disease course, the life expectancy of patients infected with HIV-1 is increased considerably, although still not to the level of the age- and gender-matched general population[12, 53, 54]. The increase in life expectancy results in a shift from AIDS-related causes of death to death because of non-AIDS–related diseases that are associated with older age. To gain further insight into the HIV-related and non-HIV-related morbidity and mortality since the introduction of cART, we studied trends in mortality, causes of death, AIDS and serious non-AIDS–defining diseases.

Mortality and incidence of AIDS

The average mortality rate in the group of 16,832 HIV-1-infected patients with a registered date of diagnosis was 1.31 (95% confidence interval [CI] 1.24-1.37) per 100 person-years, and it declined over time to 1.04 (95% CI 0.87-1.24) in 2009 (Figure 3.1A; Web Appendix Table 3.1). Despite this decline, the mortality rate was well above the mortality rate that would be expected in the same group of individuals if they were not infected with HIV. The excessive mortality rate could be explained in part by patients who already had AIDS at the time of their HIV diagnosis. As is well-known, HIV-infected individuals with AIDS have a substantially higher risk of death compared to patients without AIDS[55, 56], and by excluding these patients, the average mortality rate decreased to 1.14 per 100 person-years (Web Appendix Figure 3.1). The mortality rate was even lower (1.00) in patients who were diagnosed with HIV in 1996 or later (Web Appendix Figure 3.2). Generally, these patients received cART as their first treatment regimen instead of first being treated with mono- or dual therapy. In the same group of 16,832 patients, the incidence of AIDS decreased sharply to 1 or 2 cases per 100 patients per year in the last few years (Figure 3.1B; Web Appendix Table 3.1). Since there is some backlog in the reporting of AIDS events, we expect that the incidence in 2009 will be approximately 10% higher.

In total, 13,837 patients have started cART since 1995. The mortality rate after the start of cART substantially decreased over calendar time to 0.75 (95% CI 0.47-1.14) per 100 person-years (Figure 3.1C). This decrease should, however, be interpreted with caution, since it is due in part to a survival effect. The incidence of AIDS decreased dramatically to 0.93 per 100 person-years in 2009 (Figure 3.1D).

Cause of death

Out of the group of 13,837 patients who had started cART since 1995, 13,013 were selected for further analysis of the causes of death and of AIDS and non-AIDS–related morbidity. These 13,013 patients commenced cART between July 1996 and December 2009, were older than 16 years of age at the start of cART, and after the start of cART had available at least 1 CD4 cell count, HIV RNA measurement or clinical visit, or were known to have died. During 80,331 person-years (py) of follow-up after initiation of cART, 1232 patients died (1.53 deaths per 100 py of follow-up, 95% CI 1.48-1.62). In total, 157 deaths (12.1%) could not be classified because of insufficient clinical data. AIDS as the cause of death was recorded for 409 patients (37% of all known causes of death), and non-AIDS–defining causes of death were recorded for 732 (63%) patients (Table 3.1).

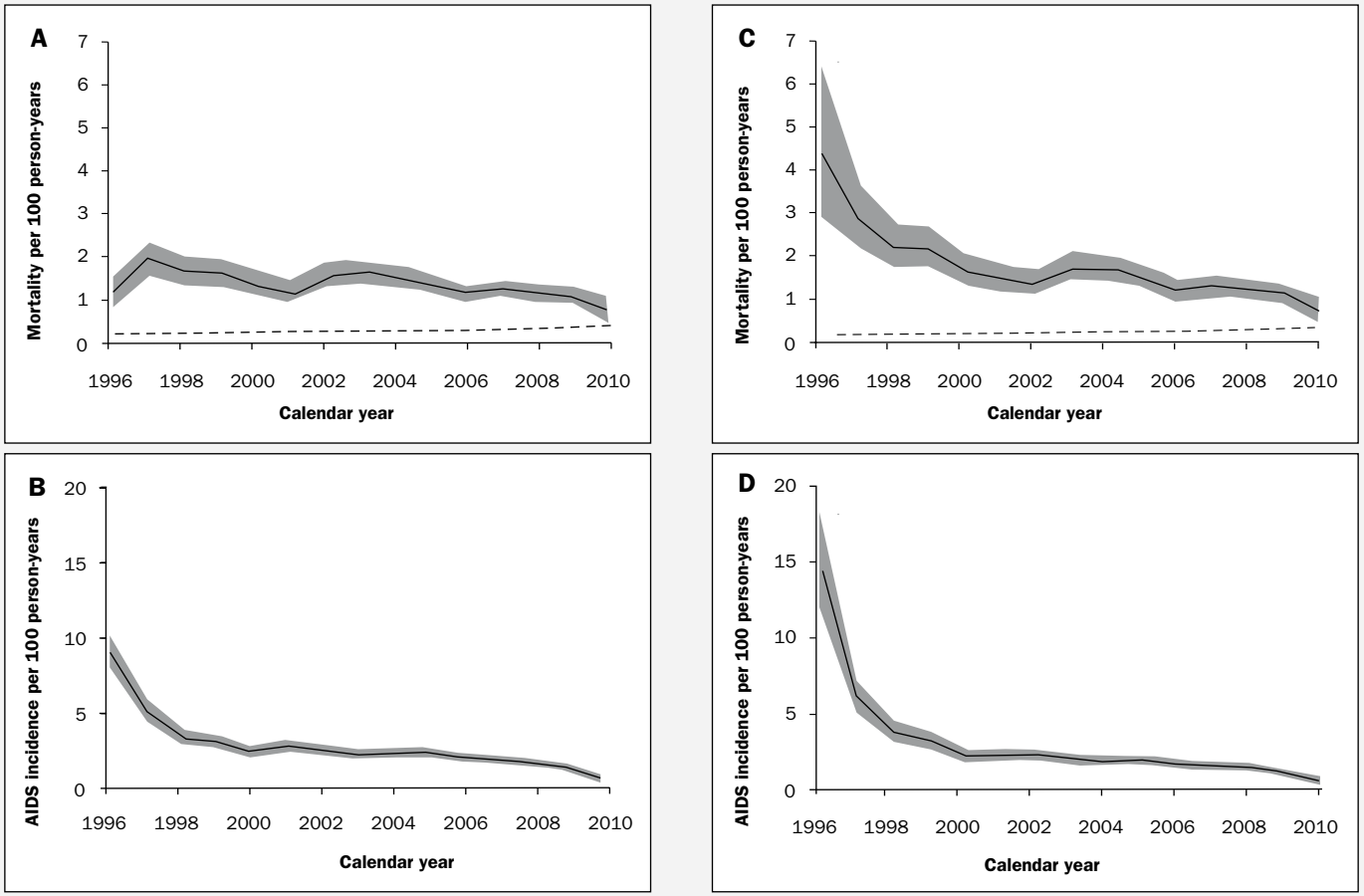


Figure 3.1: Annual mortality (A, C) and incidence of AIDS (B, D) in 16,832 HIV-1-infected patients in the Netherlands after HIV diagnosis (upper plots) and in a subpopulation of 13,837 treated patients after the start of combination antiretroviral therapy (cART, lower plots). Black lines represent the incidence, whilst the grey areas are the 95% confidence intervals. The dotted line is the mortality rate for age- and sex-matched individuals from the general population in the Netherlands. A: 1563 deaths, 119,534 person-years of follow-up; B: 2259 AIDS cases occurring at least 6 weeks after HIV diagnosis, 102,252 person-years; C: 1363 deaths, 88,693 person-years; D: 1544 AIDS cases occurring at least 4 weeks after the start of cART, 81,249 person-years.

Table 3.1: Cause of death according to year of death. On the basis of clinical data at the time of death, the cause of death was classified according to the Coding of Death in HIV (CoDe) scheme[57]. The year of death was classified into periods 1996-2000 (early cART), 2001-2005 (intermediate cART), and 2006-2010 (late cART). Some causes of death have been reclassified from last year's report. This is due to the acquisition of new information obtained via the CoDe forms, along with the information obtained from the patients' charts.

	Year of death								
	1996-2000		2001-2005		2006-2010		Total		
	N	%	N	%	N	%	N	%	Median last CD4 count (IQR)
Total	**266**	**100.0**	**488**	**100.0**	**478**	**100.0**	**1232**	**100.0**	**170 (60-370)**
Death due to AIDS-defining causes*	**121**	**45.5**	**168**	**34.4**	**120**	**25.1**	**409**	**33.2**	**60 (20-160)**
Infection	42	15.8	67	13.7	39	8.2	148	12.0	50 (10-120)
Malignancy	41	15.4	57	11.7	50	10.5	148	12.0	100 (30-220)
AIDS, not specified	38	14.3	44	9.0	31	6.5	113	9.2	40 (10-130)
Non-AIDS-defining malignancy	**21**	**7.9**	**68**	**13.9**	**85**	**17.8**	**174**	**14.1**	**210 (100-410)**
Cardiovascular diseases	**12**	**4.5**	**43**	**8.8**	**47**	**9.8**	**102**	**8.3**	**320 (200-490)**
Myocardial infarction	7	2.6	16	3.3	20	4.2	43	3.5	250 (150-420)
Stroke	2	0.8	9	1.8	4	0.8	15	1.2	260 (190-575)
Other ischemic heart disease			1	0.2	2	0.4	3	0.2	260 (190-570)
Other cardiovascular diseases	3	1.1	18	3.7	23	4.8	44	3.6	325 (190-420)
Non-AIDS-defining infection	**15**	**5.6**	**38**	**7.8**	**29**	**6.1**	**82**	**6.7**	**140 (60-300)**
Liver failure, cirrhosis and HBV/HCV co-infection at death	**10**	**3.8**	**27**	**5.5**	**34**	**7.1**	**71**	**5.8**	**220 (120-370)**
Lung related**	**1**	**0.4**	**9**	**1.8**	**18**	**3.8**	**28**	**2.3**	**190 (90-470)**
Renal failure	**2**	**0.8**	**3**	**0.6**	**3**	**0.6**	**8**	**0.6**	**205 (70-350)**
Lactic acidosis	**3**	**1.1**	**1**	**0.2**	**2**	**0.4**	**6**	**0.5**	**190 (30-420)**
Liver failure (without HBV/HCV at death)	**3**	**1.1**	**2**	**0.4**	**1**	**0.2**	**6**	**0.5**	**110 (80-240)**
Diabetes mellitus			**2**	**0.4**	**1**	**0.2**	**3**	**0.2**	**190 (30-420)**
Non-natural death	**31**	**11.7**	**46**	**9.4**	**47**	**9.8**	**124**	**10.1**	**290 (110-510)**
Accident or other violent death	5	1.9	6	1.2	10	2.1	21	1.7	400 (310-455)
Suicide	8	3.0	25	5.1	24	5.0	57	4.6	350 (220-600)
Euthanasia	18	6.8	15	3.1	13	2.7	46	3.7	165 (50-290)
Substance abuse	**7**	**2.6**	**9**	**1.8**	**7**	**1.5**	**23**	**1.9**	**240 (100-490)**
Other cause***	**10**	**3.8**	**8**	**1.6**	**14**	**2.9**	**32**	**2.6**	**175 (50-485)**
Unclassifiable causes	**2**	**0.8**	**3**	**0.6**	**2**	**0.4**	**7**	**0.6**	**295 (110-510)**
Unknown	**28**	**10.5**	**61**	**12.5**	**68**	**14.2**	**157**	**12.7**	

*According to the clinical part of the 1993 revised classification system of the U.S. Centers for Disease Control and Prevention[58].

**Primary pulmonary hypertension, lung embolus and chronic obstructive lung disease

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

Legend: IQR=interquartile range; HBV=hepatitis B virus; HCV=hepatitis C virus.

The proportion of deaths due to AIDS decreased over time from 45% between 1996 and 2000 to 25% between 2005 and 2010 ($p<0.0001$, test for trend). In the CASCADE study a similar decrease was found in the percentage of AIDS deaths in the pre-cART era (before 1996; 66%) compared with that in the cART era (1996-2003; 37%)[24].

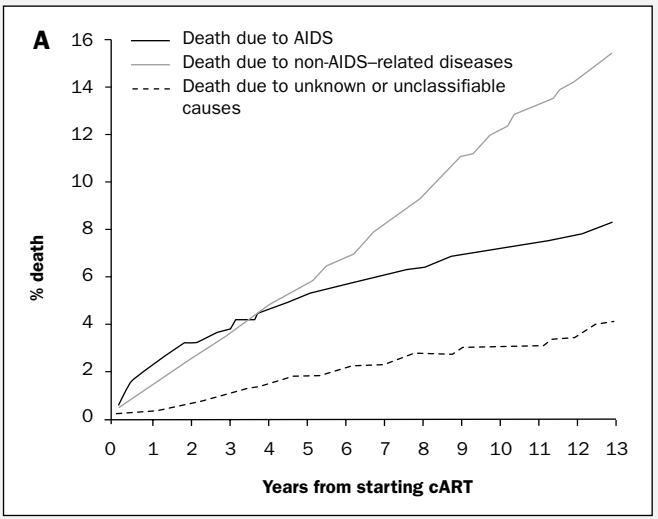
We found an increase over time in the proportion of deaths due to non-AIDS–defining cancer ($p<0.0001$) and deaths due to cardiovascular disease ($p=0.05$). The shift in the proportion of AIDS-related deaths to non-AIDS–related deaths since 1996 may be explained by the increasing proportion of patients on cART who had high CD4 cell counts (Chapter 4) and have continued to live to an old age.

Cause of death by latest CD4 cell count and other risk factors

Table 3.1 also shows the median last CD4 count for each cause of death. Causes of death related to AIDS are shown to occur in patients with lower last CD4 cell counts before death (median, 60 cells/mm^3) than in patients with non-AIDS–related causes of death. However, the low last CD4 cell counts observed in patients who died because of liver failure (110 cells/mm^3) or non-AIDS–defining infections (140 cells/mm^3) demonstrate that immune deficiency also plays a role in at least some non-AIDS–defining causes of death. The highest latest CD4 cell counts were observed when the death was caused by an accident, violence or suicide (400-350 cells/mm^3), or by cardiovascular diseases (320 cells/mm^3). The antiretroviral therapy cohort collaboration (ART-CC) and the data collection on adverse events of anti-HIV drugs (D:A:D) study group observed that each cause of death has a different set of risk factors[59, 60]. The well established inverse association between a higher risk of death due to AIDS and lower CD4 cell counts was also found for death due to non-AIDS–related malignancies, liver and renal failure, and thus supports arguments for starting cART earlier. This association was stronger for renal failure than for AIDS and a weak association was found for cardiovascular disease. The association between older age and a higher probability of death was less strong for death because of AIDS than because of non-AIDS–defining diseases. In particular, the risk of death because of cardiovascular disease and non-AIDS–defining malignancies increased with older age.

Cause of death by year after the start of cART

The Kaplan–Meier estimate of all-cause mortality 13 years after the start of cART was 18.1% (95% CI 16.9-19.2) but was lower in therapy-naïve patients (13.5%) and higher in those who were antiretroviral-drug–experienced (27.5%, $p<0.0001$). Figure 3.2 shows the cumulative incidence of competing causes of death[61, 62] for death due to AIDS, non-AIDS-related diseases, and unclassifiable and unknown causes of death after the start of cART in antiretroviral-drug–experienced and therapy-naïve patients.



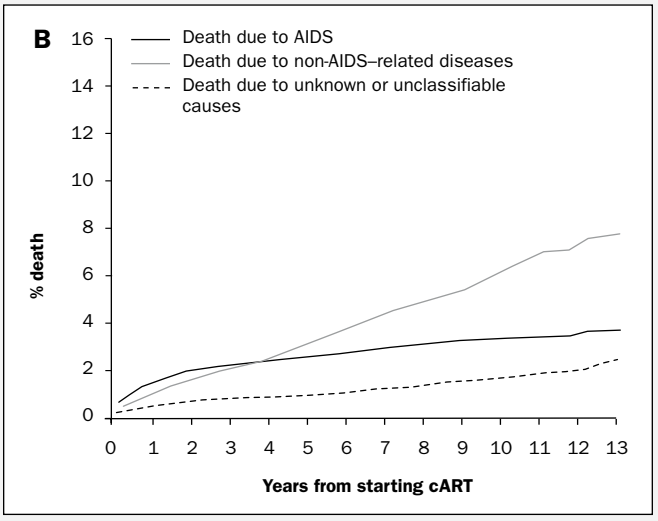


Figure 3.2: Cumulative incidence curves for death after the start of combination antiretroviral therapy (cART) in 2,044 antiretroviral-drug–experienced patients (A) and 10,969 antiretroviral-therapy–naïve patients (B), according to the Causes of Death in HIV (CoDe) scheme. The cumulative incidence 13 years after the start of cART for non-AIDS–related causes of death among antiretroviral-drug–experienced patients was 3.2% for non-AIDS–related malignancy; 2.4% for cardiovascular disease; 3.3% for violent death, suicide or euthanasia; 2.1% for non-AIDS–defining infections; 2.4% for liver failure in combination with co-infection with hepatitis C or hepatitis B virus; and 1.9% for other causes. For therapy-naïve patients these percentages were 2.3% for non-AIDS–related malignancy; 1.2% for cardiovascular disease; 1.7% for violent death, suicide or euthanasia; 0.7% for non-AIDS–related infections; 0.7% for liver failure in combination with co-infection with hepatitis C or hepatitis B virus; and 1.4% for other causes.

The cumulative incidence of death because of AIDS in ART-experienced patients continued to rise with increasing time after the first start of cART, whereas in ART-naïve patients the cumulative incidence of death because of AIDS levelled off after the first 3 years of cART; specifically, there were 7.3 deaths per 1000 py (95% CI 6.3-8.4) during the first 3 years of cART and 1.9 deaths per 1000 py (95% CI 1.3-2.5) between 3 and 7 years, with a further decrease to 1.6 deaths per 1000 py (95% CI 1.0-2.6) between 7 and 11 years. With a longer time on cART, an increasing proportion of patients reached a CD4 cell count level that conferred a minimal risk of AIDS. On the other hand, in ART-experienced patients the incidence of death due to AIDS also decreased with a longer time on cART, but it remained high at 4.4 (95% CI 2.8-6.6) per 1000 py between 7 and 11 years on cART.

We further explored whether ART-experienced patients remained at higher risk for AIDS with a longer time on cART than ART-naïve patients by analysing the length of time from 1 January 2003 to a new AIDS diagnosis in patients who began cART from 1996 through 1999 and were still in follow-up on 1 January 2003. Selected patients received continuous cART from July 2002 to January 2003. Time was censored when no death was recorded at the date of the last clinical visit or viral load or measurement of CD4 cell count. The Kaplan–Meier estimate for the probability of death by 1 January 2010 was 14.2% (95% CI 12.0-16.8) for the ART-experienced patients and for ART-naïve patients 6.2% (95% CI 5.0-7.6, p value <0.0001). On 1 January 2003, patients who were ART-experienced when cART was first initiated had a lower median CD4 cell count (520 cells/mm^3), and a higher median age (43.8 years) than patients who were ART-naïve (560 cells/mm^3, 41.6 years, $p<0.0001$ and $p=0.0002$, respectively). However, when results were adjusted for confounders, including age and CD4 cell count in January 2003, and other risk factors, ART-experienced patients had a significantly higher hazard of death than did ART-naïve patients (Web Appendix Table 3.1). Suppressed viral load and a high CD4 cell count in January 2003 were factors associated with a lower probability of death. The risk of death was 2.27 ($p<0.0001$) times higher for patients having CD4 cell counts between 200 and 350 cells/mm^3 than for patients with a count of 500 cells/mm^3 or higher. The risk of death for patients with counts between 350 and 500 cells/mm^3 in January 2003 was not significantly different ($p=0.87$) from the risk for those with counts of 500 cells/mm^3 or higher.

Longer exposure to periods of high-level viraemia prior to the start of cART may explain in part the higher mortality rate in patients with antiretroviral-drug experience at the start of cART. For most patients, the duration of the infection was unknown. The CD4 cell count at the start of cART and the interval between HIV diagnosis and the start of cART were therefore used as markers for the duration of infection. When these variables were included in the model, the hazard ratio for death for ART-drug–experienced patients compared to ART-naïve patients decreased to 1.43 (95% CI 1.12-1.83, p=0.004). The hazard rate for a longer time interval of 1 year between HIV diagnosis and cART initiation was 1.04 (95% CI 1.00-1.07, p=0.02), indicating that longer exposure to HIV may indeed play a role in a higher mortality rate.

Both in ART-experienced- and ART-naïve patients, the two most frequent causes of death other than AIDS 13 years after the first start of cART were suicide and non-AIDS–related malignancy. Suicide rates in chronic-disease populations are known to be higher compared to rates in the general population, and malignancies are the major cause of death in the general population, together with cardiovascular disease[63].

Incidence of death compared to that in the general population

Finally, we compared the incidence of death in our population due to non-AIDS–related 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 3.2).

The incidence of death due to non-AIDS–defining cancer was 3.19 (95% CI 2.37-4.19) for ART-experienced male patients and 1.43 (95% CI 0.46-3.33) per 1000 py for female patients. This compares to 1.25 and 0.60 per 1000 py for the male and female age-standardized general population, respectively. In men, the incidence

Table 3.2: Incidence of various causes of death in HIV-1 infected patients after starting cART compared to that in the age-standardized general population. The reported 95% confidence intervals (CI's) are based on the Poisson distribution. Information on causes of death in the general population in the Netherlands was obtained from Statistics Netherlands[63]. Figures for cause-specific incidence were standardized according to the age distribution in HIV-1-infected male and female patients included in this chapter over the period of the entire study and were subdivided into intervals of 3 months.

		Incidence per 1000 PY (95% CI)			
Cause of death	**Gender**	**ART-experienced at start cART**	**Age standardized population**	**ART-naïve at start cART**	**Age standardized population**
Non-AIDS–defining cancer	Male	3.19 (2.37-4.19)	1.25	2.34 (1.92-2.81)	1.11
	Female	1.43 (0.46-3.33)	0.60	0.58 (0.25-1.15)	0.61
Cardiovascular disease	Male	2.56 (1.84-3.47)	0.91	1.23 (0.93-1.59)	0.82
	Female	0.29 (0.01-1.59)	0.20	0.15 (0.02-0.53)	0.23
CVA	Male	0.31 (0.10-0.73)	0.13	0.19 (0.09-0.36)	0.12
	Female	0.00 (0.00-1.05)	0.06	0.07 (0.00-0.41)	0.06
Myocardial infarction	Male	1.12 (0.67-1.78)	0.33	0.53 (0.34-0.78)	0.29
	Female	0.00 (0.00-1.05)	0.05	0.00 (0.00-1.05)	0.05
Suicide	Male	0.75 (0.39-1.31)	0.19	0.85 (0.61-1.16)	0.18
	Female	0.57 (0.07-2.06)	0.08	0.22 (0.05-0.64)	0.07

Legend: PY=person-years of follow-up; CI=confidence interval; ART=antiretroviral therapy; CVA=cerebrovascular accident.

of death due to cardiovascular disease, myocardial infarction and suicide after starting cART was higher compared to that in the age-standardized population, both in ART-experienced and ART-naive patients. In ART-experienced women, the risk of death due to non-AIDS–defining malignancies and suicide appeared to be increased compared to the risk in the age-standardized population, although the 95% CI's were wide because of the smaller number of py. Since we could not adjust for other risk factors such as smoking, the higher incidence in the HIV-infected population cannot be attributed to HIV-infection alone. However, other studies have reported similar results for myocardial infarction and certain non-AIDS–defining cancers, even after adjustment for smoking and other risk factors[64-68]. So, although mortality rates of HIV-1 infected patients have declined over time and have shifted from AIDS as the major cause of death to diseases also seen in the general population, mortality rates for some of these diseases, such as cardiovascular disease and malignancy, are higher in patients treated for HIV-1 infection than in the general population.

A Swiss study found that although the incidence of death from suicide in male patients infected with HIV-1 was lower in the cART era than in the pre-cART era, it was still higher than in the general population. Although suicide rates in patients with chronic illnesses are higher than in the general population, it appears that rates in the HIV-infected population are higher than in those with other chronic diseases such as malignancies, multiple sclerosis or end stage renal disease[69].

AIDS and serious non-AIDS–defining diseases

Serious non-AIDS–defining diseases, such as non-AIDS–defining malignancies and cardiovascular, renal and liver disease, in the HIV-infected population are similar to those found in uninfected subjects. However, the incidence of these diseases appears higher in infected individuals than in uninfected controls[64, 66-68, 70, 71]. Apart from the known disease-specific risk factors and older age, there is increasing evidence that, in addition to certain antiretroviral therapy combinations, HIV infection itself may be associated with a higher incidence of non-AIDS–defining diseases[72]. In the remainder of this chapter, we report on the incidence of AIDS and the following non-AIDS–defining diseases: renal insufficiency (chronic and acute disease), liver disease (cirrhosis, fibrosis, or hepatocellular carcinoma), diabetes mellitus, myocardial infarction, cerebrovascular accident (CVA), osteoporosis and non-AIDS–defining malignancies (excluding basal- and squamous-cell carcinoma). Because routine data collection of some of these serious non-AIDS–defining diseases did not begin until July 2002, we report on the combined total number of these diseases from that date onwards.

Out of 13,013 patients, at least one serious non-AIDS–defining disease was recorded for 1212 patients from July 2002 onwards. A new AIDS-defining disease was recorded for 1072 patients over the same period and for 1782 patients from July 1996 onwards. The incidence of a first new AIDS diagnosis after the start of cART is shown for each calendar year in Figure 3.3, together with the incidence of a first diagnosis of one of the aforementioned serious non-AIDS–defining diseases. Figure 3.3 shows that the incidence of any AIDS-defining disease was highest in 1996 (152.1 per 1000 py), which should be interpreted with caution. In 1996, the denominator consisted of only patients within the first year of starting cART, when the incidence of AIDS was high due to immune reconstitution disease[73]. Whereas the incidence of any AIDS-defining disease per calendar year showed a decreasing trend ($p<0.0001$, test for trend), the incidence of serious non-AIDS–defining disease was stable between 2002 and 2008 ($p=0.67$). The decreasing trend in the incidence of AIDS can be explained by the increasing proportion of patients in later calendar years with high CD4 cell counts and hence, a low risk for developing AIDS.

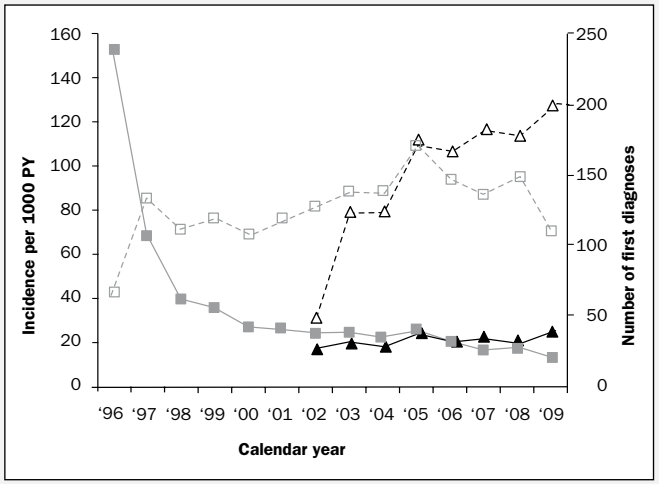


Figure 3.3: Incidence per 1000 person years of follow-up (solid lines) and number of diagnoses (dashed lines) of a first new AIDS diagnosis (grey line) and first serious non-AIDS–defining disease (black line) after the start of cART per calendar year.
Legend: PY=person-years of follow-up.

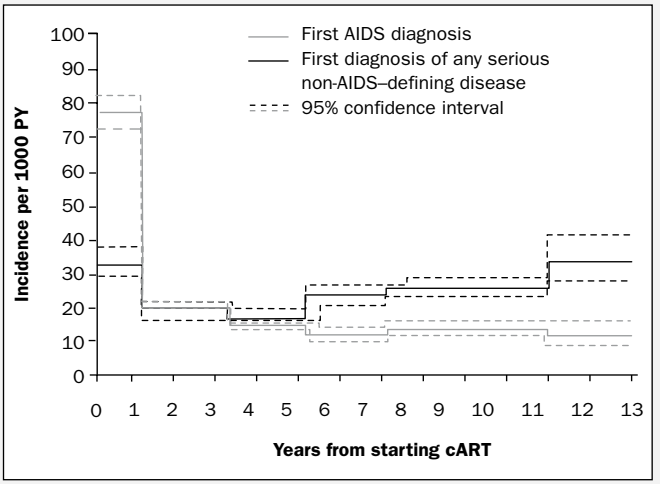


Figure 3.4: Incidence per 1000 person-years of follow-up (95% confidence interval - dashed lines) of first AIDS diagnosis (grey line) and of first diagnosis of any serious non-AIDS–defining disease (black line) after the start of cART. The reported 95% confidence intervals are based on the Poisson distribution.
Legend: PY=person-years of follow-up; cART=combination antiretroviral therapy.

The incidence for serious non-AIDS–defining disease was 18.4 per 1000 py (95% CI 13.7-24.3) in 2002 and 20.9 (95% CI 21.9-29.0) in 2008. Whereas the incidence of first AIDS diagnoses decreased over time, the annual number of first AIDS diagnoses was relatively stable between 1997 and 2008, with an average of 133 annual diagnoses. The number of serious non-AIDS–defining diseases increased from 125 in 2003 to 198 in 2009.

The incidence of both AIDS and serious non-AIDS–defining disease was highest in the first year after the start of cART; for AIDS it was 77.0 per 1000 py (95% CI 72.2-82.1) and for serious non-AIDS–defining disease it was 32.0 (95% CI 27.9-36.5). Beginning 3 years after the start of cART onwards, the incidence of serious non-AIDS–defining disease was higher than AIDS, as shown in Figure 3.4.

Incidences and the number of newly diagnosed specific types of AIDS and serious non-AIDS–defining disease can be found in Web Appendix Table 3.1 and 3.2. Overall, the most commonly diagnosed AIDS-related disease was candidiasis (386 diagnoses, of which 368 were oesophageal candidiasis), followed by Kaposi sarcoma (241 diagnoses). In 2009, the most commonly diagnosed AIDS-related disease was tuberculosis (30 diagnoses, incidence of 3.5 per 1000 py), followed by candidiasis (23 diagnoses, incidence of 2.7 per 1000 py). A recent study examined the effect of specific AIDS-related diseases during cART on mortality rates[74]. Tuberculosis, Kaposi sarcoma and candidiasis were classified as 'mild' AIDS-related diseases. Compared to patients without AIDS, the probability of death for patients who had tuberculosis was 2.8 times higher; for those with oesophageal candidiasis the probability was 2.1 times higher, and it was 1.8 times higher for those with Kaposi sarcoma. Non-Hodgkin's lymphoma and progressive multifocal leucoencephalopathy were the two types of AIDS-defining illnesses that increased the

probability of death most; patients with those diseases had a 10 times higher probability of death compared to patients without AIDS. Whilst diagnoses of progressive multifocal encephalopathy were rare in our study (6 diagnoses, incidence of 0.7 per 1000 py in 2009), non-Hodgkin's lymphoma was more common with 17 diagnoses and an incidence of 1.7 per 1000 py (95% CI 1.1-3.1).

Amongst the serious non-AIDS–defining diseases, non-AIDS–related malignancy was most common with a total of 397 diagnoses (61 in 2009). The incidence showed an increasing trend over time ($p<0.0001$, test for trend) and was 7.1 per 1000 py (95% CI 5.4-9.1) in 2009. The most frequently recorded non-AIDS–related malignancy was lung cancer (15.4%), followed by anal cancer (14.5%), Hodgkin's lymphoma (9.1%), and head and neck cancer (8.6%).

AIDS and serious non-AIDS–defining diseases by gender and age

Table 3.3 shows an increasing incidence with older age for all serious non-AIDS–defining diseases, except for liver disease. The incidence of any of the serious non-AIDS–defining diseases was 8.0 per 1000 py (95% CI 4.6-13.0) for male patients less than 30 years of age, and it was 57.4 (95% CI 48.8-66.9) for patients older than 60 years. In accordance with incidences in the general population, the incidence of any serious non-AIDS–defining disease in female patients was lower than that in men, but it showed a similar strong increase with older age. In contrast, the incidence of AIDS was stable in female patients with older age, and it decreased in male patients with older age. The most common serious non-AIDS–defining disease for those 60 years of age or more was non-AIDS–defining malignancy for male patients (17.3 per 1000 py) and osteoporosis for female patients (17.5 per 1000 py). Liver disease was the only serious non-AIDS–defining disease for which the trend did not increase with older age, probably because of the strong effect of co-infection with hepatitis B and C virus on the risk of liver disease.

The increasing age of patients living with HIV-1 partly explains the increasing trend of serious non-AIDS–defining diseases over time. Serious non-AIDS–defining diseases such as cardiovascular disease, osteoporosis, malignancies and renal disease are associated with older age in the general population. However, a higher number of older patients living with HIV, when considered alone, does not completely explain the increasing incidence of certain co-morbidities over time. Compared to HIV-negative individuals, HIV-infected patients have a higher rate of both fatal and non-fatal non-AIDS–defining diseases.

Figure 3.5 illustrates the incidence of non-AIDS–defining malignancies, diabetes mellitus and acute myocardial infarction for HIV-1-infected patients and the general population according to age and gender. In male HIV-infected patients, the incidence of non-AIDS–defining malignancies and myocardial infarction is higher than in the general population across all age groups. In contrast, the incidence of diabetes mellitus in HIV-infected male patients appeared only slightly higher than in the general population. The incidence of diabetes mellitus in HIV-infected women was higher than in the general female population (in women <45 years of age), whereas the incidence of non-AIDS–defining malignancies and myocardial infarction seemed similar in HIV-infected women and in the general female population. Because of the fewer person-years of follow-up, the confidence intervals for female patients are wide.

The higher incidence of non-AIDS–defining malignancies and myocardial infarction in male HIV-infected patients cannot be solely attributed to the infection. Long-term exposure to protease inhibitor treatment was independently associated with higher risk of

Table 3.3: Incidence per 1000 person-years (py) of newly diagnosed, routinely collected serious co-morbidities and AIDS per age group for male and female patients after starting cART. The reported 95% confidence intervals are based on the Poisson distribution.

		Male			Female		
	Age during follow-up (yrs)	Diagnoses	PY	Incidence per 1000 PY (95% CI)	Diagnoses	PY	Incidence per 1000 PY (95% CI)
Any AIDS	<30	106	3074	34.5 (28.2-41.7)	77	3254	23.7 (18.7-29.6)
	30-40	452	16656	27.1 (24.7-29.8)	178	6635	26.8 (23.0-31.1)
	40-50	505	22192	22.8 (20.8-24.8)	85	4064	20.9 (16.7-25.9)
	50-60	266	11096	24.0 (21.2-27.0)	19	1075	17.7 (10.6-27.6)
	>=60	82	3719	22.1 (17.5-27.4)	12	489	24.5 (12.7-42.9)
Any serious non-AIDS defining disease	<30	16	1999	8.0 (4.6-13.0)	21	2462	8.5 (5.3-13.0)
	30-40	148	11051	13.4 (11.3-15.7)	64	5285	12.1 (9.3-15.5)
	40-50	366	17190	21.3 (19.2-23.6)	90	3512	25.6 (20.6-31.5)
	50-60	290	8474	34.2 (30.4-38.4)	35	895	39.1 27.2-54.4)
	>=60	161	2807	57.4 (48.8-66.9)	21	386	54.5 (33.7-83.3)
Renal insufficiency	<30	5	2017	2.5 (0.8-5.8)	7	2509	2.8 (1.1-5.7)
	30-40	44	11345	3.9 (2.8-5.2)	7	5494	1.3 (0.5-2.6)
	40-50	80	18563	4.3 (3.4-5.4)	21	3836	5.5 (3.4-8.4)
	50-60	71	9589	7.4 (5.8-9.3)	13	991	13.1 (7.0-22.4)
	>=60	44	3493	12.6 (9.2-16.9)	5	456	11.0 (3.6-25.6)
Liver disease	<30	6	3105	1.9 (0.7-4.2)	6	3309	1.8 (0.7-3.9)
	30-40	59	17206	3.4 (2.6-4.4)	32	7092	4.5 (3.1-6.4)
	40-50	117	23442	5.0 (4.1-6.0)	31	4442	7.0 (4.7-9.9)
	50-60	46	12079	3.8 (2.8-5.1)	7	1162	6.0 (2.4-12.4)
	>=60	9	4139	2.2 (1.0-4.1)	1	539	1.9 (0.0-10.3)
Diabetes mellitus	<30	2	3111	0.6 (0-.1-2.3)	10	3288	3.0 (1.5-5.6)
	30-40	42	17255	2.4 (1.8-3.3)	28	7147	3.9 (2.6-5.7)
	40-50	99	23549	4.2 (3.4-5.1)	24	4444	5.4 (3.5-8.0)
	50-60	91	11813	7.7 (6.2-9.5)	7	1151	6.1 (2.4-12.5)
	>=60	43	3897	11.0 (8.0-14.9)	7	508	13.8 (5.5-28.4)
Myocardial infarction	<30	0	2547	0.0 (0.00-1.4)	0	2964	0.0 (0.0-1.2)
	30-40	11	14360	0.8 (0.4-1.4)	3	6483	0.5 (0.1-1.4)
	40-50	61	21343	2.9 (2.2-3.7)	4	4306	0.9 (0.3-2.4)
	50-60	64	10902	5.9 (4.5-7.5)	0	1130	0.0 (0.0-3.3)
	>=60	34	3762	9.0 (6.3-12.6)	5	502	10.0 (3.2-23.3)

		Male			Female		
	Age during follow-up (yrs)	Diagnoses	PY	Incidence per 1000 PY (95% CI)	Diagnoses	PY	Incidence per 1000 PY (95% CI)
Osteoporosis	<30	1	2030	0.5 (0.0-2.7)	2	2517	0.8 (0.1-2.9)
	30-40	8	11446	0.7 (0.3-1.4)	3	5547	0.5 (0.1-1.6)
	40-50	40	18738	2.1 (1.5-2.9)	11	3879	2.8 (1.4-5.1)
	50-60	27	9756	2.8 (1.8-4.0)	6	1012	5.9 (2.2-12.9)
	>=60	15	3585	4.2 (2.3-6.9)	8	456	17.5 (7.6-34.6)
CVA	<30	3	2541	1.2 (0.2-3.5)	1	2964	0.3 (0.0-1.9)
	30-40	13	14362	0.9 (0.5-1.5)	7	6457	1.1 (0.4-2.2)
	40-50	28	21530	1.3 (0.9-1.9)	7	4303	1.6 (0.7-3.4)
	50-60	42	11105	3.8 (2.7-5.1)	4	1115	3.6 (1.0-9.2)
	>=60	28	3854	7.3 (4.8-10.5)	4	505	7.9 (2.2-20.3)
Non-AIDS malignancy	<30	5	3112	1.6 (0.5-3.7)	2	3320	0.6 (0.1-2.2)
	30-40	39	17275	2.3 (1.6-3.1)	13	7204	1.8 (1.0-3.1)
	40-50	109	23721	4.6 (3.8-5.5)	24	4533	5.3 (3.4-7.9)
	50-60	117	12091	9.7 (8.0-11.6)	7	1159	6.0 (2.4-12.4)
	>=60	80	3972	20.1 (16.0-25.1)	6	538	11.2 (4.1-24.3)

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

cardiovascular disease[77]. Other antiretroviral drugs have been associated with renal dysfunction (eg. tenofovir) and heart disease (eg. abacavir). Furthermore, known risk factors such as smoking and lifestyle certainly play a role and may point to a higher rate of smoking in the HIV-infected population compared to that in the general population. However, other studies have shown that the incidence of non-AIDS–defining malignancies, renal disease and myocardial infarction[64, 66-68, 70, 71] in HIV-1-infected patients compared to uninfected controls was higher still, even after adjusting for age and other risk factors including smoking. This has led to the hypothesis that HIV itself is associated with an accelerated ageing process, further supported by a study showing increased frailty amongst HIV-infected patients compared to uninfected individuals[78]. An independent role of HIV disease in causing accelerated aging is suggested by observations that inflammatory markers did not normalize during anti-HIV therapy[79] and that elevated inflammation levels predict risk of non-AIDS-defining diseases. A large meta-analysis comparing the standardized incidence of non-AIDS–defining malignancies in HIV-infected patients according to the age and gender with that of the general population also demonstrated increased incidence of cancer especially of an infectious cause, suggesting that HIV-infected patients may be disproportionately infected with oncogenic viruses[80].

AIDS and serious non-AIDS–defining diseases by latest CD4 cell count

Assuming HIV-infection plays a role in the pathogenesis of non-AIDS–defining diseases, we can expect an association between the incidence of non-AIDS-defining diseases and CD4 cell counts and duration of HIV exposure. The incidence of AIDS, but also

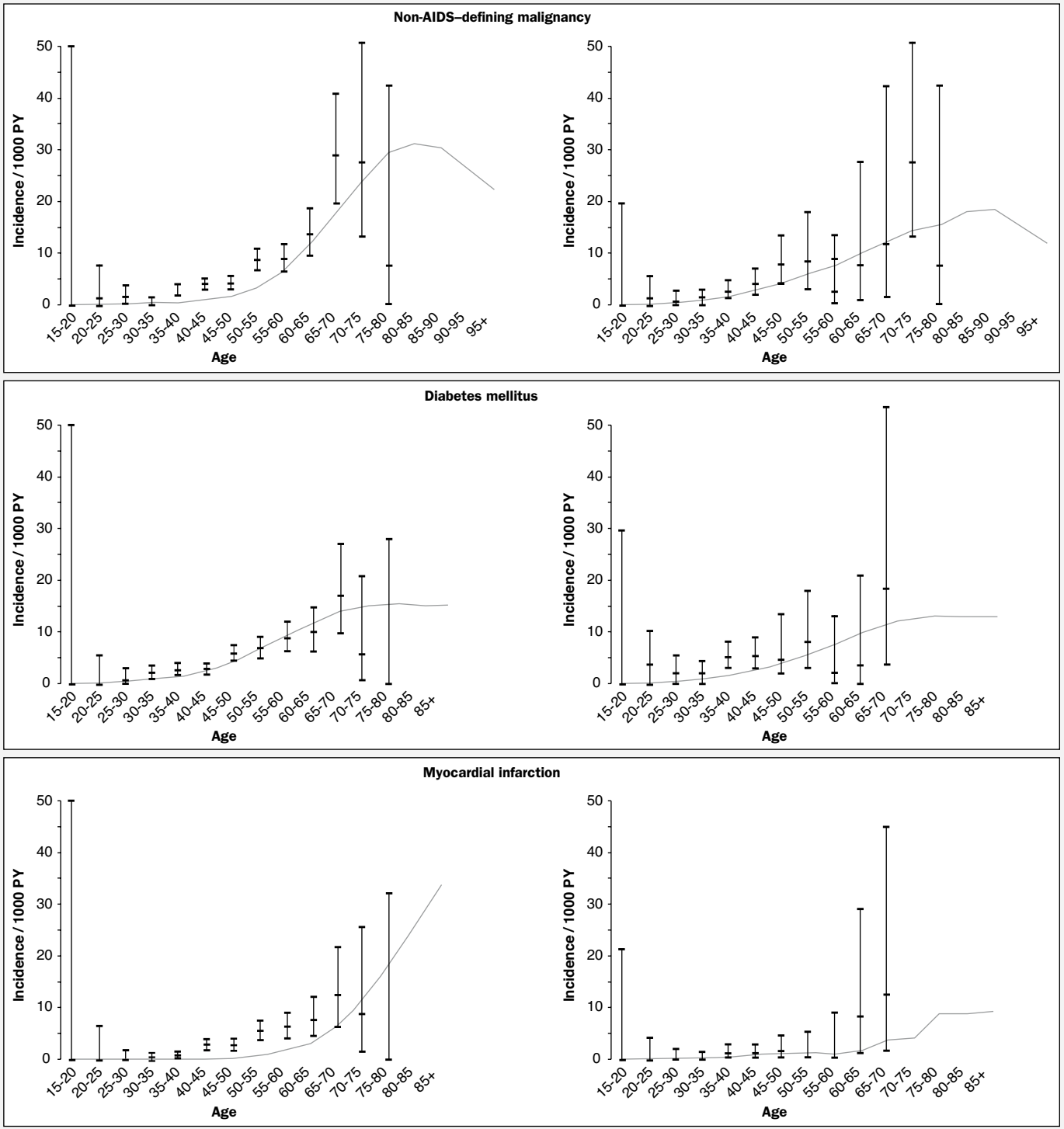

Non-AIDS–defining malignancy
Incidence / 1000 PY
Age
Diabetes mellitus
Incidence / 1000 PY
Age
Myocardial infarction
Incidence / 1000 PY
Age

Figure 3.5: Incidence (95% confidence interval [CI] – black bars) of non-AIDS–defining malignancies (top), diabetes mellitus (middle), and myocardial infarction (bottom) after the start of cART during follow-up for male (left plots) and female (right plots) patients per age category. The grey line shows the incidence of non-AIDS–defining malignancies in the general population between 2004 and 2008. Age- and gender-specific incidence figures for non-AIDS–defining malignancy for the general population between 2004 and 2008 according to site were obtained from the website of the Association of Comprehensive Cancer Centres[75]. The age-specific incidence figures for non-AIDS-defining malignancies in last year's report are much lower compared to those this year, due to an error in the estimates in last year's report. Estimates of age- and gender-specific incidence figures for diabetes mellitus and myocardial infarction in 2007 for the general population were obtained from the website from the National Institute of Public Health and the Environment[76]. The reported 95% confidence intervals are based on the Poisson distribution, and the incidence in the HIV-infected population was calculated only for age categories with at least 100 person-years of follow-up.
Legend: PY=person-years of follow-up.

serious non-AIDS–defining diseases, is higher when the latest CD4 cell counts are lower, as shown in Table 3.4. This relationship is stronger for AIDS but is also clearly present for non-AIDS–defining diseases. Among serious non-AIDS–defining diseases, the association of a higher incidence with a lower latest CD4 count was strongest for renal insufficiency and weakest for myocardial infarction. In a recent study, older age (≥60 years), lower latest CD4 cell counts (<100 cells/mm^3), and HCV co-infection, as well as higher latest plasma viral load levels (≥10,000 copies/ml), were independently associated with a higher incidence of serious non-AIDS–defining diseases[81]. This indicates that a timely start of cART and a quick suppression of viral production will reduce the incidence of non-AIDS–defining diseases. It is therefore important to start cART in a timely manner to suppress plasma viral load to undetectable levels, to allow patients to spend as little time as possible at low CD4 cell counts, and to identify patients at risk for specific co-morbidities.

Table 3.4: Incidence per 1000 person-years (PY) of newly diagnosed, routinely collected, serious co-morbidities and any AIDS-defining disease per the latest CD4 cell count after the start of cART. Follow-up of each patient was split into periods of 3 months, and for each period the latest CD4 cell count was selected. The 95% CI's are based on the Poisson distribution.

	Latest CD4 cell count (cells/mm^3)	Diag-noses	PY	Incidence/ 1000 PY	95% CI	
Any AIDS	<50	424	724	585.4	531.0	643.9
	50 - 200	560	6336	88.4	81.2	96.0
	200 - 350	344	14096	24.4	21.9	27.1
	350 - 500	195	17163	11.4	9.8	13.1
	≥500	187	32375	5.8	5.0	6.7
Any serious non-	<50	58	523	110.8	84.1	143.3
AIDS– defining	50 - 200	205	4151	49.4	42.9	56.6
disease	200 - 350	272	10327	26.3	23.3	29.7
	350 - 500	246	13336	18.4	16.2	20.9
	≥500	424	24982	17.0	15.4	18.7
Renal insufficiency	<50	39	554	70.4	50.0	96.2
	50 - 200	90	4596	19.6	15.7	24.1
	200 - 350	61	11147	5.5	4.2	7.0
	350 - 500	41	14261	2.9	2.1	3.9
	≥500	65	26989	2.4	1.9	3.1
Liver disease	<50	12	959	12.5	6.5	21.9
	50 - 200	55	6927	7.9	6.0	10.3
	200 - 350	79	15032	5.3	4.2	6.5
	350 - 500	61	18165	3.4	2.6	4.3
	≥500	102	33961	3.0	2.4	3.6
Diabetes mellitus	<50	12	956	12.6	6.5	21.9
	50 - 200	45	7017	6.4	4.7	8.6
	200 - 350	71	15056	4.7	3.7	5.9
	350 - 500	75	18085	4.1	3.3	5.2
	≥500	149	33575	4.4	3.8	5.2
Myocardial	<50	3	749	4.0	0.8	11.7
infarction	50 - 200	18	5855	3.1	1.8	4.9
	200 - 350	44	13225	3.3	2.4	4.5
	350 - 500	36	16392	2.2	1.5	3.0
	≥500	78	31008	2.5	2.0	3.1

Table 3.4: (continued)

	Latest CD4 cell count (cells/mm^3)	Diag-noses	PY	Incidence/ 1000 PY	95% CI	
Osteoporosis	<50	3	579	5.2	1.1	15.1
	50 - 200	14	4719	3.0	1.6	5.0
	200 - 350	29	11298	2.6	1.7	3.7
	350 - 500	31	14403	2.2	1.5	3.1
	≥500	44	27221	1.6	1.2	2.2
CVA	<50	7	751	9.3	3.7	19.2
	50 - 200	28	5883	4.8	3.2	6.9
	200 - 350	34	13280	2.6	1.8	3.6
	350 - 500	30	16522	1.8	1.2	2.6
	≥500	38	31229	1.2	0.9	1.7
Non-AIDS	<50	10	921	10.9	5.2	20.0
malignancy	50 - 200	70	6774	10.3	8.1	13.1
	200 - 350	109	14761	7.4	6.1	8.9
	350 - 500	80	17953	4.5	3.5	5.5
	≥500	125	33737	3.7	3.1	4.4

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

The independent contribution of latest CD4 cell counts, age, exposure time to HIV and other risk factors for any serious non-AIDS–defining disease was analysed with adjusted Poisson models (Web Appendix Table 3.5). Apart from older age and lower latest CD4 cell counts, patients with a history of mono- or dual therapy at the start of cART had an increased risk of non-AIDS–defining disease, as did patients with a longer time period between HIV diagnosis and cART initiation. This suggests that HIV itself might contribute to the development of some of these diseases. If HIV does indeed play a role, one might also observe an association between the incidence of non-AIDS-defining diseases and longer periods of viremia after the start of cART, but we did not observe such an effect (p=0.95), possibly because of a lack of power to detect a difference. Patients co-infected with HBV and HCV also had an increased risk of non-AIDS–defining diseases, probably because they are at high risk of liver disease.

Loss to follow-up

Loss to follow-up is an important issue mainly in resource-limited settings, but also in industrialized countries. Regular clinical follow-up is required to recognise problems with the management of HIV infection in an early stage. Complete patient follow-up is also required for unbiased evaluation of the effect of antiretroviral therapy on survival and disease progression. We therefore investigated the rate of loss to follow-up after the start of cART.

Among 11,254 patients who started cART before 1 June 2008, 954 patients were lost to follow-up. Twelve years after the start of cART, the Kaplan–Meier estimate of the cumulative incidence of loss to follow-up was 16.5%, but this differed significantly according to the region of origin of the patients, as Figure 3.6 shows.

We calculated the incidence of loss to follow-up according to latest CD4 cell counts, with the goal of characterizing the reasons for loss to follow-up. As shown in Table 3.5, the incidence in patients from the Netherlands did not decrease with higher CD4 cell counts, in contrast to that in patients from sub-Saharan Africa. Patients from sub-Saharan Africa at an advanced stage of the disease might have returned to their country of birth to die, whereas the probability of patients from the Netherlands being lost to follow-up did not depend on disease stage. A similar inverse association between the latest CD4 cell count and incidence of loss to follow-up in patients from sub-Saharan Africa was observed in patients from the Caribbean or South America and other Western countries. Other risk factors significantly associated with a higher probability of being lost to follow-up were

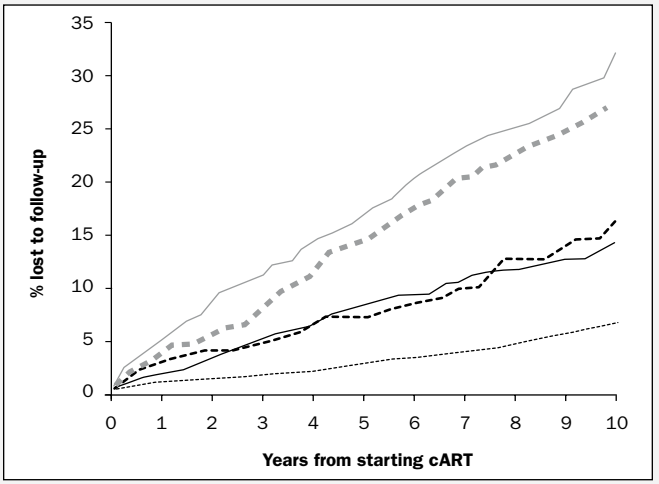


Figure 3.6: Cumulative incidence of loss to follow-up after the start of combination antiretroviral therapy (cART) according to patients' region of origin. Patients were considered lost to follow-up if the date of their last available CD4 cell count, HIV RNA measurement, or clinical visit was more than 1 year before 1 June 2008. This date was chosen in order to minimize the number of patients being lost to follow-up due to a backlog in data entry. Death was not considered as a loss to follow-up.
Black dotted line: Netherlands; black solid line: Caribbean / South America; grey dashes: other Western countries; grey solid line: sub-Saharan Africa; black dashes: other region of origin.

younger age, male gender, or intravenous drug use or heterosexual sex as the most likely route of HIV transmission (HR compared to homosexual sex 1.92 ($p<0.0001$) and 1.29 ($p=0.01$), respectively).

When loss to follow-up is a random process, the censoring of patients in survival analyses does not introduce bias in effect estimates. When loss to follow-up depends on disease stage, survival estimates are biased. Therefore, results from survival analyses need to be carefully interpreted, especially when comparing patients from different regions. Possible solutions are sensitivity analyses in which all patients lost to follow-up are assumed to have died (worst case scenario) or imputation of a date of death for patients lost to follow-up.

Table 3.5: Incidence of loss to follow-up according to the latest CD4 cell count in patients from the Netherlands and sub-Saharan Africa.

Latest CD4 cell count (cells/mm^3)	Netherlands			Sub-Saharan Africa		
	PY	Lost to fup	Incidence /1000 PY (95% CI)	PY	Lost to fup	Incidence /1000 PY (95% CI)
<200	4708	20	4.25 (2.59-6.56)	1685	82	48.67 (38.71-60-41)
200 - 350	9033	54	5.98 (4.49-7.80)	2929	108	36.87 (30.25-44.51)
350 - 500	11,026	57	5.17 (3.92-6.70)	3064	84	27.41 (21.86-33.94)
>500	21,893	93	4.25 (3.43-5.20)	4397	92	20.92 (16.87-25.66)

Legend: PY=person-years; fup=follow-up; CI=confidence interval

Conclusion

As causes of death in the ageing HIV-infected population come to resemble more closely those seen in the general population, it will be necessary to address risk factors for lifestyle-related causes of death and to monitor and provide care for diseases associated with old age to further lower mortality rates. Further studies are needed to determine to what extent the increased risk for these diseases is due to immune deficiency, exposure to antiretroviral drugs, or exposure to HIV itself.

The absolute number of AIDS diagnoses has remained stable over time, as has the number of patients starting cART with low CD4 counts. If the rate of testing for HIV in populations at risk for HIV is increased, it may contribute to a reduction in the number of patients with low CD4 cell counts at diagnosis, the number starting cART at low CD4 cell counts, and the number of new AIDS diagnoses.

4. Effect of cART on HIV RNA concentration in plasma, CD4 cell count, and toxicity-driven therapy changes

Luuk Gras, Colette Smit

cART in adults

In 2009, 1002 patients infected with HIV-1 started combination antiretroviral therapy (cART) with a median of 280 CD4 cells/mm^3, which, although higher than in previous years, is well below the currently recommended threshold of 350 cells/mm^3. Of all patients diagnosed between 1996 and 2009 with CD4 cell counts of 350 cells/mm^3 or more, 13% started cART too late (<200 CD4 cells/mm^3; from 1996 to 2008 the recommendation was to initiate therapy before cells dropped to this level).

After starting cART, 50% of the patients achieved HIV RNA plasma concentrations of less than 50 copies/ml within 4.8 months. After the initial suppression, <50 copies/ml, the probability of maintaining that level increased with a longer time on cART and with later calendar years. Virological suppression was better in female patients, patients who were of older age, and patients with lower CD4 cell counts, which may be explained by a lesser perceived necessity and, consequently, a lesser level of adherence to cART in younger, male patients with high CD4 cell counts.

Seven years of cART-induced viral suppression resulted in an increase of CD4 cell counts to a median of 750 cells/mm^3, provided that therapy was started when the counts were between 350 and 500 cells/mm^3. This result is only slightly lower than normal values in uninfected individuals. Interestingly, with a longer time on cART, older age and higher CD4 cell counts during follow-up, the counts decreased in an increasing proportion of patients on virologically successful cART. Decreased thymic output with older age, chronic inflammation and persistent immune activation have been shown to be associated with reduced CD4 cell count restoration, but persistent low-level viral replication may have an effect as well.

Finally, on the basis of the declining incidence of toxicity-driven therapy changes since 2000, it appears that less toxic drugs, together with better insights into prevention of toxicity, have improved the clinical management of HIV-infected patients on cART. Regimens that are easy to tolerate are especially important when cART is initiated at higher CD4 cell counts and the perceived necessity of treatment in the patient is lower.

In conclusion, HIV testing rates will need to improve for a timely start of cART (≥350 cells/mm^3) in most patients. Monitoring changes in viral load and CD4 cell count remains important in patients on cART to identify those at risk for disease. Measuring markers for immune activation and low- level plasma viral load below the detection limit of 50 copies/ml and introduction of a clear definition of decreasing CD4 cell counts, taking the natural variability into account, may also help in this respect.

cART in children and adolescents

Most HIV-infected children treated with paediatric cART are now surviving to adulthood. The results of the analyses on treatment response in children and adolescents indicate that the immunologic and virologic

responses to cART are age-dependent. Compared to younger children (aged ≤ 2 years) the immune and virologic responses are stronger in older children (aged 3-12 years). The virologic response is less strong in adolescents (aged 13-18 years), which probably reflects poor adherence in this group. Protease-inhibitor (PI)-based regimens increase the risk of hyperlipidaemia in children; long-term exposure to hyperlipidaemia may put children at risk for cardiovascular disease at a later age.

cART in volwassenen

Mediane CD4 cel aantallen van HIV-1 geïnfecteerde patiënten die in 2009 met combinatie antiretrovirale therapie (cART) waren gestart waren hoger dan in eerdere jaren, maar toch waren ruim onder de grens van 350 cellen/mm^3 die in de huidige richtlijnen wordt aanbevolen. Bij 13% van alle tijdig gediagnosticeerde patiënten met een CD4 cel aantal hoger dan 350 cellen/mm^3 bij HIV diagnose werd cART toch te laat, namelijk onder de 200 cellen/mm^3, gestart.

Binnen 5 maanden na het starten van cART bereikt 50% van de patiënten plasma virale load levels van minder dan 50 kopieën/ml. De kans om het virus blijvend te onderdrukken na initiele nam toe naarmate patiënten langer op therapie zaten en in latere kalenderjaren. De supressie kans was ook hoger in oudere patiënten, vrouwen en bij hogere CD4 cel aantallen bij start van cART. Andere studies hebben laten zien dat patiënten minder therapietrouw zijn als de behandeling minder noodzakelijk door hen wordt geacht.

Als cART tussen de 350 en 500 CD4 cellen/mm^3 wordt gestart en de hoeveelheid virus in plasma tot onder detecteerbare niveaus blijvend onderdrukt, wordt na 7 jaar CD4 waarden benaderd die als normaal worden gezien in de ongeïnfecteerde bevolking. Bij hogere leeftijd, het bereiken van hogere CD4 cel aantallen, en een langere tijd op cART neemt de kans op dalende CD4 cel aantallen toe. Onderzoek heeft aangetoond dat een verminderde werking van de thymus op oudere leeftijd, chronische ontsteking en voortdurende activatie van het immuunsysteem samenhangen met onvolledig herstel van CD4 cel aantallen. Ook is het mogelijk dat de mate van virus replicatie onder de detectielimiet van de huidige assays invloed heeft op CD4 cel aantallen.

De incidentie van wijzigingen in de therapie als gevolg van bijwerkingen is sinds 1996 gehalveerd, waarschijnlijk door het op de markt komen van minder toxische middelen en een beter inzicht in de preventie van toxiciteit. Middelen met eenvoudige doseringen die weinig bijwerkingen opleveren zijn vooral belangrijk nu cART steeds vaker wordt gestart bij hogere CD4 aantallen, wanneer patiënten nog geen nadelige gevolgen van HIV infectie ervaren.

Om de meerderheid van HIV-1 patiënten tijdig met cART te kunnen laten starten, dus voordat CD4 cel aantallen zijn gedaald tot onder de 350 cellen/mm^3, is een actiever testbeleid noodzakelijk. Het monitoren van virale load en CD4 cel aantallen blijft belangrijk in het identificeren van patiënten met een verhoogd risico op ziektes. Daarnaast kan het monitoren van markers voor immuunactivatie, het meten van plasma HIV RNA waardes onder de detectielimiet van 50 kopieën/ml en de introductie van een goede definitie van dalende CD4 cel aantallen die rekening houdt met de natuurlijke variabiliteit, hierbij helpen.

cART in kinderen en adolescenten

Door de behandeling met cART bereiken met HIV geïnfecteerde kinderen nu een volwassen leeftijd. Resultaten van analyses laten zien dat de immunologische en virologische response op cART leeftijdafhankelijk is. In vergelijking met jonge kinderen (≤2 jaar) hebben oudere kinderen (3-12 jaar) een sterkere immuun en virologisch response, terwijl de response bij adolescenten juist wee minder sterk is, mogelijk als een gevolg van minder therapie trouw. Wanneer kinderen met een PI worden behandeld wordt het risico op hyperlipidemie verhoogd; langdurige blootstelling aan hyperlipidemie vergroot mogelijk het risico op cardiovascular aandoeningen op latere leeftijd voor deze kinderen.

cART in adults

Lower pill burden and dosing schemes of once or twice daily, together with declining toxicity, have improved HIV treatment management over time, although continuous and life-long combination antiretroviral therapy (cART) is still needed to prevent disease progression to AIDS and death[82]. During the first 6 months of cART, plasma HIV RNA concentration levels in most patients infected with HIV-1 decline below 50 copies/ml whilst CD4 cell counts rapidly increase. When cART is started in a timely manner and is continued without interruption for several years, CD4 cell counts have been shown to approach the normal levels in uninfected subjects[83], and plasma HIV RNA can be maintained at <50 copies/ml for long periods of time, providing adherence to therapy is high. Still, questions about the long-term effect of cART remain. It is uncertain whether CD4 cell counts can reach normal levels when cART is initiated at low CD4 cell counts[83, 84]. Studies have suggested that CD4 cell counts reach a plateau after 3 to 5 years of virologically successful cART, at least in some patients[83, 85, 86, 87]. Furthermore, there is ongoing debate concerning at which stage of HIV infection cART should be initiated[88-90]. When it is started in an early stage, adherence may be poor because of the perceived loss of quality of life due to the toxic effect of antiviral drugs on cells and cell metabolism. Adverse events and toxicity may result in poorer patient adherence or even discontinuation of treatment, causing suboptimal drug levels and possibly treatment failure[91, 92] and drug resistance[93]. Furthermore, long-term exposure to antiretroviral (ART) drugs, as well as high-level viraemia, increases the risk of clinical events [77, 81, 94-96].

Serious complications as a result of inadequate therapy may take a long time to emerge. To avoid these long-term complications, it is important to recognize potential problems at an early stage. In this chapter we therefore describe trends over time following cART initiation in markers for efficacy (viral load in plasma and changes in CD4 cell count) and tolerability of therapy (incidence of toxicity-driven therapy changes).

Demographic and clinical characteristics at the start of cART

Out of the 16,382 patients with an HIV-1 infection and a known date of diagnosis, 13,013 started cART between July 1996 and December 2009 and had follow-up available after the start. An additional 620 females started cART during a pregnancy and were excluded from further analysis. These women are described in Chapter 2. Out of the remaining 12,393 patients, 2012 were mono- or dual ART-experienced, and 10,381 were ART-naïve at the start of cART. To study changes over time in demographic and clinical characteristics at the start of cART that were possibly associated with efficacy and tolerability of cART, we further classified ART-naïve patients according to the calendar year of their start date. In total, 5857 started cART prior to 2005 (early cART), 3522 between 2005 and 2008 (recent cART), and 1002 in 2009 (Table 4.1).

A higher proportion of men having sex with men (MSM) ($p=0.0001$) and of patients originating from the Netherlands ($p<0.0001$) with a later calendar year of starting cART were found in the group of ART-naïve patients, similar to the reported changes over time in the proportion of MSM from the Netherlands amongst the annual number of patients newly diagnosed with HIV (Chapter 2). According to current guidelines [97, 98], starting cART is recommended before CD4 counts reach a threshold of 350 cells/mm^3; this is reflected in the higher median CD4 count at the start of cART in 2008 and 2009 than that in previous years. Median counts at the start of cART were 240 CD4 cells/mm^3 in 2008, 280 cells/mm^3 in 2009, and only 200 cells/mm^3 between 2005 and 2007 ($p<0.0001$). Of patients starting

Table 4.1: Baseline characteristics of 12,393 patients starting cART between 1 July 1996 and 31 December 2009.

				ART-naïve					
		ART-experienced		Start cART <2005		Start cART 2005-2008		Start cART 2009	
		N	%	N	%	N	%	N	%
Total		2012	16.2	5857	47.3	3522	28.4	1002	8.1
Gender	Male	1653	82.2	4678	79.9	2922	83.0	869	86.7
Transmission risk group	MSM	1186	58.9	3100	52.9	2073	58.9	683	68.2
	IDU	455	22.6	2004	34.2	1064	30.2	258	25.7
	Heterosexual contact	226	11.2	328	5.6	127	3.6	16	1.6
	Blood-blood contact	145	7.2	425	7.3	258	7.3	45	4.5
	Other	83	4.2	271	5.3	237	7.5	53	5.2
Region of origin	Netherlands	1274	63.3	3268	55.8	2050	58.2	636	63.5
	Western Europe/North America/Australia	257	12.8	490	8.4	244	6.9	58	5.8
	Caribbean/Latin America	182	9.0	623	10.6	419	11.9	107	10.7
	Sub-Saharan Africa	179	8.9	1068	18.2	510	14.5	117	11.7
	Other	120	6.0	408	7.0	299	8.5	84	8.4
Clinical stage CDC-C		772	38.4	1751	29.9	871	24.7	174	17.4
HBV	Negative	1646	81.8	5051	86.2	3132	88.9	880	87.8
	Positive	178	8.8	388	6.6	231	6.6	65	6.5
	Unknown	188	9.3	418	7.1	159	4.5	57	5.7
HCV	Negative	1380	68.6	4593	78.4	2932	83.2	842	84.0
	Positive	263	13.1	428	7.3	291	8.3	108	10.8
	Unknown	369	18.3	836	14.3	299	8.5	52	5.2
Initial regimen	NNRTI-based	267	13.3	1959	33.4	2419	68.7	763	76.1
	PI-based	1659	82.5	3489	59.6	940	26.7	191	19.1
	Other	86	4.2	409	7.0	163	4.6	48	4.8
		Med	**IQR**	**Med**	**IQR**	**Med**	**IQR**	**Med**	**IQR**
Age at starting cART		38.7	33.4-45.8	37.6	31.9-44.7	40.6	34.3-47.5	41.3	34.5-47.8
CD4 cell count at starting cART (cells/mm^3)		200	90-340	190	70-310	210	100-280	280	190-350
HIV RNA at starting cART (log_{10} cps/ml)		4.38	3.31-5.00	5.00	4.55-5.43	5.00	4.58-5.40	4.90	4.30-5.32

Legend: ART=antiretroviral therapy; cART=combination antiretroviral therapy; MSM=men having sex with men; IDU=injecting drug use; CDC=Centers for Disease Control and Prevention; HBV=hepatitis B virus; HCV=hepatitis C virus; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; med=median; IQR=interquartile range.

cART in 2009, 25% did so with a CD4 count of less than 200 cells/mm^3, compared to 35% in 2008 ($p<0.0001$). However, when the current threshold of 350 CD4 cells/mm^3 was taken into account, in 2009, 77% of the patients started cART too late.

The percentage of patients with a Centers for Disease Control and Prevention (CDC)-C diagnosis before the start of cART was lower for those starting in 2008 (18.3%) and 2009 (17.4%) than for those starting between 2005 and 2007 (28.2%, both $p<0.0001$ compared to 2008

and 2009). The median plasma HIV RNA concentration at the start of cART was lower for those starting in 2009 compared to those starting between 2005 and 2008 ($p<0.0001$). Both these observations are in accordance with the higher CD4 cell counts found in those starting cART in 2009.

From 2005 onwards, the percentage of patients with hepatitis B virus (HBV) co-infection at the start of cART has been stable over time (test for trend, $p=0.37$). In contrast, the percentage of patients with hepatitis C virus (HCV) co-infection at the start of cART showed a modest increase from 7.4% between 2004 and 2007 to 9.5% in 2008 and 10.8% in 2010 (test for trend, $p=0.01$).

Whilst the majority of ART-experienced and therapy-naïve patients starting cART before 2005 started on a protease inhibitor (PI)-based regimen, from 2005 onwards, an increasing proportion of ART-naïve patients started with a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based regimen.

In conclusion, the recommendation in the recently changed guidelines to initiate therapy before CD4 cell count levels have declined below 350 cells/mm^3 has led to a higher proportion of patients in less advanced disease stages starting cART in 2009 than in earlier years. Nevertheless, the vast majority (77%) of patients starting in 2009 began when they had counts below this threshold.

Late cART initiation

We aimed for further insight into the reasons for a late start of cART. In total, 7363 ART-naïve patients for whom CD4 cell counts at HIV diagnosis and at the start of cART were available, were selected and further analysed. As it was recommended to start cART before CD4 cell counts had dropped below 200 cells/mm^3 throughout most of the cART era, this threshold was used to define late starters (patients starting cART with counts <200 cells/mm^3). By this definition, 3555 (48.3%) ART-naïve patients were late starting cART (Table 4.2).

Table 4.2: Number (%) of patients with both a timely diagnosis and timely start of combination antiretroviral therapy (cART) and who had both a known CD4 cell count at HIV diagnosis and at start of cART.

	CD4 cell counts at the start of cART (cells/mm^3)		
CD4 cell count at HIV diagnosis (cells/mm^3)	<200 N (%)	≥200 N (%)	**Total** **N**
<350	3219 (66.8)	1598 (33.2)	4817
≥350	344 (13.5)	2210 (86.5)	2546
Total	**3555 (48.3)**	**3808 (51.7)**	**7363**

An obvious prerequisite for a timely start of cART is a timely diagnosis, which was defined as having CD4 cell counts of 350 cells/mm^3 or more at HIV diagnosis. Despite a late diagnosis in 4817 patients, 1598 of these (33.2%) started cART in time. In total, 2546 (34.6%) had a timely diagnosis. Of these, 344 patients (13%) had less than 200 CD4 cells/mm^3 when cART was initiated. Because these patients did not have an apparent reason for starting cART late, we studied their characteristics. The 344 patients were compared with the 2268 remaining patients who had ≥350 CD4 cells/mm^3 at diagnosis and started cART in time. Logistic regression models were used with late cART initiation as the outcome variable. All variables included in Table 4.1 were considered potential risk factors for late cART initiation. The median time between HIV-1 diagnosis and the start of cART was 2.7 years in late starters and 1.5 years in patients with a timely start. Intravenous drug use as the most likely route of HIV transmission and receipt of an HIV diagnosis between 2001 and 2003 were the only risk factors significantly associated with late cART initiation. Only weak associations were found for patients <50 years of age (odds ratio [OR] 1.37, 95% confidence interval [CI] 0.93-2.03, $p=0.11$), those with a

tuberculosis diagnosis prior to starting cART (OR 1.65, 95% CI 0.78-3.48, p=0.19) or those who had anti-HCV treatment prior to starting cART (OR 1.65, 95% CI 0.78-3.48, p=0.16).

The Swiss cohort study found that late cART initiation, apart from late presentation, occurred predominantly because patients had missed medical visits[99]. Patients' refusal to initiate cART is probably responsible for a substantial proportion who present early in the disease course but delay cART. Reasons for refusal include fear of adverse events, no perceived necessity for starting cART, too much of an extra psychological burden of living with HIV, and fear of stigmatization when taking pills[100, 101]. Another possibility for late start is the physician's perception of lack of patients' readiness to start cART and thus their inability to adhere to treatment. This was one of the most common reasons for not prescribing treatment in a Swiss study[102]. Social support is important in patients expected to have difficulties adhering to cART, such as alcohol and/or substance abusers, patients with depression, illegal immigrants and those without permanent residence[103]. A delayed uptake of cART among injecting drug users has been reported previously, but little information exists about other difficult-to-manage groups[104]. Data regarding reasons for late cART initiation were not collected, preventing a more thorough analysis of why those with high CD4 cell counts at diagnosis started cART late.

Virological response

Response short-term

The short-term virological response to cART is an important marker for longer-term clinical outcome. The level of HIV RNA in plasma after 36 weeks of cART still has additional prognostic value for predicting the onset of AIDS, even after adjustment for viral load levels at 3 years after the first start of cART[105].

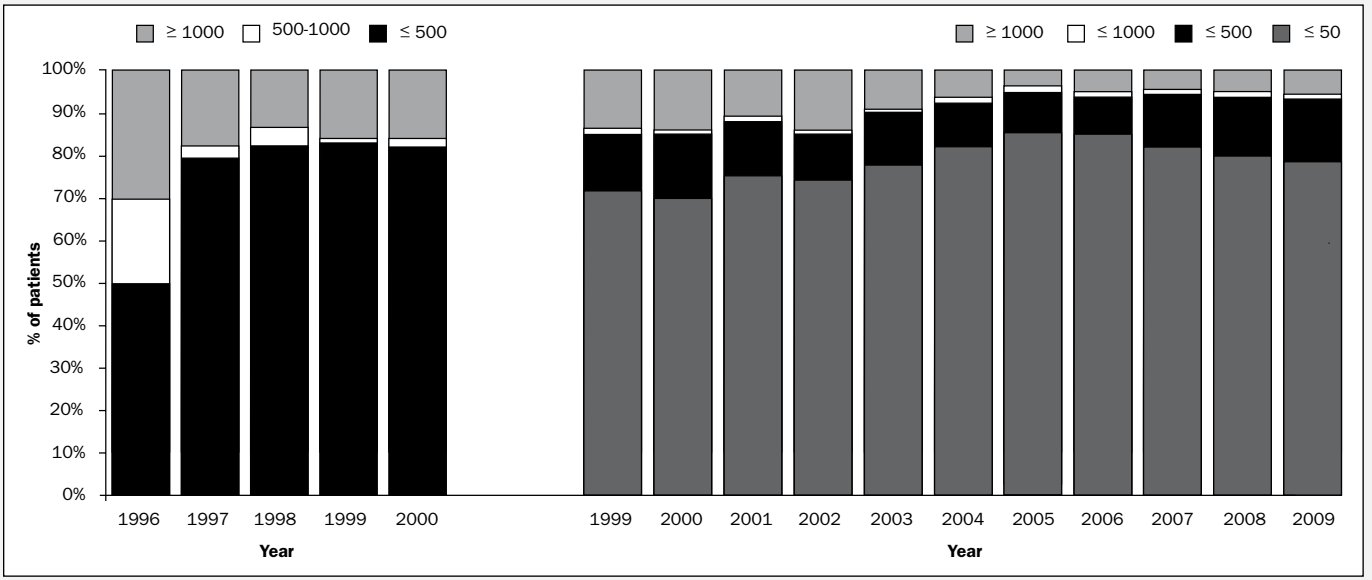


Figure 4.1: Plasma HIV RNA (copies/ml) at week 36 (measurement between 24 and 48 weeks closest to 36 weeks) determined with assays with a lower detection limit of 400 or higher (left) and with a lower detection limit of 50 or lower (right) according to calendar year of the start of cART. Only calendar years with at least 200 measurements are shown. The left figure includes a combination of assays for plasma viral load with a lower detection limit of 1000 copies/ml and those with limits of 400 or 500.

We therefore monitored the virological response after 36 weeks of cART over time (Figure 4.1).

Amongst patients who started cART, the plasma viral load was measured in 86% of patients at 36 weeks. The low percentage of patients with a plasma viral load <500 copies/ml at week 36 in 1996 can be explained by the use of assays with a lower detection limit of 1000 copies. However, the percentage of patients with a plasma viral load <1000 copies/ml was also lower compared to that in 1997. This might be due, in part, to the high proportion of ART-experienced patients starting cART in 1996 who were known to have a poorer virologcal short-term response than ART-naïve patients[106] and, in part, to the fact that some cART regimens in use during the early calendar years were not as virologically effective as those used in later calendar years[107]. The percentage of patients with a plasma viral load less than 1000 copies/ml 36 weeks after starting cART increased from 79% in 1996 to between 95% and 96% in recent years. From 2005, we observed a trend toward a smaller percentage of patients with <50 copies/ml at 36 weeks (86% in 2005 vs. 78% in 2009, p<0.0001, test for trend over time between 2005 and 2009). The decreasing trend over time could not be explained by changes in clinical or demographic characteristics of patients.

Recently, however, studies have been published comparing the new Roche COBAS AmpliPrep COBAS TaqMan HIV-1 assay version 2.0 (CAP/CTM v2.0) for measuring HIV RNA concentration in plasma with earlier assays with lower detection limits of 50 copies/ml. HIV RNA concentrations below 50 copies/ml measured with earlier assays were frequently found to be higher than 50 copies when measured with the new CAP/CTM v2.0 assay[108]. From 2008 onwards, some laboratories have been using the CAP/CTM v2.0 assay in routine practice. When we excluded patients who started cART in 2008 or later and who had samples measured in laboratories using the new CAP/CTM v2.0 assay, the trend over time of longer time to virological suppression was no longer observed. The median time to observing HIV RNA <50 copies/ml was 4.8 months after the start of cART. More studies are needed to determine whether changes in management are required when patients who previously had viraemia below the lower detection limit with other assays are found to have detectable low-level viraemia in plasma measured with the CAP/CTM v2.0 assay. It is obvious, however, that results from virological response studies may be biased when the effect of the type of assay used to determine viral load levels is not taken into consideration. Therefore, in the remainder of this paragraph, we have excluded patients with plasma samples measured in laboratories using the new CAP/CTM v2.0 assay.

Factors associated with a shorter time to initial suppression of HIV RNA to <50 copies/ml were studied using Cox proportional hazards models. Table 4.3 shows that the probability of reaching viral load levels below 50 copies/ml was higher when patients started cART on an NNRTI-based regimen, although the difference was not significant in patients who started before 2004. NNRTI- based regimens were also found to

Table 4.3: Hazard ratios (95% CI) obtained from an adjusted Cox proportional hazards model of time from the start of cART to the first of two consecutive plasma HIV RNA concentrations <50 copies/ml in 5723 patients who were antiretroviral-therapy–naive and who had HIV RNA measured with assays with a lower detection limit of 50 copies/ml.

	Calendar year of starting cART		
Starting regimen	**2000-2003**	**2004-2007**	**2008-2009**
NRTI + NNRTI	1	1	1
NRTI + PI	0.95 (0.87-1.04)	0.87 (0.78-0.97)	0.79 (0.66-0.95)

Legend: CI=confidence interval; cART=combination antiretroviral therapy; NRTI=nucleoside reverse transcriptase inhibitor, NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

be more virologically effective than PI-based regimens in a meta-analysis of randomised clinical trials, which did not otherwise find significant differences in clinical outcomes between PI- and NNRTI-based regimens[109]. In concordance with other studies[110, 111], time to suppression was significantly longer in patients aged <30 years (hazard ratio [HR] compared to 40 years or more 0.82, 95% CI 0.75-0.89, p<0.0001), in male patients (HR 0.87, 95% CI 0.79-0.95, p=0.002), those infected through intravenous drug use (HR compared with MSM 0.77, 95% CI 0.67-0.89, p=0.0004), patients with higher CD4 cell counts at the start of cART (HR 350-500 compared to 200-350 cells/mm^3 0.86, 95% CI 0.77-0.96, p=0.006) and a lower plasma HIV RNA concentration at the start. Adherence to therapy may be lower in these patient groups. Lower adherence is strongly correlated with a lower perceived necessity for therapy, and such a perception is associated with higher CD4 cell counts at the start of cART[112].

Figure 4.2 shows that 82% to 84% of the patients had a plasma viral load <50 copies/ml after week 36 from the start of cART. This percentage was 90% to 91% for those continuously on cART. The percentage of patients on cART with a plasma viral load >500 copies/ml after 48 weeks fluctuated between 1% and 3%. A higher percentage of the patients on cART, 5% to 7%, had low-level viraemia between 50 and 500 copies/ml. In a recent study, more than 30% of patients on cART experienced episodes of viraemia[113]. High-level viraemia has been associated with a poorer clinical outcome and smaller increases in CD4 cell count[114, 115], but the clinical significance of low-level viraemia is still unclear. Low-level viraemia was not associated with AIDS or death[113]. Low-level, single occurrences, or 'blips', do not seem to have an effect on CD4 cell counts or virological outcome[116, 117], but frequent or persistent periods of low-level viraemia have been reported to be associated with treatment failure and emergence of drug resistance[118, 119].

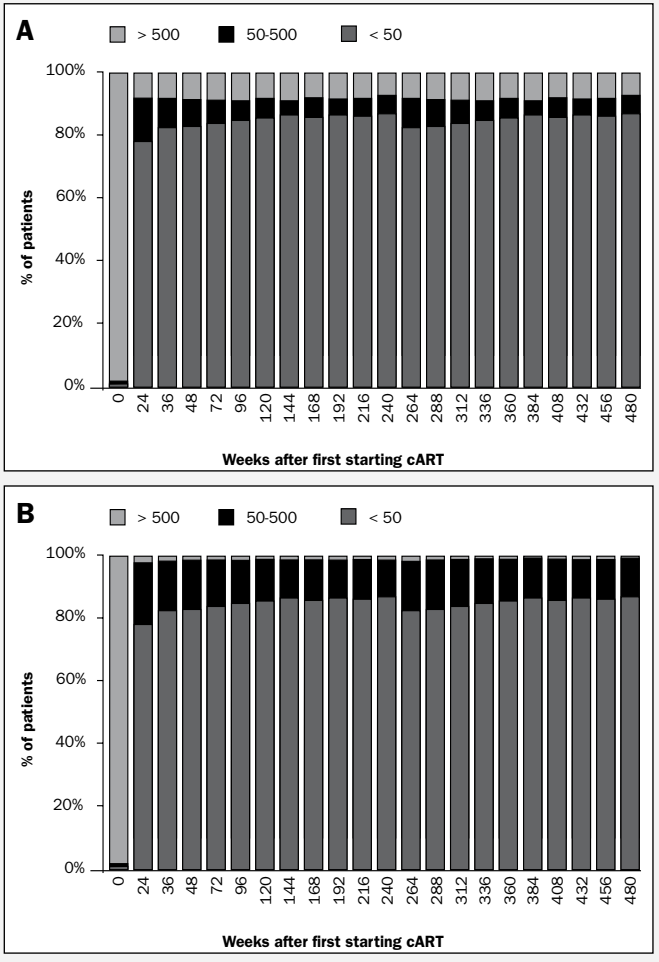


Figure 4.2: Plasma HIV RNA concentration (copies/ml) at weeks 24, 36, and 48 and at every 24 weeks of follow-up thereafter. Only plasma samples measured with assays with a lower detection limit ≤50 copies are included. Plot A shows results from all patients after starting combination antiretroviral therapy (cART) and plot B shows a subgroup of patients continuously on cART, allowing for a therapy interruption of <2 weeks.

Factors associated with plasma viral load levels <50 copies/ml in patients on cART were studied with longitudinal logistic regression models including the calendar year of follow-up and the number of years after the start of cART (Figure 4.3).

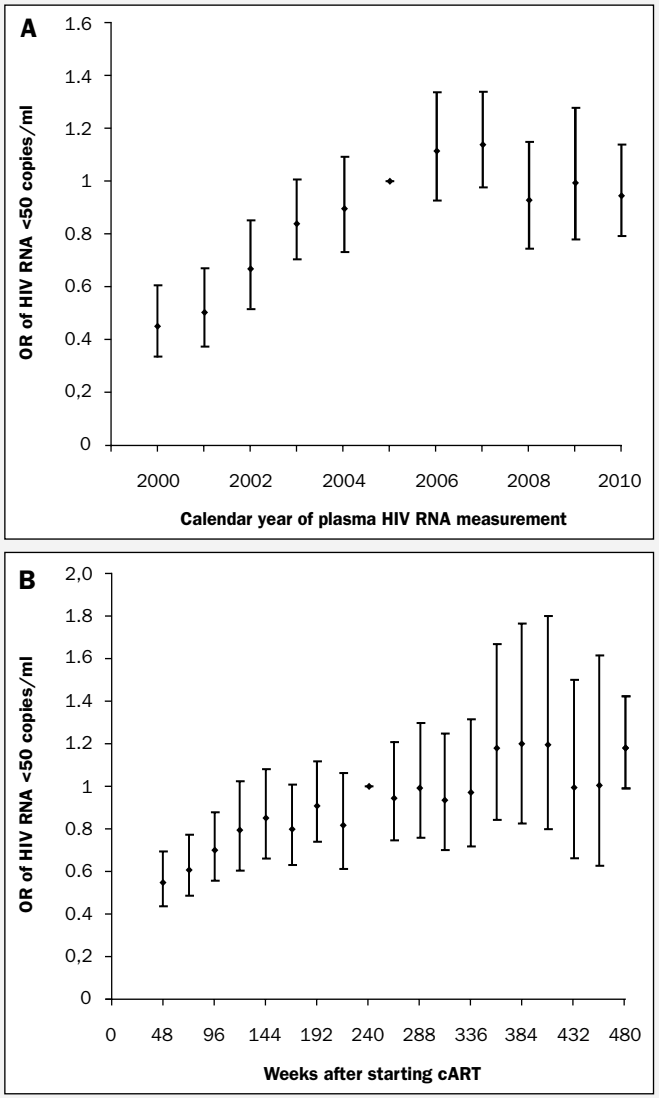


Figure 4.3: Odds ratios and 95% confidence intervals for the probability of having a plasma HIV RNA measurement <50 copies/ml according to (A) the year of measurement and (B) the number of weeks after the start of cART. Samples were taken when the patients were on cART. Logistic regression models were used including a generalised estimating equations (GEE) correlation structure to account for serial measurement per patient. Estimates are adjusted for gender, age, region of origin, transmission risk group, and plasma HIV RNA and CD4 cell count at the start of cART, allowing for a therapy interruption of <2 weeks.

The probability of having a plasma HIV RNA measurement <50 copies/ml in patients on cART increased in 2000 and 2005 and peaked in 2006 and 2007, whilst the probability in 2008 to 2010 was lower compared to 2007 (OR 0.84, 95% CI 0.73-0.97, p=0.01). The increasing trend between 2000 and 2005 may be explained by the introduction of new drugs that allowed for easier patient adherence. The reason for the lower probability in and after 2008 compared to 2007 is unclear and will need further study.

In Figure 4.3, plot B shows that with longer time on cART the probability of plasma concentrations <50 copies/ml increased. With a longer time after the start of cART, the 95% CIs increased because the number of patients still on cART decreased. The observed increase in probability with a longer time on cART may be because patients who are doing well on cART remain on cART and are compliant, whilst patients possibly less compliant who experience toxicity stop cART at an early stage. Another possibility is that with a longer time on cART, undetectable HIV RNA levels continue to decrease below the detection limit of 50 copies/ml. Other factors associated with a lower probability of HIV RNA <50 copies/ml were younger age (OR <30 years compared with ≥40 years 0.75, 95% CI 0.60-0.94, p=0.01), and sub-Saharan African origin (OR compared to Netherlands 0.63, 95% CI 0-.52-0.77, p<0.0001).

Immunologic response

No CD4 count at the start of cART was available for 1163 (9.4%) of the 12,393 patients, and these patients were excluded from further analyses of the immunologic response to cART.

Immune status in the treated population by calendar year

In Chapter 3 we observed that the number of AIDS diagnoses after starting cART has changed very little over calendar time. Figure 4.4 shows the immune status of patients in each calendar year after starting cART.

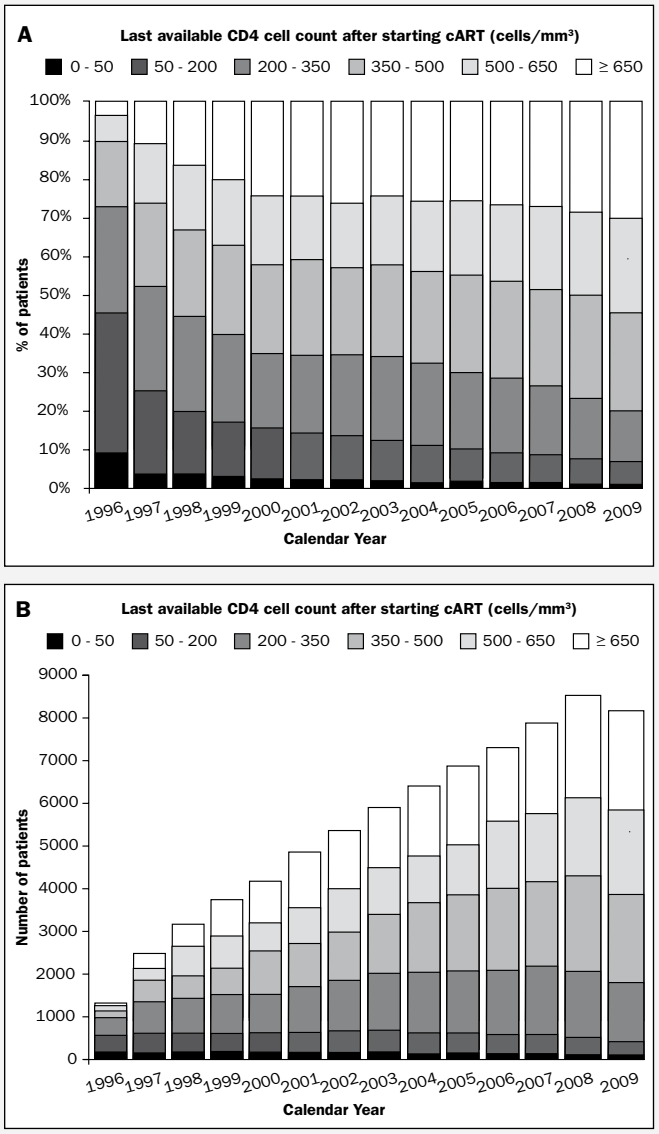


Figure 4.4: Last available CD4 cell count in each calendar year after the start of cART. The plot A shows the percentage and plot B the number of patients with CD4 cell counts 0-50, 50-200, 200-350, 350-500, 500-650 and ≥650 cells/mm^3. For each patient, the last available CD4 cell count after the start of cART between July and December of each year was selected.

After starting cART, the percentage of patients with counts <200 cells /mm^3, which indicates a higher risk for AIDS, dropped from 46% in 1996 to 5% in 2009. However, the absolute number of patients with low CD4 cell counts during the period 1998 to 2007 fluctuated between 614 and 712 (in 2003). The number of patients with low CD4 cell counts started to decrease as of 2003 and reached 539 in 2008. Figures for 2009 should be interpreted with caution, as they are not yet complete.

The trend of starting cART with higher CD4 cell counts in later calendar years explains the recent drop in absolute number and the percentage of patients with low CD4 cell counts at the end of each calendar year.

Longitudinal CD4 cell count changes after starting cART

Longitudinal modelling of the long-term effect of cART on the immune status of the patients can aid in determining guidelines on when best to start cART.

First, to study CD4 count changes in the whole population who had started cART, we included all patients, those on cART and those having a therapy interruption, in our analyses. ART-experienced patients started cART at median CD4 counts of 200 cells/mm^3 (interquartile range [IQR], 91-336) and increased to 325 CD4 cells/mm^3 (IQR, 190-500) at 48 weeks; 450 (IQR, 280-650) at 240 weeks; 500 (IQR, 320-710) at 480 weeks; and 520 (IQR, 340-740) at 576 weeks (Figure 4.5A, grey lines). The median CD4 cell count at the start of cART in ART-naïve patients was similar to that in ART-experienced patients with a median of 210 cells/mm^3 (IQR, 90-300) at the start of cART, but showed greater increases to 380 (IQR, 246-520) at 48 weeks, 500 (IQR, 360-690) at 240 weeks, 580 (IQR, 410-770) at 480 weeks, and 610 (IQR, 440-820) at 576 weeks (Figure 4.5 B, grey lines). Median CD4 cell counts for patients starting cART with <50 and 50 to 2000 cells/mm^3 and for those with 200 to 350 and 350 to 500 cells /mm^3 seemed to converge after 10 years. Different levels of adherence in these patient groups is

an explanation for these converging CD4 cell counts, even though adherence in all groups was high enough to maintain virological suppression.

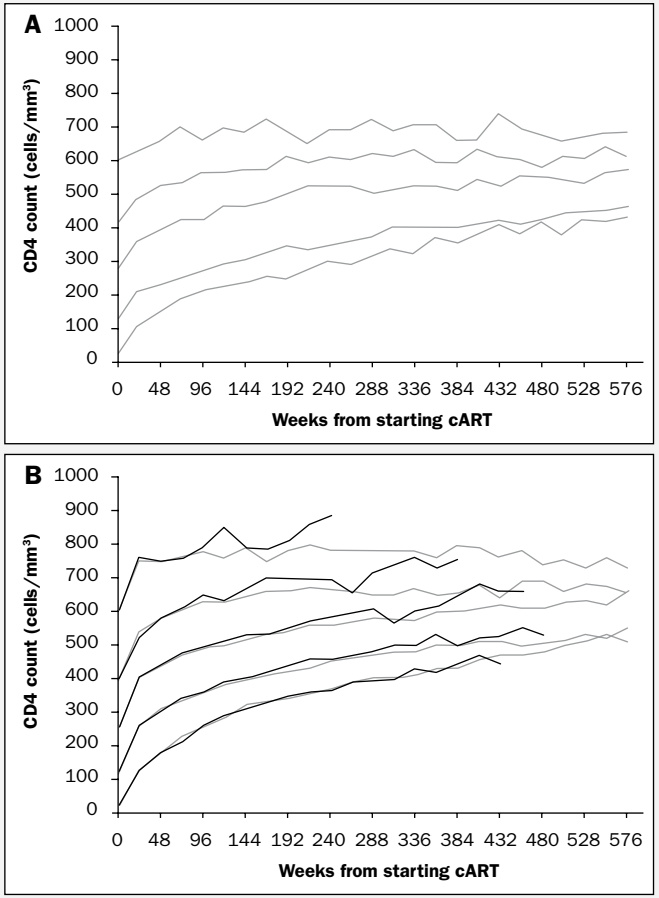


Figure 4.5: Median CD4 count according to CD4 count at the start of combination antiretroviral therapy (cART) in ART-experienced patients (A) and ART-naïve patients (B) according to CD4 cell count at the start of cART (<50, 50-200, 200-350, 350-500 and ≥500 cells/mm^3). Grey lines show the median CD4 cell counts in all patients after starting cART, including patients on cART and patients having a therapy interruption. Black lines in the right plot show the median CD4 cell counts for patients with an initial suppression to below 50 copies/ml within 9 months after starting cART and with plasma HIV RNA concentration levels <50 copies/ml thereafter. In this last subgroup, CD4 cell counts were censored at the first of two consecutive measurements of HIV RNA >50 copies/ml after the initial suppression of <50 copies/ml. The trend line was stopped when the number of patients in a subgroup dropped below 50 patients.

In addition, to study the maximum capacity of cART to restore CD4 cell counts, we restricted analyses to therapy-naive patients with continuous viral suppression to <50 copies/ml. Only patients were included who had reached HIV RNA levels of <50 copies/ml within 9 months from the start of cART. CD4 cell counts after virological failure (defined as two consecutive viral load measurements >50 copies/ml) were excluded. Increases in CD4 count up to week 384 ranged between 420 cells/mm^3 for patients starting with <50 cells/mm^3 to 330 for patients starting between 350 and 500 cells/mm^3 (Figure 4.5 B, black lines). In cases where cART was started when CD4 counts were still high, the median CD4 counts after 384 weeks of virologically successful cART were 645 cells/mm^3 (IQR, 470-790) for patients starting between 200 and 350 cells/mm^3 and 750 (IQR, 570-970) for those starting between 350 and 500 cells/mm^3. Although the median CD4 cell counts fluctuated over time and occasionally decreased, the trend was an increase over time in median CD4 cell counts in patients who were being successfully treated with cART.

To minimize the effect of random CD4 cell count fluctuations, a mixed effects regression analysis was performed including all available CD4 cell counts after the start of cART up to the first date of either the end of virological suppression <50 copies/ml or 8 years after the start of cART. Between 4 and 8 years of successful virological suppression by cART, the mean estimated slopes ranged between 29 cells/mm^3 per year (95% CI 22-36, p<0.0001) for patients who had started cART with <50 CD4 cells to 17 cells/mm^3 per year (95% CI 3-32, p=0.02) for those who had started with counts ≥500 cells/mm^3. Patients aged 50 years or more at the start of cART had significantly smaller increases of 26 cells/mm^3 per year between 0 and 6 months and 21 cells/mm^3 per year between 6 and 24 months compare to patients younger than 50. No significant differences according to age were found in patients after 2 years on cART. In summary, these results show that the mean CD4 cell counts in patients on virologically successful

cART continue to increase up to 8 years after the start of cART.

CD4 cell counts plateau

Although mean CD4 cell counts may continue to increase with a longer time on cART, this does not preclude the fact that, for some individual patients, CD4 cell counts do not increase with a longer time on cART. We therefore modelled individual patient slopes using a model similar to that in the previous paragraph. The total number of patients with enough follow-up to contribute to each period after the start of cART (0-0.5 years, 0.5-2 years, 2-4 years, 4-6 years and 4-8 years) is shown in Table 4.4, together with the number of patients who were estimated to have decreasing CD4 cell counts during each period.

Table 4.4: Number (%) of patients on virologically successful cART with an estimated decreasing CD4 cell count 0-0.5 years, 0.5-2 years, 2-4 years, 4-6 years, and 6-8 years after the start of cART, according to the estimated CD4 cell count at the beginning of each period. Using a mixed effect model, we estimated the slope of the CD4 cell count over time after the start of cART. The model included random slopes for each patient and for each aforementioned period. Only patients with virological suppression within 9 months after the start of cART were included, and CD4 cell counts were censored when the patients no longer had viral suppression <50 copies/ml.

		CD4 cell count at start of period (cells/mm^3)			
Years after starting cART		<500 N (%)	500-800 N (%)	≥800 N (%)	Total N (%)
0-0.5	**Total patients**	**3751**	**140**	**12**	**3903**
	With estimated decrease in CD4 cell count	279 (7)	47 (34)	2 (17)	328 (8)
0.5-2	**Total patients**	**2022**	**409**	**59**	**2490**
	With estimated decrease in CD4 cell count	99 (5)	60 (15)	11 (19)	170 (7)
2-4	**Total patients**	**897**	**447**	**85**	**1429**
	With estimated decrease in CD4 cell count	91 (10)	90 (20)	31 (36)	367 (26)
4-6	**Total patients**	**354**	**275**	**94**	**719**
	With estimated decrease in CD4 cell count	56 (16)	82 (30)	49 (41)	236 (33)
6-8	**Total patients**	**137**	**126**	**56**	**319**
	With estimated decrease in CD4 cell count	29 (21)	36 (29)	17 (30)	82 (26)

Because of the end of the follow-up or the end of virological suppression to <50 copies/ml, the total number of patients decreased with a longer time after the start of cART from 3903 between 0 and 0.5 years after the start of cART to 319 between 6 and 8 years. In patients with <500 CD4 cells/mm^3 at the start of each period, the proportion who experienced a period of decreasing CD4 cell counts increased with a longer time on cART. The proportion of patients with decreasing CD4 cell counts was also higher when CD4 cell counts at the start of the period were high (between 500 and 800 cells/mm^3) or at normal levels (≥800 cells/mm^3). A logistic regression analysis on the 319 patients with at least 8 years of virologically successful cART revealed that, apart from the CD4 cell count at 6 years, the only variable associated with a higher probability of decreasing CD4 cell counts was older age (OR per 10 years' increase 1.16, 95% CI 1.01-1.34, p=0.04). Reduced thymic function with older age probably explains the smaller increases in older patients[120, 121]. However, we also found an independent effect of poor CD4 count restoration with a longer time on cART, which may be explained by persistent immune activation in treated patients. There is evidence that the level of immune activation is higher in successfully cART-treated patients than in uninfected individuals[79], and higher levels of immune activation are associated with incomplete CD4 cell restoration[122-124]. Chronic inflammation and a higher degree of immune activation are recognized as risk factors for atherosclerosis[125, 126], and it is also possible that persistent low-level viral replication below detectable limits of current assays may prove to be harmful[127]. Markers for elevated levels of inflammation or coagulation were also associated with a higher risk for all-cause mortality[128] and opportunistic disease[129].

The discrepancy between studies reporting a plateau effect[83-85, 130, 131] and those reporting no plateau effect[132, 133] might reflect different levels of ongoing viraemia, immune activation, or different age distributions among studies. Also, there could be differences in the definition

of decreasing CD4 cell counts, CD4 'plateaus', or CD4 setpoints across studies. More research is needed to determine the best definition that is also suitable for use in clinical practice. By our definition in this paragraph, we have used mixed effect models to minimize the effect of random fluctuations in CD4 cell counts, but for practical use this may not be the best definition.

The median CD4 cell count after 384 weeks of continuous, virologically successful cART in patients who started according to current guidelines is still lower than normal CD4 cell ranges. Normal CD4 levels in uninfected subjects are reported to be 1050, 840, and 800 cells/mm^3 for women, heterosexual men and MSM, respectively[134], with a likely geographic variation in normal CD4 ranges[135]. Normal ranges are also reported to be lower with older age. Therefore, it might be beneficial, especially in older patients, to start cART at even higher CD4 cell counts, i.e., before CD4 cell counts drop to below 500 cells/mm^3.

Toxicity

ART is associated with clinical adverse events and laboratory toxicities. This may lead to poor adherence and treatment discontinuation, which are major reasons for treatment failure and development of drug-resistant strains[91-93]. Since switching to sequential regimens leads to less effective virological suppression compared to the response on first regimens, the avoidance of toxicity is important[136]. In this paragraph we report on trends over time in treatment-limiting toxicities during the first 3 years after the start of cART and routinely measured lipid values.

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

During the first 3 years after starting cART, patients were followed for a total of 29,105 person-years (PY); of that number, 28,429 person-years (97.7%) included cART (PYcART). The overall incidence of toxicity-driven regimen changes was 21.7 (95% CI 21.2-22.3) per 100 PYcART. Patients could change the regimen more than once. During follow-up, 8274 of the 12,393 patients (66.8%) did not have toxicity-related regimen changes. The maximum number of changes because of toxicity in a single patient was 14.

Table 4.5: Toxicity-driven therapy changes during the first 3 years after the start of cART. 95% confidence intervals for the incidence per 100 PYcART were obtained with the Poisson distribution. Adjusted relative risk estimates were obtained from logistic regression models including age, gender, region of origin, transmission risk group, and time after starting cART (0-6, 6-12, 12-24 and 24-36 months)

Year of starting cART	PYcART	N	Incidence per 100 PYcART (95% CI)	Adjusted relative risk (95% CI)
1996	3238	934	28.8 (27.0-30.8)	1.60 (1.34-1.91)
1997	3361	904	26.9 (25.2-28.7)	1.56 (1.36-1.79)
1998	2051	530	25.8 (23.7-28.1)	1.50 (1.30-1.74)
1999	1918	447	23.3 (21.2-25.6)	1.37 (1.18-1.59)
2000	1771	512	28.9 (26.5-31.5)	1.59 (1.38-1.84)
2001	1972	421	21.3 (19.4-23.5)	1.24 (1.07-1.43)
2002	1881	374	19.9 (17.9-22.0)	1.20 (1.01-1.41)
2003	1862	355	19.1 (17.1-21.2)	1.14 (0.98-1.33)
2004	2017	369	18.3 (16.5-20.3)	1.11 (0.96-1.28)
2005	2091	346	16.5 (14.8-18.4)	1.00
2006	1993	316	15.9 (14.2-17.7)	0.97 (0.83-1.13)
2007	2033	300	14.8 (13.1-16.5)	0.82 (.70-0.97)
2008	1634	245	15.0 (13.2-17.0)	0.71 (0.60-0.84)
2009	607	142	23.4 (19.7-27.6)	0.74 (0.60-0.91)

Legend: cART=combination antiretroviral therapy; PYcART=person-years on cART during the first 3 years following the start of cART; N=number of toxicity-driven therapy changes; CI=confidence interval

The incidence was highest (55.1 per 100 PYcART) during the first 3 months after the start of cART; it declined to 24.4 per 100 PYcART between 3 and 6 months, 18.7 per 100 PYcART between 6 and 12 months, and 13.9 per 100

PYcART between 24 and 36 months ($p<0.0001$). The incidence of toxicity-driven therapy changes during the first 3 years after cART initiation was highest in 2000 and declined with a later calendar year of cART initiation (Table 4.5). The increase in incidence in 2009 can be attributed to patients not yet having 3 years of follow-up after starting cART. A relatively large part of the total person-years on cART were person-years during the first 3 months after starting cART. During this time period the number of toxicity-driven therapy changes was high, as shown by the lower relative risk for patients starting in 2008 and 2009 relative to 2005, which was obtained by analyses adjusted for the period after the start of cART and other risk factors.

When cART was started in later calendar years, the relative risk for toxicity-driven therapy declined; that, together with the improvement in virological response over time shown earlier, demonstrates that improving treatment of HIV-1 is a continuing process. An important risk factor for a toxicity-driven change in therapy was having had a prior toxicity-driven change. The risk for a new toxicity-driven therapy change increased by more than 80% ($p<0.0001$) if there had been a prior toxicity-driven therapy switch, showing the importance of selecting an initial cART regimen easy for the patient to tolerate. In accordance with results from other studies[137-139], we found that female gender was associated with a higher risk of toxicity-driven therapy changes (relative risk [RR] compared to men 1.41, 95% CI 1.28-1.54, $p<0.0001$). This has been attributed to a lower body mass index[140] and a higher drug concentration in plasma in women[141], but differences in men and women remained in our analysis after adjusting for weight. There was a significantly reduced risk for a toxicity-driven therapy change only for patients weighing ≥85 kg compared to those weighing <85 kg. The risk for a toxicity-driven therapy change did not differ significantly amongst patients weighing <85 kg. The risk for toxicity-driven therapy changes was increased more than 20% in patients older than 50 years compared to patients aged between 30 and 40 years. Furthermore, the risk was increased in patients with high CD4 cell counts (RR 1.35 ≥500 compared to 200-350 cells/mm^3, $p<0.0001$). Patients in an early stage of HIV infection were more likely to stop when they experienced therapy induced loss of quality of life than were patients in a more advanced stage[137, 142]. However, other observers did not find an increased risk for discontinuation of antiretroviral drugs because of toxicity at higher CD4 cell counts[139, 143]. Finally, patients infected through homosexual sex had a 15% higher risk for a toxicity-driven therapy change than patients with a different mode of HIV transmission.

Lipid values on cART over time

Dyslipidaemia is common in treated patients infected with HIV-1 and has been defined as a total cholesterol level of ≥6.2 mmol/l, a high-density lipoprotein (HDL) cholesterol level of ≤0.9 mmol/l, a triglyceride level of ≥2.3 mmol/l, or the receipt of lipid-lowering drugs[144]. Dyslipidaemia may increase the risk of cardiovascular disease[145]. The prevalence of hypercholesterolaemia (total cholesterol level above 6.2 mmol/l) was 27% in patients on cART including PIs, and it was 23% when NNRTIs were included, as compared to 8% in untreated patients. The prevalence of hypertriglyceridaemia (triglyceride level above 2.3 mmol/l) was 40% in patients on cART including PIs, 32% when NNRTIs were included, and 15% in untreated patients[146]. Exposure to certain drugs or drug classes has been associated with increased risk of dyslipidaemia[147, 148], but hypertriglyceridaemia was also commonly observed before the cART era[149]. In the figures below, we report on changes in total cholesterol, HDL-cholesterol, and triglyceride levels in the cART-treated population over time.

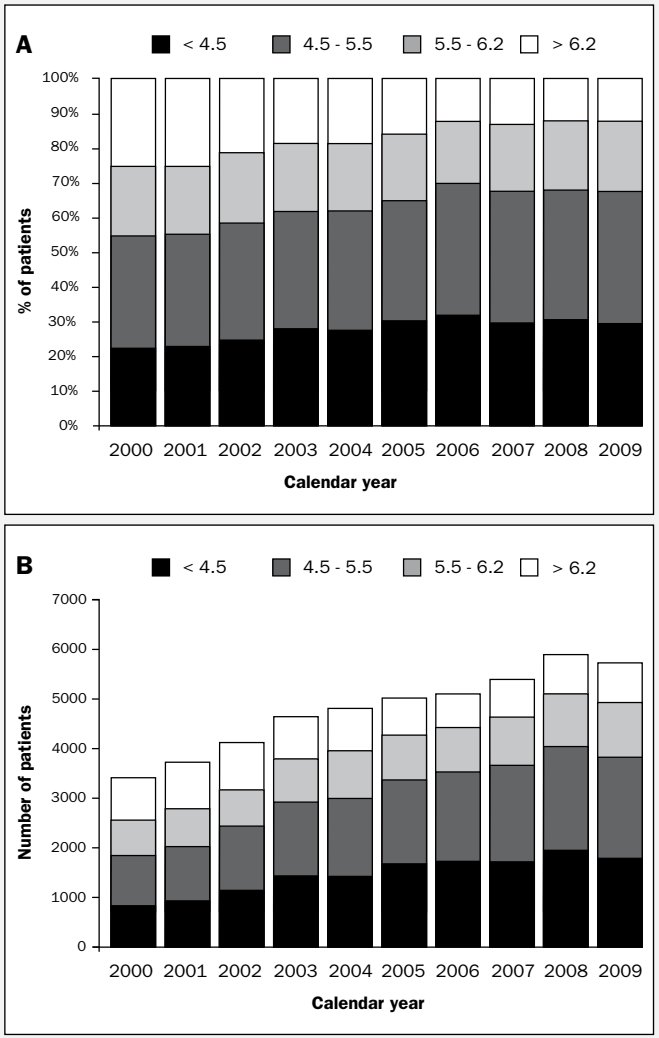


Figure 4.6: Last available total cholesterol in each calendar year after the start of cART. Plot A shows the percentage and Plot B the number of patients with total cholesterol levels <4.5, 4.5-5.5, 5.5-6.2 and >6.2 mmol/l. The last available total cholesterol measurement after the start of cART between July and December of each year was selected for each patient.

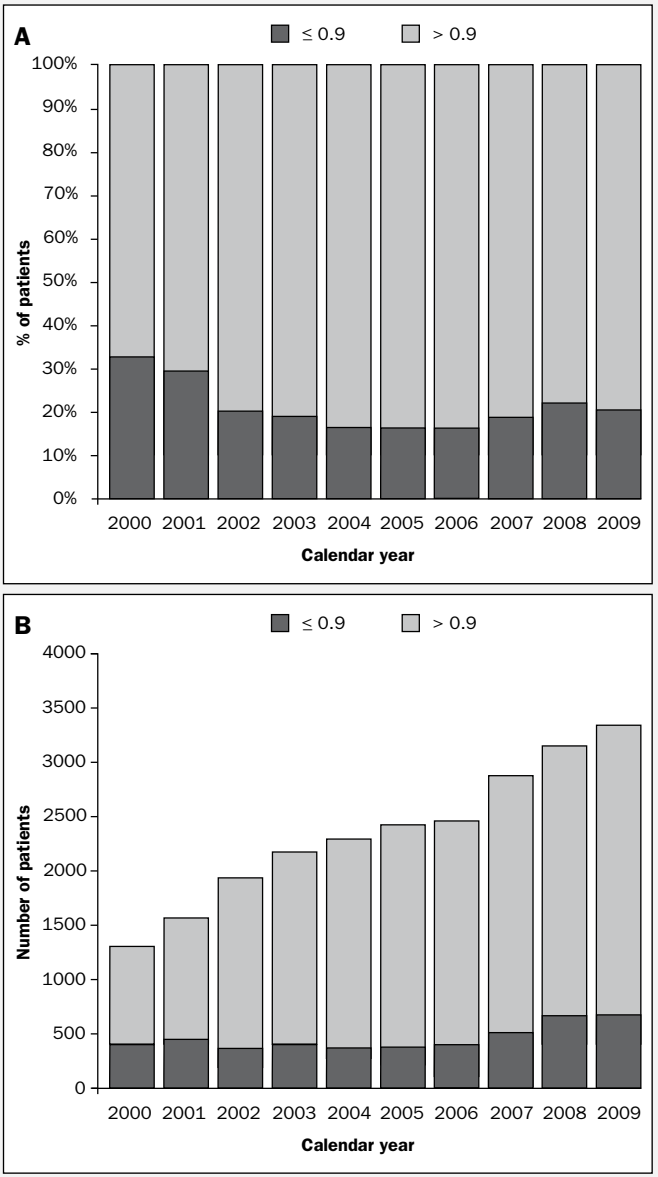


Figure 4.7: Last available total high density lipoprotein (HDL) cholesterol in each calendar year after the start of cART. Plot A shows the percentage and Plot B the number of patients with total cholesterol levels ≤0.9 and >0.9 mmol/l. For each patient the last available HDL cholesterol measurement after the start of cART between July and December of each year was selected.

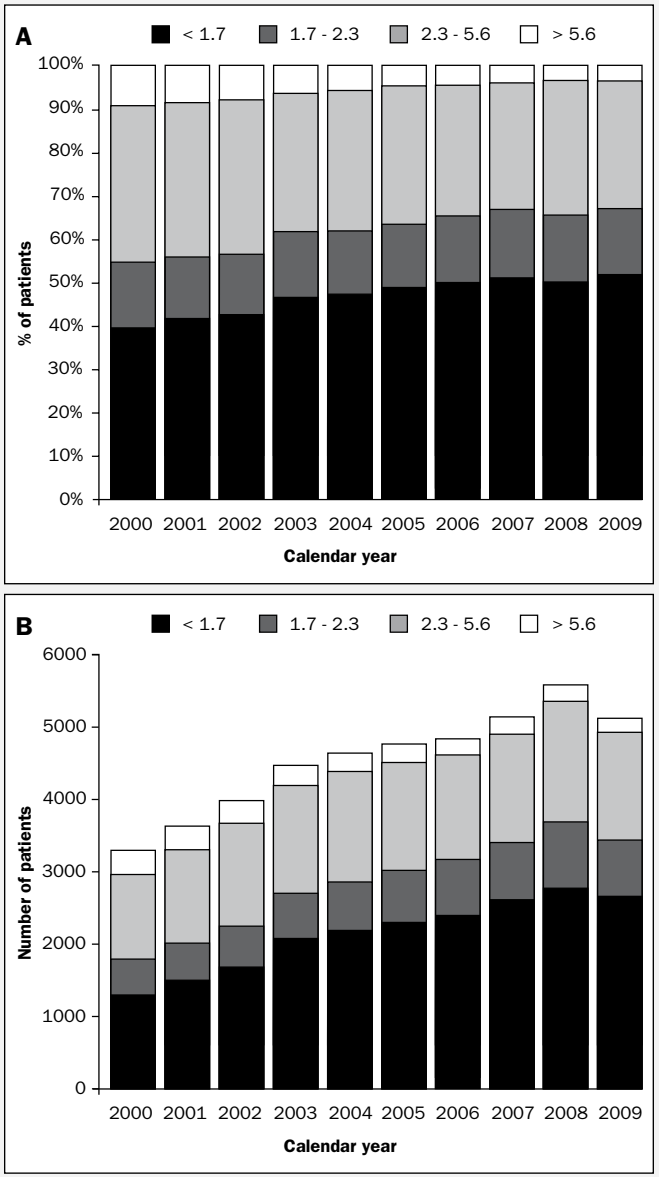


Figure 4.8: Last available triglyceride level in each calendar year after the start of cART. Plot A shows the percentage and Plot B the number of patients with triglyceride levels <1.7, 1.7-2.3, 2.3-5.6 and >5.6 mmol/l. For each patient the last available total cholesterol measurement after the start of cART between July and December of each year was selected. No information on fasting was recorded.

Figures 4.6-4.8 show that the proportion of patients with high total cholesterol and triglyceride levels has declined in later calendar years. Better management of patients at risk for dyslipidaemia, such as the substitution of drugs associated with increases in lipid levels for drugs with limited effect, more frequent monitoring of lipid levels, lifestyle alterations including smoking cessation, and a better understanding of pathways may explain the decreasing proportion over time. The proportion of patients with low-level HDL-cholesterol decreased to 16% in 2005 and then increased to 22% in 2009. The number of patients with hypercholesterolaemia declined slightly from 920 in 2001 to 770 in 2008. The number of patients with an HDL-cholesterol measurement available was nearly half that of patients with cholesterol or triglyceride levels. The number of patients with low levels of HDL-cholesterol increased from 380 in 2004 to 700 in 2008. The number of patients with hypertriglyceridaemia increased from 1575 in 2001 to 1850 in 2008.

Although in later calendar years we observed a smaller proportion of treated patients with hypercholesterolaemia or hypertriglyceridaemia, the increasing absolute number of patients with hypertriglyceridaemia or a low level of HDL-cholesterol, together with an aging HIV population, means that close monitoring of lipid levels in HIV-infected patients will remain an important issue in future management.

Conclusion

In summary, although CD4 cell counts at which cART is initiated have increased in the last few years, HIV testing rates will need to improve in order to achieve a timely start of cART (≥350 cells/mm^3) in the majority of patients.

Ensuring a quick suppression of plasma viral load and maintaining viral loads to <50 copies/ml is important because high-level or longer periods of low-level viraemia is associated with smaller increases in CD4 cell count, higher probability of virological failure and

development of drug resistance. In younger patients, measures to improve adherence might improve virological response to cART.

CD4 cell counts reached after 8 years of continuous virologically successful cART, started according to the current guidelines (before CD4 cell counts have dropped to below 350 cells/mm^3), approach the normal levels in uninfected individuals. A longer time on cART and higher CD4 cell counts, together with older age, were independently associated with a higher probability of decreasing CD4 cell counts with virologically successful cART. Ensuring a timely start of cART is therefore especially important for older patients.

The incidence of toxicity-driven therapy changes has nearly halved since the introduction of cART in 1996. Regimens that are easy to tolerate are especially important when cART is initiated at higher CD4 cell counts, when the patients have a lower perceived necessity of treatment. Monitoring of lipid levels in an aging population infected with HIV-1 will remain important in identifying those at higher risk of cardiovascular disease and other serious non-AIDS–defining diseases.

cART in children and adolescents

In Europe, paediatric PI-based cART was introduced in 1997, followed by non-nucleoside reverse transcriptase inhibitor (NNRTI)-based cART from 1999 to 2000. As with adults, cART has led to an increased survival of HIV-infected children, and today almost all of them are surviving to adulthood[150]. The primary objective of HIV treatment amongst children is to achieve viral suppression. However, minimizing potential negative effects of cART on the growth and development of children into adulthood is essential.

cART initiation

In the Stichting HIV Monitoring (SHM) database, 151 out of 216 children and 102 out of 165 adolescents initiated treatment between 1997 and 2010 during follow-up in one of the Dutch treatment centres. A PI-based cART regimen was initiated in the majority of children, whereas amongst adolescents, there was an equal distribution of PI-based and NNRTI-containing regimens (Table 4.6).

According to the guidelines of the new Paediatric European Network for the Treatment of AIDS (PENTA) [150], cART initiation is recommended as early as possible in all HIV-infected children aged less than 1 year. The reason to start as early as possible is substantiated by the recent finding that the risk of HIV disease progression and mortality is 4 times lower when cART is initiated when the patients are less than 3 months of age than when cART is started at a later age[151]. This means that successful treatment of HIV in young children depends on its timely diagnosis. In the Netherlands, cART is initiated very shortly after HIV diagnosis (median time, 0.5 months; interquartile range [IQR], 0.2-1.1) in children diagnosed with HIV before the age of 1 year (Table 4.6).

For children who are older than 1 year, cART is recommended for those who are symptomatic; for children without HIV-related symptoms, cART initiation is recommended when CD4 cell counts decline to values below age-related thresholds. According to the PENTA 2009 guidelines, these thresholds are below 1000 cells/mm^3 for children aged 1 to 3 years and 500 cells/mm^3 for children aged 3 to 5 years, whereas a threshold of 350 cells/mm^3 is recommended for children aged more than 5 years. In earlier years, cART was initiated too late for most of the children aged 1 to 2 years and 5 to 12 years. This late start is largely explained by the late entry into care for the children aged 1 to 2 years at the time of HIV diagnosis, when the median CD4 cell count

Table 4.6: Clinical characteristics of HIV-1-infected children (age 0-12 years at time of HIV diagnosis) and adolescents (age 13-17 years at time of HIV diagnosis) ever in follow-up up until 1 June 2010 in the SHM database.

	Children	Adolescents
Clinical characteristics at cART initiation		
cART use	151	102
NNRTI	40 (26%)	46 (45%)
PI	96 (64%)	44 (43%)
PI+NNRTI	4 (3%)	3 (3%)
Unknown/missing	11 (7%)	9 (9%)
Baseline CD4 cell counts (x10^6 cells/l) (median, IQR) according to age at baseline		
<12 months	1080 (381-1585)	
1-3 years	667 (225-1310)	
4-5 years	630 (420-1280)	
6-12 years	261 (72-390)	
>12 years		256 (155-395)
Median time in months (median, IQR) between diagnosis and baseline according to age at baseline		
<12 months	0.5 (0.2-1.1)	
1-3 years	3.7 (1.8-11.5)	
4-5 years	9.6 (3.7-21.6)	
6-12 years	16 (2.0-77.5)	
>12 years		8.4 (2.2-45.1)
Baseline Total Cholesterol (mmol/l) (median, IQR)	3.30 (2.87-3.70)	4.09 (3.30-4.51)
Baseline triglycerides (mmol/l) (median, IQR)	1.21 (0.94-1.96)	1.04 (0.70-1.33)
Clinical characteristics at 24 weeks after cART initiation		
CD4 cell counts (x10^6 cells/l) (median, IQR)		
≤2 years of age	1420 (800-2040)	
>2 years of age	530 (330-790)	390 (250-600)
Detectable HIV RNA levels	24 (16%)	22 (22%)
Total cholesterol (mmol/l) (median, IQR)	4.52 (3.68-5.26)	4.10 (3.40-4.90)
Triglycerides (mmol/l) (median, IQR)	1.04 (0.78-1.72)	0.94 (0.64-1.28)
At least 1 total cholesterol measurement >5.17 mmol/l	33 (22%)	19 (19%)
At least 1 triglycerides measurement> 1.69 mmol/l	36 (24%)	22 (22%)

Legend: cART=combination antiretroviral therapy; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; IQR=interquartile range; MTCT=mother to child transmission; baseline is date of cART initiation

at entry was already below the threshold of cART initiation (970; IQR 600-1940). In children aged 5 to 12 years, cART appeared to be initiated when CD4 cell counts were between 200 and 350 cells/mm^3, which was in accordance with the previous PENTA 2004 guidelines[152].

Virologic response

At the time of cART initiation, 75% of the children and 67% of the adolescents had a detectable viral load. These proportions decreased to 16% for children and 22% for adolescents after the initial 24 weeks on cART. Figure 4.9 presents the proportion of children and adolescents with an undetectable load after the start of cART. The highest proportion of children with an undetectable load was found in children aged 3 to 12 years, followed by the younger children (aged ≤2 years).

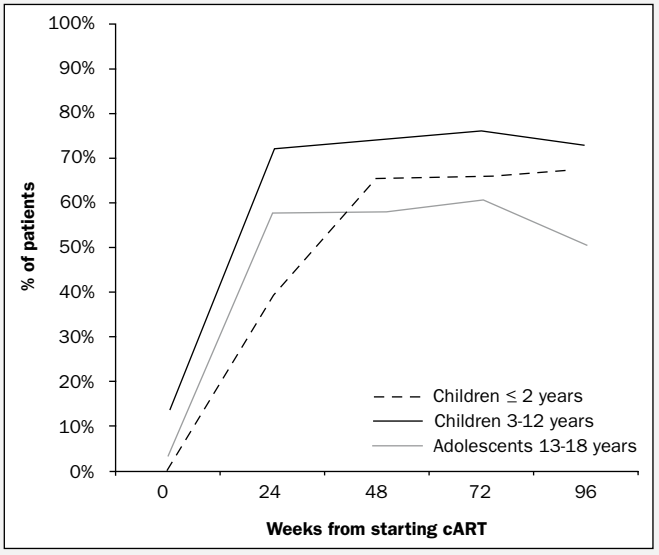


Figure 4.9: Percentage of undetectable HIV RNA levels after the start of cART in children aged ≤2 years, in those aged 3-12 years, and in adolescents aged 13-18 years at the time of HIV diagnosis.

The lowest proportion of undetectable loads was seen amongst the adolescents. Compared to the younger children, time from cART initiation to the first of two consecutive undetectable HIV RNA levels was significantly shorter for children aged 3-12 years (Table 4.7).

Table 4.7: Results from an adjusted Cox proportional hazard model of the time from the start of cART to the first of 2 consecutive plasma HIV RNA concentrations <50 copies/ml in 151 children and 102 adolescents who started cART between 1 January 1997 and 1 January 2010.

	Hazard ratio*	95% Confidence interval	p-value
According to age at time of HIV diagnosis			
Children ≤ 2 years of age	1		
Children 3-12 years of age	2.04	1.30-3.22	0.002
Adolescents 13-18 years of age	0.29	0.11-0.79	0.02

*Adjusted for gender, calendar year of HIV diagnosis, transmission risk group, region of origin, baseline log RNA levels and baseline CD4 cell counts

Older children starting cART were more likely to achieve an undetectable load than young children; this poorer virologic response in young children has been described previously[153]. On the other hand, adolescents showed a slower virologic response compared to young children. This slower response probably reflects the possibly less organised lifestyles of adolescents, which, in turn, may have an impact on adherence[154].

Immunologic response

CD4 cell counts were higher amongst the younger children and declined with their increasing age. Figure 4.10 shows the trajectory of CD4 cell counts after the initiation of cART amongst the younger (aged ≤ 2 years at the time of HIV diagnosis) and older (aged 3-12 years at the time of HIV diagnosis) children, and adolescents (aged 13-18 years at the time of HIV diagnosis).

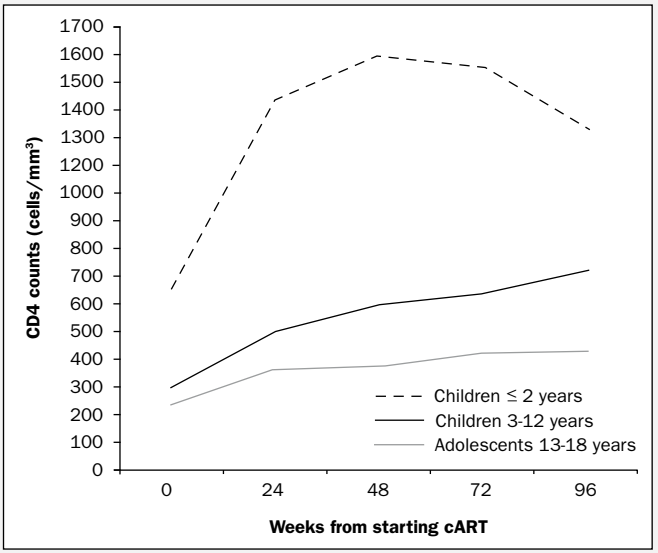


Figure 4.10: Median CD4 count after the start of cART in children aged ≤2 years (at the time of HIV diagnosis), children aged 3-12 years, and adolescents aged 13-18 years.

In all three groups, CD4 cell counts increased after the start of cART. This increase was steepest among the young children (aged ≤2 years). In this group the CD4 cell counts started to decrease after 72 weeks of cART. This decrease in CD4 cell counts is probably a reflection of the age-related variation in CD4 cell counts amongst children; Figure 4.11 shows the decline in CD4 cell counts during the first 10 years of life in HIV-uninfected children. In general, values of CD4 cell counts vary with age in HIV-infected children as well as in those who are not infected, especially in the first 5 years of life[155]. CD4 cell counts fall with increasing age and the slopes of this decease are steeper in the first 5 years of life, resulting in a natural CD4 cell count decline, even despite the use of cART (Figure 4.11). After 24 weeks of treatment with cART, the median CD4 cell count in those aged 2 years or less approaches the median reference CD4 cell counts of HIV-uninfected black children living in Europe (reference value: 1650 cells/mm^3 at age 2). This successful recovery of CD4 cell counts in the young children to

normal standards has not been achieved for the older children; for those aged 3-12 and 13-18, the CD4 cell counts at week 24 were close to the lowest percentile (5%) of age-related standards (this reference is 530 cells/mm^3 at age 7.5 years and 470 cells/mm^3 at 10 years)[155]. These findings support the results of an earlier study, which showed a benefit, with respect to CD4 cell count recovery, in initiating cART at a young age, as soon as possible after the HIV diagnosis[156].

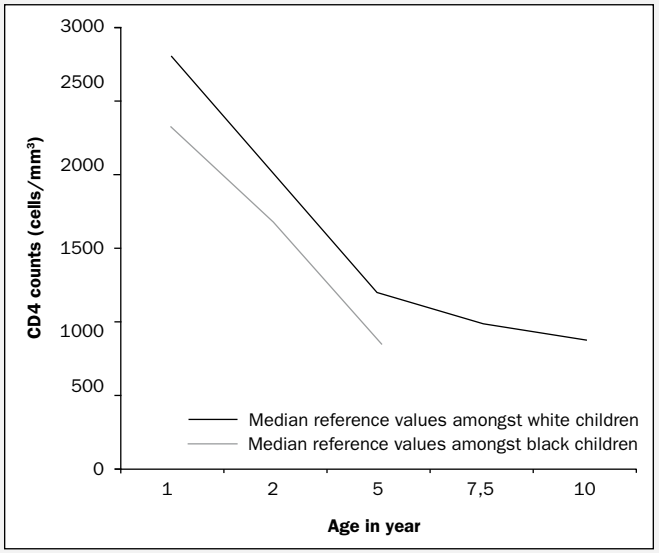


Figure 4.11: Median reference values for CD4 count cell counts for HIV-uninfected children according to age, data used in this figure is from the European Collaborative Study[155]

Dyslipidaemia

Several studies in adults not affected by HIV have demonstrated an association between high cholesterol levels during childhood and the development of cardiovascular disease later in life[154]. In adults and children PI-containing regimens have been associated with an increased risk of dyslipidaemia[157]. This side effect may put children at risk for cardiovascular disease in early adulthood.

At the time of cART initiation, total cholesterol levels of children and adolescents did not differ from the normal laboratory ranges for uninfected children in the same age groups (Table 4.8). However, 24 weeks after cART initiation, median total cholesterol levels of children aged 0-13 years increased from 3.2 mmol/l to 4.52 mmol/l. Hypercholesterolaemia (total cholesterol > 5.17 mmol/l) occurred in 22% of the children and 19% of the adolescents. Adolescents on PI-based and NNRTI-based regimens were more likely to have hypercholesterolaemia (Table 4.8).

Table 4.8: Odds of hypercholesterolaemia (HC) and hypertriglyceridaemia (HG) amongst children and adolescents treated with a PI-based regimen compared to an NNRTI-based regimen. HC was defined as a cholesterol level>200 mg/dl (>5.17 mmol/l) and HG as a triglycerides level >150 mg/dl (>1.69 mmol/l). The odds of HC and HG were estimated within a logistic regression model, using a generalised estimating equation (GEE) to adjust for correlations between lipid measurements within the same individual.

	Children		Adolescents	
	OR*	95% CI	OR*	95% CI
Hypercholesterolaemia				
NNRTI	1		1	
PI	1.53	0.70-3.38	2.94	0.88-9.97
PI+NNRTI	1.04	0.34-3.18	5.05	1.39-17.99
Hypertriglyceridaemia				
NNRTI	1		1	
PI	2.36	1.15-4.85	0.96	0.50-1.84
PI+NNRTI	5.93	1.75-19.98	1.84	0.71-4.80

*Adjusted for age at time of HIV diagnosis, gender, region of origin

Legend: NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor

Hypertriglyceridaemia was observed in 24% of the children and 22% of the adolescents. Children on a PI-based regimen were at least 2 times more likely to have a hypertriglyceridaemia (triglycerides, > 1.69 mmol/l) compared with children on an NNRTI-based regimen. Children who were using a regimen that contained both a PI and an NNRTI were 6 times more

likely to have a hypertriglyceridaemia (Table 4.8). The prevalence of cardiovascular disease is 3% for HIV-infected children treated with cART and 4% for HIV-infected adolescents who are receiving cART. A cardiovascular event developed in four children during follow-up. Three of these children were less than 6 years of age when they were diagnosed with a cardiovascular accident, and one patient who had been in follow-up since the age of 8 years and treated with cART from 1996 on was diagnosed with angina pectoris at 32 years of age. Amongst the patients who were diagnosed with HIV as adolescents, four were diagnosed with cardiovascular disease between the ages of 25 and 34 years. None of the deaths of children or adolescents were related to cardiovascular disease. This data shows that children on a PI regimen may be at higher risk of hypertriglyceridaemia compared to children on a NNRTI regimen. Measuring lipid levels at regular intervals, together with interventions such as lipid lowering diet or drugs and stimulating exercise may be of benefit in preventing cART-related dyslipidaemia in HIV-infected children.

Conclusion

The results of these analyses indicate that the immunologic and virologic responses to cART in HIV infected children are age dependent. Although young children have higher CD4 cell counts, the immune response and virologic response is stronger in older children, while the virologic response is less strong in adolescents, which probably reflects poor adherence. Children on a PI-based regiment have an increased risk of hypertriglyceridaemia; long-term exposure to hypertriglyceridaemia may put children at risk for developing cardiovascular disease at a later age.

5. Virologic failure and drug resistance

Ard van Sighem

By far the majority of patients treated with combination antiretroviral treatment (cART) achieve sustained suppression of HIV viral load. For a small group of patients, however, suppression was incomplete, which may be a marker of inadequate adherence to therapy and may herald the presence of drug resistance. In the Netherlands, incomplete suppression, or virologic failure, is observed in 8% to 10% of the treated patients annually, and 39% of the patients have one or more episode of failure. Resistance to lamivudine and emtricitabine and to non-nucleoside reverse transcriptase (RT) inhibitors is found in approximately 50% of patients experiencing virologic failure. Amongst patients previously treated with non-cART regimens, resistance to other nucleoside RT inhibitors and to protease inhibitors is found in a substantial proportion. Altogether, 9% of patients currently in follow-up are resistant to at least one antiretroviral drug, which is probably an underestimation, since a sequence is obtained in less than one third of patients with virologic failure. Evidence of transmission of resistant virus is found in less than 5% of newly diagnosed patients; this indicates that the number of infections originating from the reservoir of treated patients with resistance is limited and that new infections mainly occur from untreated infected individuals who may not yet be aware of their infection.

Het leeuwendeel van de patiënten die met combinatie-therapie (cART) behandeld worden, heeft langdurige onderdrukking van hun virale load. In een kleine groep patiënten is onderdrukking echter onvolledig wat een teken kan zijn van verminderde adherentie en ook op de aanwezigheid van resistentie kan duiden. In Nederland heeft jaarlijks 8% tot 10% van de behandelde patiënten onvolledige onderdrukking oftewel virologisch falen en 39% van de patiënten heeft een of meerdere perioden van falen. Bij ongeveer 50% van de patiënten met virologisch falen wordt resistentie tegen lamivudine en emtricitabine en tegen non-nucleoside RT-remmers gevonden. Alleen bij patiënten die eerder met niet-cART regimes behandeld zijn, heeft een aanzienlijk deel ook resistentie tegen andere nucleoside RT-remmers en tegen proteaseremmers. Van de patiënten die momenteel nog in zorg zijn, is 9% resistent tegen minstens een antiretroviraal middel. Waarschijnlijk is dit een onderschatting van het werkelijke percentage, omdat in minder dan een derde van patiënten met virologisch falen een resistentieprofiel bepaald is. Minder dan 5% van de recent met hiv gediagnosticeerden is besmet met een resistente virusvariant. Dit duidt erop dat het aantal infecties vanuit de populatie behandelde en resistente patiënten beperkt is en dat nieuwe infecties derhalve vooral plaatsvinden vanuit onbehandelde hiv-geïnfecteerden die zelf misschien nog niet van hun infectie op de hoogte zijn.

In HIV-infected patients, treatment with combination antiretroviral therapy generally results in sustained suppression of viral load to levels below the limit of quantification. However, when adherence to treatment is not optimal (for instance, because of toxic side effects of the treatment regimen), drug concentrations may be too low to halt the replication of HIV. In an environment of suboptimal concentrations, selected HIV virus strains may be resistant to one or more drugs in the treatment regimen. The presence of such resistant strains may limit future therapy options and diminish the patients' prognosis or, more generally, their quality of life.

Here, we report on the small group of patients who cannot keep viral load levels below the quantification limit, which is so-called virologic failure. Recently,

the Pursuing Later Treatment Options II (PLATO II) project team reported that virologic failure to all three available drug classes was found in almost 9% of patients after 9 years of treatment[158] Resistance to the prescribed treatment combination may have developed in some of the patients experiencing virologic failure, and we will look at the patterns of resistance present in this group. Since patients with resistant HIV may transmit their virus to hitherto uninfected individuals, we will also present data on the group of patients who are infected with resistant HIV.

Resistance during treatment

Incomplete suppression of viral load

Incomplete suppression of HIV viral replication usually betrays itself by quantifiable viral load levels. Nowadays, the most widely used assays have a quantification limit of 50 copies/ml, or less. However, rather than using 50 copies/ml as a fingerprint of incomplete suppression, we used 500 copies/ml as a threshold level. Many patients who otherwise have viral load levels consistently below 50 copies/ml occasionally have a single measurement above 50 copies/ml, but the clinical relevance of these so-called blips appears to be limited[113]. The occurrence of blips may be related partially to random assay variations or even to a recently introduced more sensitive viral load assay[108, 159]. By using a threshold of 500 copies/ml, we minimised the effect of blips and assay variation.

Virologic failure in treated patients

Accordingly, incomplete suppression of viral load, also referred to as virologic failure, was defined as at least two consecutive viral load measurements above 500 copies/ml or at least one measurement above 1000 copies/ml. This definition differs from the one used by PLATO II in that failure whilst on treatment is considered rather than virology failure involving individual drugs or drug classes. Of all patients starting cART in 1995 or later, 61% never experienced an episode of virologic failure, whereas 21% had one episode, 9% had two episodes, and 10% had three or more episodes. Almost one third (31%) of the episodes of virologic failure occurred when no treatment was used.

In the past few years, virologic failure has been observed annually in 8% to 10% of patients. In patients who had been pre-treated with mono- or dual therapy before switching to a cART regimen, virologic failure after start of cART was more common, but it decreased from 51% in 1998 to levels comparable with those in previously therapy-naive patients in recent years. In part, this decline is due to a healthy survivor effect in which those for whom treatment has failed are also the ones who die prematurely. In addition, in recent years new antiretroviral drugs have become available that are able to suppress viral load in patients who have experienced multiple episodes of virologic failure.

Scanning for drug resistance

To detect drug resistance, viral load levels need to be above a certain minimum threshold. Hence, drug resistance in treated patients can be assessed only in those who experience virologic failure. The prevalence of resistance in these patients was determined by scanning genotypic sequences of the reverse transcriptase (RT) and protease genes for specific major mutations known to be associated with resistance to the three original classes of drugs: nucleoside RT inhibitors (NRTIs), non-nucleoside RT (NNRTIs), and protease inhibitors (PIs)[160]. A genotypic resistance interpretation algorithm developed by Stanford University was used to infer a drug susceptibility score for each sequence according to a 5-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance and high-level resistance[161].

Genotypic sequences

Altogether, 3682 genotypic sequences were obtained from 2368 patients after they started cART. Although pre-treated patients comprised only 17% of the entire treated population, they were overrepresented in this sample, with 1496 (41%) sequences compared to 2186 (59%) sequences from the previously therapy-naive population. In 2570 (70%) sequences, at least one resistance-associated mutation was found, and 2375 (92%) of these sequences were obtained whilst the patients were undergoing treatment.

Resistance to NRTIs

The prevalence and the nature of resistance to antiretroviral drugs observed per calendar year changed over time and were conspicuously different between pre-treated and previously therapy-naive patients (Figure 5.1; Web Appendix Figures 5.1 and 5.2). In both groups, resistance to lamivudine and emtricitabine was frequently observed, but its prevalence declined over time in therapy-naive patients. Resistance to other NRTIs was below 20% in therapy-naive patients and approximately 60% in pre-treated patients. In the latter group, a modest decline was observed in resistance levels, which was chiefly due to a decrease in resistance to zidovudine and stavudine. A substantial degree of cross-resistance exists between these two drugs, such that resistance to one confers resistance to the other. Nowadays, the use of these drugs is not as common as it was in the early years of the cART era, which may explain the decline.

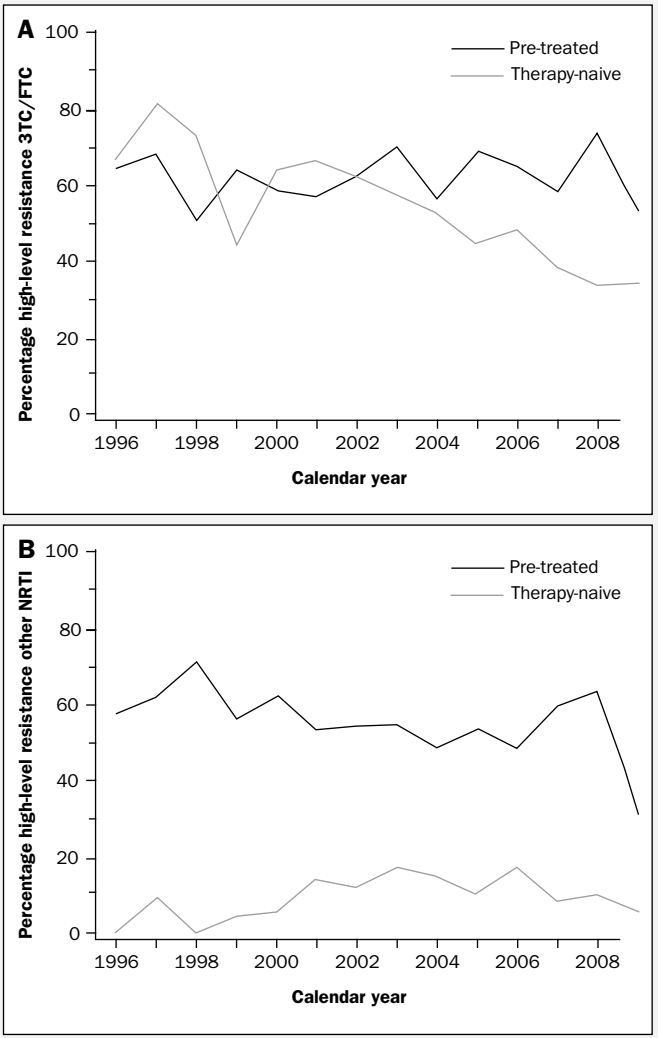
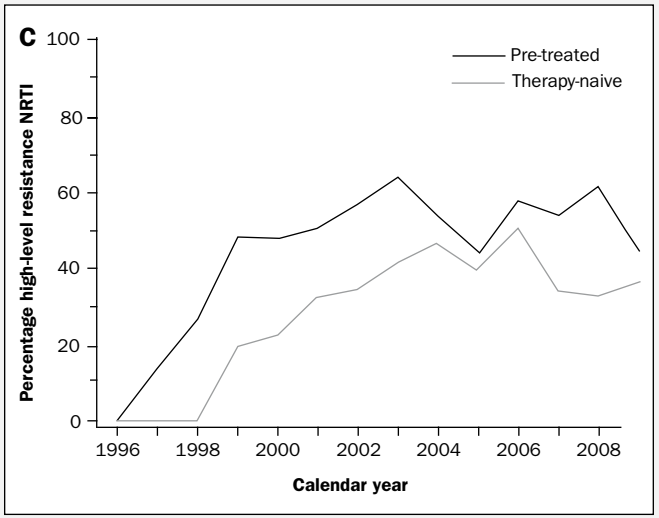
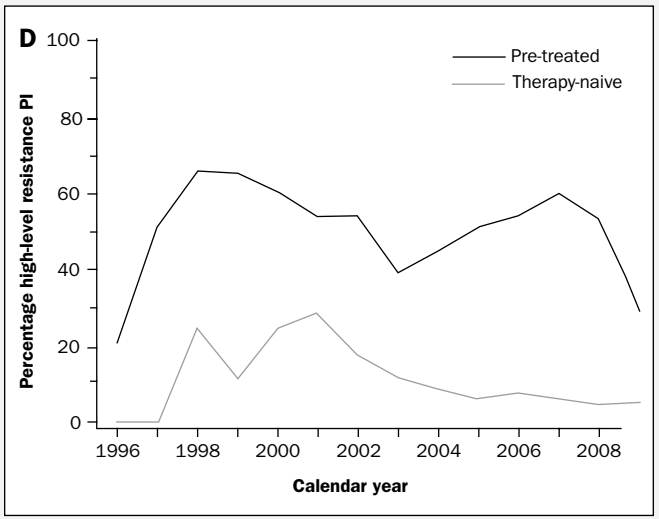


Figure 5.1: Annual percentage of sequences with high-level resistance according to the Stanford interpretation algorithm, in patients pre-treated with regimens considered not combination antiretroviral therapy (cART), and in previously therapy-naive patients who started a cART combination as their first treatment. (A) resistance to lamivudine (3TC) and emtricitabine (FTC), (B) resistance to other nucleoside reverse transcriptase (RT) inhibitors (NRTI), (C) resistance to non-nucleoside RT inhibitors (NNRTI), (D) resistance to protease inhibitors (PI).





Resistance to NNRTIs

Resistance to NNRTIs increased after the introduction of nevirapine and efavirenz as part of the cART regimens in the late 1990s. In recent years, the prevalence of resistance to these two drugs has been approximately 40% in previously therapy-naive patients and 50% in pre-treated patients. Also, there is a considerable amount of cross-resistance between the two drugs, although the prevalence of high-level resistance to efavirenz appears to be somewhat lower than to nevirapine. Since both drugs are frequently used in first-line treatment regimens, resistance to these drugs is expected to be common in patients who experience virologic failure.

Resistance to PIs

Protease inhibitors were introduced in the mid-1990s, and thereafter resistance to this drug class rapidly increased. Resistance levels were between 40% and 60% in pre-treated patients, whereas in recent years less than 10% of therapy-naive patients have had resistance to PIs. In pre-treated patients, the prevalence of resistance was highest for the older generation of inhibitors, including nelfinavir, saquinavir and indinavir.

Overall prevalence of resistance

As of June 2010, a total of 13,035 HIV-infected adults were still in active follow-up. Resistance-associated mutations were found in 1582, or 12%, of these patients, and three-quarters of them (9%, or 1166 patients, which included 514 who had been treated earlier with non-cART regimens) had high-level resistance to at least one antiretroviral drug. These numbers most likely underestimate the true prevalence of resistance, because resistance tests were performed in less than 30% of patients with virologic failure. In addition, in other European countries, the prevalence of resistance in the HIV-infected population is much higher. For example, in Switzerland, approximately 40% of the antiretroviral therapy-exposed population were found to have resistance mutations[162].

Of the 1582 patients with evidence of resistance, 60% of patients had resistance to lamivudine and emtricitabine, whilst 29% had resistance to at least one other NRTI. Resistance to at least one PI was found in 21% and to at least one NNRTI in 49%. High-level resistance to drugs from one class was observed in 36% of patients,

resistance to two classes in 34%, and resistance to all three drug classes in 11%. Web Appendix Table 5.1 shows the inferred resistance level for each antiretroviral drug.

Transmission of drug-resistant virus

Testing for pre-cART resistance

Since infection with a resistant HIV strain may limit future therapy options, current treatment guidelines recommend obtaining a genotypic sequence of the reverse transcriptase (RT) and protease gene at the time of HIV diagnosis. This recommendation has been in use in routine clinical care since its implementation in 2003. In total, 3113 patients diagnosed in 2003 or later had a genotypic sequence within one year after diagnosis but before the start of treatment, which is 40% of the total of 7713 patients diagnosed with HIV during the same period.

Recent infections and new diagnoses

Altogether, 955 (31%) of the 3113 patients were recently infected, whereas the remaining 2158 patients were classified as newly diagnosed. These two groups differed somewhat in demographic characteristics. Dutch homosexual men represented 71% of the recently infected patients, but only 42% of the newly diagnosed group, whilst sub-Saharan Africans comprised 18% of the newly diagnosed patients, but only 3% of those with recent infections.

Transmitted drug resistance

Major resistance-associated mutations were found in 271 patients, or 8.7%, but only 123 (4.0%) had intermediate or high-level resistance to at least one antiretroviral drug, according to the Stanford interpretation algorithm (Table 5.1)[160, 161]. In the majority of patients with mutations associated with resistance to NNRTIs, resistance levels to these drugs were interpreted as high. However, only about one third of patients harbouring mutations associated with resistance to PIs or NRTIs actually had resistance to one or more drugs from these two classes. Altogether, 108 patients had intermediate or high-level resistance to drugs from one class, 8 patients to two classes, and 7 patients to all three classes.

Table 5.1: Number of patients with mutations associated with resistance to protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), or non-nucleoside RT inhibitors (NNRTI) and the number of patients with intermediate or high-level resistance, according to the Stanford genotypic interpretation algorithm[161]. Only patients diagnosed in 2003 or later were considered.

	Recent infection, N=955		New diagnoses, N=2158		All diagnoses, N=3113	
	N	%	N	%	N	%
RAMS						
Overall	87	9.1	184	8.5	271	8.7
PI	30	3.1	34	1.6	64	2.1
NRTI	52	5.4	125	5.8	177	5.7
NNRTI	12	1.3	47	2.2	59	1.9
Intermediate or high-level resistance						
Overall	33	3.5	90	4.2	123	4.0
PI	7	0.7	16	0.7	23	0.7
NRTI	19	2.0	45	2.1	64	2.1
NNRTI	12	1.3	46	2.1	58	1.9

Legend: Recent infections=patients diagnosed during the acute phase of the HIV infection or tested positive for HIV less than 1.5 years after their last negative test; New diagnoses=patients with diagnosed HIV infection not classified as recent; RAMS=resistance-associated mutations.

Mutations but no resistance

No differences in the prevalence of resistance-associated mutations or in interpreted resistance levels were observed between patients with recent infections and newly diagnosed patients, except that a higher proportion of patients with recent infections had resistance mutations in protease. A closer look at the 41 patients who had protease mutations but did not have high-level resistance to protease inhibitors revealed

that all of them had only one mutation in protease, including 25 with an M46L mutation and 9 with an L33F mutation. Eighteen patients with an M46L mutation (and also a V118I mutation in RT) appeared to form a cluster involving possibly related transmission events (Figure 5.2).

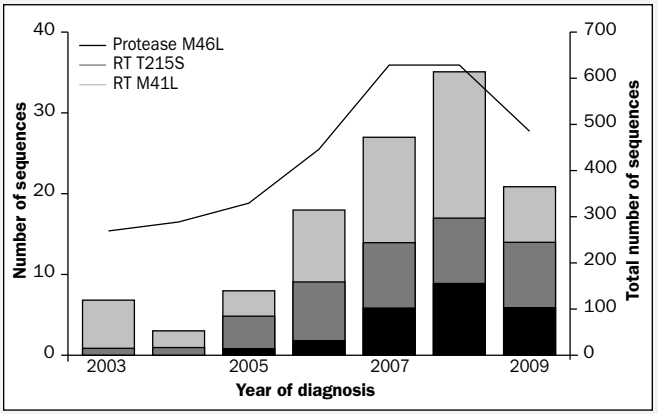


Figure 5.2: Annual number of patients with a pre-treatment genotypic sequence within 1 year after HIV diagnosis who had either M46L as the only mutation in protease or T215S or M41L as the only mutation in reverse transcriptase (RT). The solid line shows the total number of patients with a genotypic sequence.

Likewise, all patients with mutations in RT but no inferred resistance to NRTIs had only a single mutation in RT. In total, 59 patients had an M41L mutation, which is associated with resistance to zidovudine and stavudine, and 37 had a T215S (Figure 5.2). Virus strains with revertant mutations, such as 215S or 215D, had the same replicative capacity as wild-type virus with 215T and reportedly established themselves as subepidemics[11, 163]. Also, M41L in isolation does not lead to a marked deficit in fitness compared to the wild-type variant[164].

Conclusion

A substantial proportion of patients receiving antiretroviral therapy experience virologic failure and have high-level resistance to one or more antiretroviral drugs. However, almost half of the patients with evidence of resistance are those who have been treated with non-cART regimens. In the group of patients who have been treated with only cART combinations, the overall risk of resistance is considerably lower. In recent years, resistant strains have been transmitted in less than 5% of patients with new diagnoses. This observation could be interpreted as good news, that is, the reservoir of resistant patients in clinical care who do not achieve viral suppression is limited, and they almost never infect new individuals. Conversely, it could mean that new HIV infections are primarily caused by infected individuals who are not yet treated or who are even not yet aware of their infection[8].

6. Co-infections: Hepatitis B, Hepatitis C and sexually transmitted infections

Colette Smit

Hepatitis B and C co-infection

Hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are highly prevalent amongst HIV-infected individuals. Irrespective of co-infection with HIV, HBV and HCV are associated with progression to liver-related disease. Here we report on the prevalence and risk factors of HBV and HCV co-infection amongst registered HIV-infected patients, as well as the impact of these co-infections on the risk of dying.

Amongst the patients screened for co-infection, the prevalence was 7% for HBV, 11% for HCV and 1% for triple infection. HBV co-infection was associated with younger age and being male, and HCV co-infection was associated with injecting drug use (IDU) and being of a European origin other than Dutch. However, amongst homosexual men the prevalence of HCV significantly increased over time, making homosexual men the largest group of patients co-infected with HCV. This increase is likely to have been caused by sexual transmission. After adjustment for demographic and clinical differences, the risk of dying in the co-infected population was no longer higher than in the population of patients infected solely with HIV; this could be a result of the success of treatment of HBV and HCV co-infections in delaying the progression of liver-related disease and death.

Sexually transmitted diseases

Sexually transmitted infections (STIs) are relatively frequent amongst HIV-infected individuals and especially amongst young adults and homosexual men. In 2008, we started the prospective collection of data regarding STIs such as chlamydia, lymphogranuloma venereum (LGV), gonorrhoea and syphilis. These data confirm that STIs frequently occur in the HIV-infected population. A remarkable number of patients (n=46) were diagnosed with neurosyphilis between 2000 and 2010. However, these high rates cannot be generalized to the total HIV-infected population, since most patients were screened because they presented with symptoms. Further studies are needed to study the impact of STIs on HIV disease progression and the HIV epidemic and the development of neurosyphillis among HIV-infected individuals.

Hepatitis B en C co-infectie

Hepatitis B (HBV) en C (HCV) zijn frequent voorkomende co-infecties bij HIV patiënten. Ongeacht co-infectie met HIV, zijn HBV en HCV geassocieerd met het ontstaan van lever gerelateerde aandoeningen. Onder de bij SHM geregistreerde HIV-geïnfecteerde patiënten zijn de prevalentie en risicofactoren voor HBV en HCV co-infectie onderzocht, daarnaast is ook gekeken naar het effect van HBV en HCV co-infectie op de sterfte kans bij HIV patiënten.

Van de HIV-geïnfecteerde personen die gescreend zijn voor de aanwezigheid van co-infecties, bleek 7% geïnfecteerd met HBV, 11% met HCV en 1% van de HIV geïnfecteerde personen was geïnfecteerd met zowel HBV als HCV. HBV co-infectie was geassocieerd met mannelijk geslacht en jongere leeftijd en HCV met injecterend drugsgebruik en afkomstig zijn uit een Europees land anders dan Nederland. Onder homoseksuele mannen is de HCV prevalentie significant toegenomen sinds 2000 en op dit moment zijn homoseksuele mannen de grootste groep HIV patiënten met een HCV co-infectie. Deze toename lijkt vooral veroorzaakt door seksuele transmissie van HCV. Na correctie voor verschillen in demografische en

klinische factoren, hebben patiënten met een co-infectie geen significant hogere sterfte kans vergeleken met patiënten die alleen met HIV zijn geïnfecteerd. Dit is mogelijk het gevolg van een succesvolle behandeling van HBV en HCV, waardoor de progressie van lever-gerelateerde ziekte wordt vertraagd.

Seksueel overdraagbare aandoeningen

Seksueel overdraagbare aandoeningen (SOA's) komen veel voor in de met HIV geïnfecteerde populatie, vooral bij jong volwassenen en homoseksuele mannen. In 2008 is de SHM gestart met de verzameling van gegevens over SOA's, waaronder Chlamydia, Lymphogranuloma venereum, gonorroe en syfilis. Deze data bevestigen de hoge prevalentie van SOA's in de HIV-geïnfecteerde populatie in zorg. Meer dan een helft van de patiënten met een positieve syfilis testuitslag hadden een actieve syfilis infectie. Opmerkelijk is het aantal van 46 patiënten met neurosyfilis dat tussen 2000 en 2010 werd gediagnosticeerd. De gevonden SOA cijfers kunnen niet zonder meer worden vertaald naar de totale populatie HIV geïnfecteerde patiënten, omdat de meeste patiënten gescreend zijn voor SOA's op basis van symptomen. Vervolg onderzoek is nodig om het effect van co-infectie met SOA's op het HIV ziekte progressie, de HIV epidemie, maar ook om de ontwikkeling van neurosyfilis in kaart te brengen.

Hepatitis B and C co-infection

As a result of shared routes of transmission, hepatitis B (HBV) and hepatitis C (HCV) infections are highly prevalent amongst HIV-infected individuals[165, 166]. HBV is a common infection amongst injecting drug users and homosexual men. HCV is mostly transmitted by injecting drug use or through blood or blood contact. Since 2000, HCV infections amongst HIV-infected men who have sex with men (MSM) who did not report injecting drug use have been observed in Western countries[167]. These infections were not likely to be caused by blood contact, suggesting that acquisition of HCV infection amongst MSM is predominantly through sexual contact.

Irrespective of co-infection with HIV, HBV and HCV infections are associated with liver fibrosis, cirrhosis and hepatocellular carcinoma[168, 169]. However, HIV infection alters the natural history of HBV and progression of HBV-related liver disease is accelerated by the presence of HIV. The impact of HBV on the progression of HIV is still unclear[170, 171]. Also, liver fibrosis and cirrhosis develop more rapidly in patients co-infected with HIV and HCV than they develop in HCV mono-infected patients [33]. However, the impact of HCV co-infection on HIV disease progression is contradictory[172, 173].

Here we report on trends in the prevalence of HBV and HCV infection and the impact of HBV and HCV co-infection on the risk of dying among HIV-infected patients in the Netherlands.

Definition of HBV and HCV

HBV was defined by a positive result either on a hepatitis B surface antigen (HBsAg) test (EIA, Axsym) or on an HBV DNA test. HCV co-infection was defined by a positive result on a qualitative or quantitative RNA test. We assumed that patients with a positive HCV antibody (EIA, Axsym) but without an available HCV RNA test were also co-infected with HCV (n=441). However, patients with a positive result on an HCV antibody test and a negative result on an HCV RNA test were classified as HCV-negative, since a HCV co-infection could not be confirmed (n=223).

Prevalence

In total, out of 16,451 HIV-infected patients aged 18 years or older at the time of HIV diagnosis, 15,734 (96%) were tested for HBV or HCV co-infection. The proportion of patients screened for co-infection increased from 64%

Table 6.1: Demographic characteristics of HIV-infected patients with a hepatitis B virus (HBV) and/or C (HCV) co-infection.

	Total screened	HIV only	HBV	HCV	HBV & HCV
	N (%)	N (%)	N (%)	N (%)	N (%)
Total	15734 (96%)	12842 (82%)	1030(7%)	1686 (11%)	176 (1%)
Gender					
Male	12564 (80)	10174 (79)	883 (86)	1357 (80)	150 (85)
Female	3170 (20)	2668 (21)	147 (14)	329 (20)	26 (15)
Transmission					
MSM	9014 (57)	7599 (59)	633 (61)	711 (42)	71 (40)
Heterosexual	4951 (31)	4384 (34)	315 (31)	232 (14)	20 (11)
IDU	640 (4)	50 (0.4)	8 (1)	518 (31)	64 (36)
Blood (products)	186 (1)	129 (1)	6 (1)	49 (3)	2 (1)
Other/unknown	943 (6)	680 (5)	68 (7)	176 (10)	19 (11)
Age category (years)					
18-24	1696 (11)	1347 (10)	118 (11)	203 (12)	28 (16)
25-34	5758 (37)	4597 (36)	413 (40)	672 (40)	76 (43)
35-44	5096 (32)	4134 (32)	332 (32)	580 (34)	50 (28)
45-54	2261 (14)	1938 (15)	122 (12)	183 (11)	18 (10)
55-64	766 (5)	677 (5)	43 (4)	42 (2)	4 (2)
≥65	157 (1)	149 (1)	2 (0.2)	6 (0.4)	0
Region of origin					
The Netherlands	8985 (57)	7326 (57)	508 (49)	1032 (61)	119 (68)
Sub-Saharan Africa	2470 (16)	2105 (16)	244 (24)	107 (6)	14 (8)
Europe, except the Netherlands	1423 (9)	1013 (8)	89 (9)	300 (18)	21 (12)
Latin America	1173 (7)	1002 (8)	71 (7)	95 (6)	5 (3)
Caribbean	584 (4)	518 (4)	31 (3)	27 (2)	8 (5)
Other	1099 (6)	878 (7)	87 (8)	125 (7)	9 (5)
Calendar year of HIV diagnosis					
<2000	5803 (37)	4312 (34)	472 (46)	909 (54)	110 (63)
2000-2004	4538 (29)	3803 (30)	292 (28)	408 (24)	35 (20)
2005-2010	5393 (34)	4727 (37)	266 (26)	369 (22)	31 (18)
Calendar year of hepatitis screening					
<2000	3037 (19)	1975 (15)	354 (34)	498 (30)	87 (49)
2000-2004	3187 (20)	3056 (24)	328 (32)	403 (24)	49 (28)
2005-2010	9510 (60)	7811 (61)	49 (5)	785 (47)	40 (23)
Liver events	430 (3)	80 (1)	92 (9	221 (13)	34 (19)
Deaths	1361 (9)	948 (7)	112 (11)	259 (15)	42 (24)
cART use	13083 (83)	10526 (82)	914 (89)	1489 (88)	154 (88)

Legend: MSM=men who have sex with men; IDU=injecting drug user; cART= combination antiretroviral therapy

in 2006 to 96% in 2010. Amongst the patients screened for HBV or HCV co-infection, 1030 (7%) had a positive HBsAG test result. Amongst patients tested for the presence of HCV RNA or HCV antibodies, 1686 (11%) had a positive result. The prevalence of a triple infection (HIV, HBV and HCV) was 1%. Demographic characteristics of the co-infected population are shown in Table 6.1.

Risk factors for HBV

The risk factors for HBV and HCV co-infection were determined with the logistic regression model in Table 6.2. In the multivariate model, HBV co-infection was associated with younger age and being male. Patients who were diagnosed with HIV before 2000 had a significantly higher risk of HBV co-infection. Furthermore, injecting drug users had a higher risk of HBV co-infection, compared to that of homosexual men. Patients with a HBV co-infection more often received a cART regimen, which probably included HBV treatment.

Risk factors for HCV

Factors associated with HCV co-infection in the multivariate analyses were the HIV transmission group, age of HIV diagnosis, region of origin and cART use (Table 6.2). Compared to homosexual men, patients who became infected with HIV through heterosexual contact had a significantly lower risk of HCV co-infection, whereas amongst injecting drug users and receivers of blood and blood products the risk of HCV co-infection was significantly higher compared to homosexual men. After adjustment for age, gender, transmission group and region of origin, calendar year of HIV diagnosis was no longer associated with HCV co-infection.

Table 6.2: Risk factors for HBV and HCV co-infection amongst HIV-infected patients in the Netherlands: Results from the univariate and multivariate logistic regression models.

	HBV		HCV	
	Multivariate	**p-value**	**Multivariate**	**p-value**
Gender				
Male	1.97 (1.60-2.43)	<0.001	0.92 (0.75 -1.12)	0.40
Female	1		1	
Transmission				
MSM	1	0.01	1	<0.0001
Heterosexual	0.80 (0.65–0.97)		0.71 (0.59-0.87)	
IDU	1.21 (0.91-1.59)		97.9 (70.52-136.0)	
Blood (products)	0.42 (0.20-0.88)		4.31 (3.02-6.16)	
Other/unknown	1.06 (0.82-1.36)		3.05 (2.53-3.70)	
Age category (years)				
18-24	1	<0.0001	1	<0.0001
25-34	0.90 (0.73-1.09)		0.95 (0.78-1.16)	
35-44	0.76 (0.62-0.94)		0.90 (0.73-1.10)	
45-54	0.63 (0.49-0.81)		0.61 (0.48-0.78)	
55-64	0.71 (0.50-0.81)		0.49 (0.34-0.70)	
≥ 65	0.15 (0.04-0.61)		0.27 (0.12-0.63)	
Region of origin				
The Netherlands	1	<0.0001	1	<0.0001
Sub-Saharan Africa	0.58 (0.09-41.2)		0.46 (0.36-0.58)	
Europe, except the Netherlands	1.11 (0.73-1.09)		1.48 (1.24-1.77)	
Latin America	1.08 (0.84-1.40)		0.72 (0.56-0.92)	
Caribbean	1.22 (0.86-1.73)		0.47 (0.32-0.70)	
Other	1.35 (0.98-1.85)		0.90 (0.68-1.21)	
Calendar year of HIV diagnosis				
<2000	1	<0.0001	1	0.61
2000-2004	0.69 (0.59-0.80)		1.02 (0.86-1.21)	
2005-2010	0.58 (0.50-0.68)		0.94 (0.78-1.12)	
cART use	1.41 (1.16-1.72)	0.0006	1.40 (1.18-1.67)	0.0001

Legend: HBV=hepatitis B virus; HCV=hepatitis C virus; MSM=men who have sex with men; IDU=injecting drug user; cART=combination antiretroviral therapy

Increase in HCV prevalence amongst homosexual men

In total, 9014 homosexual men were screened for the presence of HBV and HCV co-infection. In total, 711 men tested positive for HCV co-infection. The percentage of homosexual men who tested positive varied over calendar time (Figure 6.1).

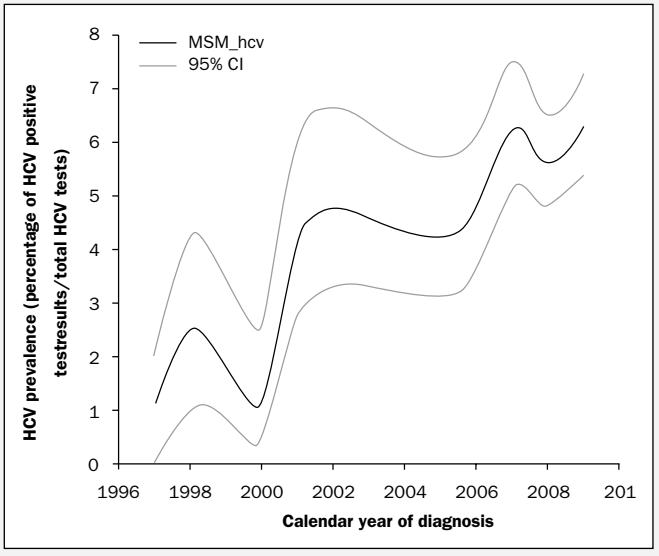


Figure 6.1: The prevalence over time of hepatitis C virus (HCV) infection amongst HIV-infected homosexual men who were screened for HCV co-infection.
Legend: MSM=men who have sex with men; CI=confidence interval

Before calendar year 2000, the prevalence of HCV co-infection among homosexual men who were screened for co-infections varied between 1.1% (95% confidence interval [CI] 0.04-2.0) and 2.5% (95% CI 1.1-4.3). Between 2000 and 2002, the HCV prevalence increased to 4.8% (95% CI 3.3-6.7). However, the HCV prevalence stabilized between 2002 and 2006, ranging between 4.2% and 4.8%. After reaching this plateau, the HCV prevalence started to increase again and rose as high as 6.3% (95% CI 5.4-7.3) in 2009. Between 2007 and 2009, the prevalence of HCV amongst homosexual men was significantly higher compared to that before

2000, making homosexual men the largest group of HCV co-infected patients amongst the HIV-infected population in the Netherlands.

HCV was genotyped in 275 homosexual men co-infected with HCV. Genotype 1 was most common and accounted for 63% of all the available genotypes amongst homosexual men, whereas genotype 4 was found in 25% of the patients. Figure 6.2 shows the HCV genotype distribution among homosexual men before and after 2004. The prevalence of HCV genotype 1 increased over time, whilst the proportion of HCV genotype 3 became smaller. Although the distribution of HCV genotypes changed over time, HCV genotype 1 and 4 remained the most common genotypes.

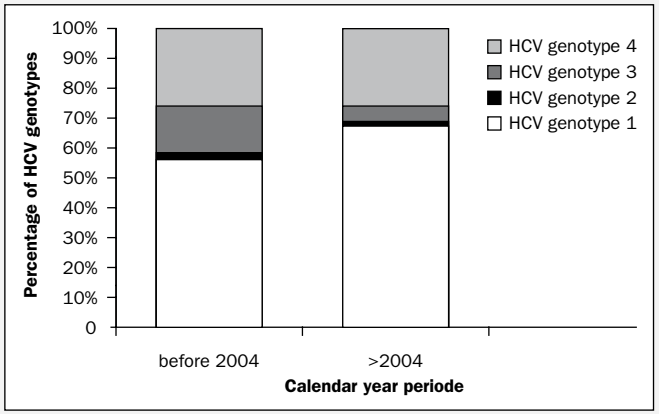


Figure 6.2: Hepatitis C virus (HCV) genotype distribution over time amongst HIV-infected homosexual men.

A substantial number of studies in Western countries report an increase in the number of sexual transmissions of HCV among HIV-infected homosexual men[167, 174, 175]. These reports have suggested that the increase in sexual transmission of HCV over time is occurring only in HIV-infected homosexual men, not in those uninfected with HIV. We do not have information on the history of injecting drug use among the HIV-infected homosexual men monitored by Stichting HIV Monitoring (SHM). However, an earlier study of an HCV outbreak among HIV-infected homosexual men in Amsterdam showed that injecting drug use is not likely to be the route of HCV transmission, because 90% of the HCV co-infected men did not report injecting drug use[176]. In addition, the Swiss cohort study showed that HCV was associated with high-risk sexual behaviour[175]. Furthermore, 42% of the patients co-infected with HCV and HIV shed HCV RNA in their semen[177], which would be consistent with sexual transmission. Although the rectal mucosa is unlikely to be susceptible to HCV, ulcerative STIs might facilitate sexual transmission[178]. Hence, the substantial number of HIV-infected homosexual men in the Netherlands who we reported to have an STI could contribute to the increasing HCV prevalence, and this suggests a potential role of STIs in the sexual transmission of HCV. However, since the increase in STIs also indicates unprotected sex and sexual risk-taking behaviour, the increasing prevalence of HCV may be associated solely with such behaviour.

Impact of HBV and HCV co-infection on the risk of death

HIV is known to accelerate the clinical progression of liver disease in HBV and HCV co-infected patients, and liver disease is an important cause of death in co-infected patients (Chapter 3). In the SHM database, all-cause mortality was 9% in the total HIV-infected population. The proportion of deaths was 11% in patients co-infected with HBV, 15% in the patients co-infected with HCV, and 24% in the patients with triple infection. Hazard ratios for time to death are summarized in Table 6.3. In the unadjusted analyses, HBV, HCV and triple co-infection were associated with a faster progression to death. However, after adjustment for differences in demographic and clinical characteristics, time to death did not differ significantly between co-infected and non-co-infected patients.

Several studies have reported an increased risk of dying in the HIV population co-infected with hepatitis, mainly

in the IDU population[34, 179]. However, the impact of co-infection on the risk of dying remains controversial, as other observers did not find an increased risk[180]. We did not find an increased risk of dying when the analyses were adjusted for differences in demographic and clinical characteristics, including HIV transmission route. Recently, much attention has been given to the increase in HCV co-infections in HIV-infected homosexual men. Most of the HCV infections in homosexual men are recently acquired infections in which progression to liver fibrosis had not yet occurred. Also, the majority of the newly diagnosed HCV co-infections were in homosexual men who were well treated for their HIV infection. This may have resulted in a greater chance of HCV clearing in homosexual men than in injecting drug users. Since clearance is associated with higher CD4 cell counts[176], successful treatment of HIV may have an impact on the clearance of HCV and add to successful treatment of HBV and HCV in limiting disease progression.

Table 6.3: Risk of dying amongst HIV-infected patients with hepatitis co-infection treated with combination antiretroviral therapy (cART) compared to patients who are infected with HIV only. To evaluate the impact of hepatitis B virus (HBV) and hepatitis C virus (HCV) co-infection on the risk of dying, time to death was estimated by a Cox proportional hazard model. Follow-up time was from the date of the initiation of cART until the date of last contact, most recent visit, death or 1 June 2010.

	Crude hazard ratio (95% CI)	p-value	Adjusted* hazard ratio (95% CI)	p-value
HIV	1	<0.0001	1	0.12
HIV/HBV	1.26 (1.02-1.54)		1.27 (0.98-1.65)	
HIV/HCV	1.76 (1.52-2.04)		0.90 (0.69-1.18)	
HIV/HBV/HCV	2.24 (1.57-3.18)		1.30 (0.81-2.08)	

Legend: CI=confidence interval

* adjusted for age, gender, region of origin, transmission risk group, calendar year of HIV diagnosis, calendar year of co-infection screening, baseline CD4 and HIV RNA levels.

Treatment

In patients co-infected with HBV, long-term use of nucleoside reverse transcriptase inhibitor (NRTI) backbones, such as tenofovir and emtricitabine or tenofovir and lamivudine[181], is recommended to improve the control of HBV by delaying the progression to liver disease. The low risk of dying among HBV co-infected patients found in those monitored by SHM probably reflects the positive effects of HBV treatment in this group. HBV co-infected patients were more likely to be treated with cART compared to the non-HBV co-infected population, and 61% of the HBV co-infected patients in the Netherlands received an NRTI backbone in their cART regimen that helps to control HBV infection. The median duration of HBV treatment amongst HBV co-infected patients is 20 months (interquartile ratio [IQR], 8-48) and the median time between HBV diagnosis and HBV treatment initiation is 23 months (IQR, 1-73).

The standard treatment for HCV is a combination of pegylated interferon (PEG-IFN) and ribavirine (RBV)[182]. Amongst the HCV co-infected population, 405 (24%) were treated with a combination of PEG-IFN and RBV. The median duration of HCV treatment was 36 weeks (IQR, 22-48). Amongst the patients currently in follow-up, 102 HCV co-infected patients were still being treated for their HCV infection as of 1 January 2010. The success of HCV treatment is determined by the HCV genotypes. Genotypes 1 and 4[183], which are the most frequent genotypes among the HIV-infected population, are hard to treat. Amongst the HCV co-infected patients with a known HCV genotype, 44% of the patients with genotype 1 and 42% of the patients with genotype 4 were treated with a combination of PEG-IFN and RBV.

The timing of the initiation of HCV treatment is associated with the success of the therapy[184]. Higher rates of sustained virologic response are achieved in

patients who initiated treatment in the acute phase of the HCV infection than in those who started treatment during the chronic phase[185]. Overall, the median time between the first positive test result for HCV and the start of treatment was 1.3 years (IQR, 0.3-5.3). However, amongst the HCV co-infected patients diagnosed with HCV after 1 January 2006, HCV treatment was initiated shortly after diagnosis. For this group, the median time between diagnosis and HCV treatment initiation was 4 months (IQR, 2-9).

Conclusion

Since 2000, most of the new HCV diagnoses in HIV-infected patients in the Netherlands have been in homosexual men. Homosexual men are now the largest group of HCV and HIV co-infected patients in the Dutch population. The increase in new HCV diagnoses in this group is most likely caused by sexual transmission. Recent studies suggest that sexual transmission is a result of high-risk sexual behaviour and that HCV transmission in HIV-infected homosexual men is not related to injecting drugs. The homosexual men who are newly diagnosed with HCV are predominantly infected by genotypes 1 and 4. Although these genotypes are difficult to treat, almost half of the patients infected with these genotypes are treated for HCV co-infection. Currently, we do not have enough clinical data available to evaluate the rates of sustained virologic responses of HCV treatment. Also, more than half of the HBV co-infected patients are treated with a cART regimen that includes a HBV-controlling NRTI backbone. Patients co-infected with HBV and HCV do not have a greater risk of dying compared to patients infected only with HIV; this suggests that the treatment of HBV and HCV co-infection may be successful in delaying the progression of liver-related disease. Larger observational studies are needed to further evaluate the impact of HBV and HCV treatment in the decrease of all-cause and liver-related mortality on the population level.

Sexually transmitted infections

Sexually transmitted infections (STIs) are relatively frequent amongst HIV-infected individuals (REF) and especially amongst young adults and homosexual men (REF). STIs are considered to be a marker for high-risk sexual behaviour in specific populations. Therefore, by monitoring trends in the occurrence of STIs amongst HIV-infected individuals, we are able to improve our understanding of changes in risk behaviour over time. In 2008, we started the prospective collection of data on STIs such as chlamydia, lymphogranuloma venereum (LGV), gonorrhoea and syphilis. In addition, we retrospectively collected STI data from patients in follow-up in HIV treatment centres with a lab link. Here we report the data regarding LGV, syphilis, gonorrhoea and chlamydia.

Lymphogranuloma venereum (LGV)

Lymphogranuloma venereum (LGV) is a sexually transmitted disease caused by serovars L1, L2 and L3 of *Chlamydia trachomatis*[186]. LGV is endemic in Africa, the Caribbean and some parts of Asia, and before 2003 the occurrence of LGV was very rare in Western countries. In 2003, an outbreak of LGV among homosexual men was described in the Netherlands[187, 188]. Since then, many Western countries have reported outbreaks of LGV in homosexual men[189, 190]. Those who were diagnosed with LGV presented with proctitis, and most were co-infected with HIV and hepatitis C[190]. Since the early outbreak in 2003, LGV is still circulating in the Netherlands. In the SHM database, 101 cases of LGV were reported in HIV-infected patients (Table 6.4). LGV was diagnosed predominantly in homosexual men aged 25 years to 44 years, and the majority of these patients were born in the Netherlands. For most

Table 6.4: Demographic and clinical characteristics of HIV-infected patients diagnosed with LGV.

	LGV positive test result
Total positive LGV test results/total tests	**101/262 (39%)**
Age at time of LGV diagnosis	
≤24	4 (4%)
25-44	61(60%)
≥45	36(36%)
Male gender	100(99%)
Region of origin:	
The Netherlands	79(78%)
Sub-Saharan Africa	2(1%)
Latin America/ the Caribbean	4(4%)
Other	16(15%)
HIV transmission route:	
MSM	95(94%)
Other/unknown	6(6%)
Year of LGV diagnosis	
<2008	18(18%)
2008	46(46%)
2009	34(34%)
2010	3(27%)
Co-infection with other STIs:	
HCV positive/total patient tested	17/95 (18%)
Gonorrhoea/total patient tested	41/88 (47%)
TPHA/total patient tested	35/60 (58%)
Location of LGV infection:	
Urogenital	4(4%)
Anorectal	76(75%)
Oral	1(1%)
Unknown/Not classified tissue	20(20%)

Legend: LGV=lymphogranuloma venereum; MSM=men who have sex with men; STIs=sexually transmitted infections; HCV=hepatitis C virus; TPHA=*Treponema pallidum* haemagglutination

patients, data on concurrent infections was available (Table 6.4). Out of 101 patients, 95 were screened for HCV; 17 were co-infected with HCV, and of those, 15 had a positive result on an HCV RNA test. The prevalence of the other STIs varied from 47% with positive test results for gonorrhoea to 58% with positive results on *Treponema pallidum* haemagglutination (TPHA) testing. The location of infection was anorectal in 76 patients, 1 patient was diagnosed with an oral LGV infection, and LGV had a urogenital location in 4 cases.

These data show that LGV is still spreading in younger Dutch HIV-infected homosexual men in the Netherlands, and given the high prevalence of co-infection with other STIs, this group of individuals is likely to be engaged in high-risk sexual behaviour. There is no evidence for LGV spreading to a wider population, such as heterosexual men and women.

Syphilis

The occurrence of syphilis, especially among homosexual men, has been re-emerging in Western Europe since the year 2000[191]. HIV infection is associated with a higher risk of syphilis. According to the current guidelines from the Centers for Disease Control and Prevention (CDC) guidelines, yearly syphilis screening is recommended in HIV-infected patients in clinical care[192].

In the SHM database, data on syphilis testing were available for 7211 HIV-infected patients. Of this group of patients, 1342 (19%) had a positive result on TPHA assay, and 711 (53%) of these patients had a positive result on a venereal disease research laboratory (VDRL) or rapid plasma regain (RPR) test (Table 6.5). The high proportion of patients with active syphilis stresses the importance of annual testing in HIV-infected patients, according to the current CDC guidelines[193, 194].

Patients with a positive TPHA test were predominantly male and were infected with HIV by homosexual contact. The median age at the time of the positive TPHA serology was 42 years (IQR, 36-49), and these patients were significantly older compared to those

Table 6.5: Demographic and clinical characteristics of HIV-infected patients classified by the results of serologic tests for syphilis.

	TPHA positive serology	VDRL/RPR positive	Reported neurosyphilis	TPHA negative serology
N	1342/7211 (19%)	711/1342 (53%)	46	5869/7211 (81%)
Age at Syphilis testing date				
≤24	56 (4%)	27 (4%)	0	431 (7%)
25-44	766 (57%)	437 (61%)	33 (72%)	3446 (59%)
≥45	520 (39%)	247 (35%)	13 (28%)	1992 (34%)
Gender:				
Male	1263 (94%)	686 (96%)	44 (96%)	4608 (79%)
Female	79 (6%)	18 (3%)	2 (4%)	2603 (44%)
Region of origin:				
The Netherlands	916 (68%)	490 (69%)	25 (54%)	3312 (56%)
Sub-Saharan Africa	55 (4%)	20 (3%)	2 (4%)	905 (15%)
Latin America/ the Caribbean	165 (12%)	88 (12%)	11 (24%)	645 (11%)
Other	206 (15%)	113 (16%)	8 (17%)	621 (11%)
HIV transmission route				
MSM	1142 (85%)	629 (88%)	39 (85%)	3381 (57%)
Heterosexual	119 (9%)	51 (7%)	6 (13%)	1884 (32%)
Other/unknown	81 (6%)	31 (4%)	1 (2%)	604 (10%)
Year of Syphilis diagnosis				
<2008	386 (29%)	231 (32%)	39 (85%)	
2008	574 (43%)	280 (39%)	6 (13%)	
2009	336 (25%)	177 (25%)	1 (2%)	
2010	46 (3%)	23 (3%)	0 (%)	
Source:				
Serum/plasma	1140 (85%)	607 (85%)		
Cerebrospinal fluid	51 (4%)	44 (6%)		
Unknown/ Not classified	151 (11%)	60 (8%)		
Receiving cART	1044 (77%)	532 (75%)	49 (88%)	4883 (83%)
Years of known HIV infection (median, IQR)	2.6 (0.1-7.9)	2.1 (0.5-7.4)	5.1 (0.15-8.8)	2.7 (0.1-8.7)

Legend: TPHA=*Treponema pallidum* haemagglutination; VDRL/RPR=venereal disease research laboratory/rapid plasma reagin; MSM=men who have sex with men; cART=combination antiretroviral therapy; IQR=interquartile ratio

with a negative TPHA test result ($p < 0.003$). Compared to TPHA-negative patients, a smaller proportion of the TPHA-positive patients were receiving cART ($p < 0.0001$).

Between 2000 and 2010, neurosyphilis was reported by clinicians in the medical records of 46 patients (Figure 6.3).

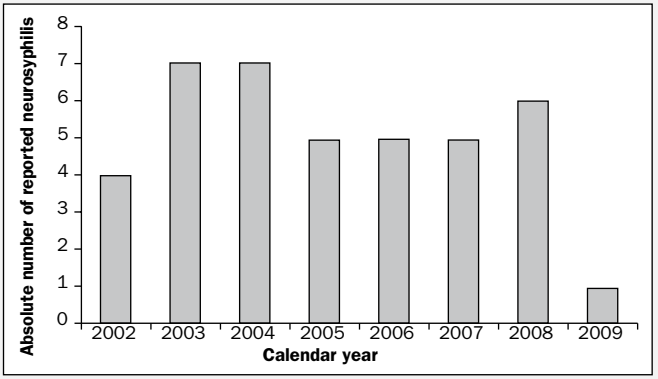


Figure 6.3: Absolute number of HIV-infected patients with neurosyphilis reported in the Stichting HIV Monitoring database between 2002 and 2009.

The absolute number of patients with neurosyphilis varied between 4 and 7 per year for the calendar years 2002 to 2008. The median time of known HIV infection was significantly longer for patients who were diagnosed with neurosyphillis compared to patients with positive or negative results of a TPHA test (Table 6.5).

Chlamydia and Gonorrhoea

In several Western countries, chlamydia and gonorrhoea are common STIs[195]. Chlamydia is the most frequently diagnosed bacterial STI in the Netherlands[41], and positive test results range from 12% amongst homosexual men to 17% amongst young women. An increase in gonorrhoea has been observed recently in the Netherlands[41]; the rate of positive test results for gonorrhoea has been highest in HIV-infected individuals and homosexual men.

Table 6.6: Demographic and clinical characteristics of HIV-infected patients diagnosed with chlamydia or gonorrhoea by a positive test result.

	Chlamydia	Gonorrhoea
Total positive test results/total tests	695/2825 (20%)	727/3240 (22%)
Age at date of positive test result median, IQR	39 (32-46)	38 (30-47)
≤24 years	43 (6%)	53 (7%)
25-44 years	427 (61%)	469 (66%)
≥45 years	225 (32%)	205 (28%)
Male gender	635 (91%)	700 (96%)
Region of origin:		
The Netherlands	511 (73%)	559 (77%)
Sub-Saharan Africa	21 (3%)	16 (2%)
Latin America/ the Caribbean	84 (12%)	74 (10%)
Other	79 (11%)	78 (11%)
HIV transmission route		
MSM	582 (84%)	661 (91%)
Heterosexual	83 (12%)	42 (6%)
Other/unknown	30 (4%)	24 (3%)
Calendar year of chlamydia or gonorrhoea diagnosis		
<2008	198 (28%)	238 (33%)
2008	242 (35%)	222 (31%)
2009	215 (31%)	224 (31%)
2010	40 (6%)	43 (1%)
Location of the infection:		
Urogenital	176 (25%)	287 (39%)
Anorectal	324 (47%)	281 (39%)
Oral	16 (2%)	57 (8%)
Unknown/Not classified tissue	179 (26%)	102 (14%)

Legend: IQR=interquartile range; MSM=men who have sex with men

In the SHM database, a total of 2825 patients were tested for chlamydia, and of those, 695 (20%) had a positive test result. A comparable percentage of patients with a positive test result for gonorrhoea (22%) was reported (Table 6.6). The median age at the time of the first positive test result for chlamydia or gonorrhoea was lower than the median age for the diagnoses of LGV and syphilis. Chlamydia and gonorrhoea were found mostly in Dutch homosexual men between the ages of 25 and 44 years. Compared to syphilis, LGV and gonorrhoea, chlamydia was more often diagnosed in heterosexual patients; 12% of the patients with chlamydia were infected with HIV through heterosexual contact.

The prevalence of chlamydia and gonorrhoea in the HIV-infected population in care in the Dutch HIV treatment centres is higher than the prevalence reported by the national institute for public health[41] and higher than in earlier studies on the prevalence of STIs in homosexual men[196, 197] or HIV-infected individuals[198]. Screening for chlamydia and gonorrhoea amongst HIV-infected patients seen in the clinic was probably limited to patients with symptoms, and this may have resulted in a high prevalence of these STIs compared to the prevalence in earlier studies. However, chlamydia and gonorrhoea are infections that are often asymptomatic, which makes them likely to go undetected. Most of the asymptomatic STIs are detected by STI clinics and are not reported to SHM. The absolute numbers of cases of chlamydia and gonorrhoea in the SHM database are therefore probably at the lower limit of the actual number of HIV-infected patients co-infected with chlamydia and gonorrhoea.

Conclusion

From 2008 onwards, data on STIs have been prospectively collected in the SHM database. In this chapter we report the first results of this data collection. Although high rates of STIs are found in this population, these results need to be interpreted with care. Data on STIs in the SHM database have been available for only 2 years and most patients probably underwent STI screening during their routine clinic visit because they had symptoms, whereas most HIV-infected patients with an STI are asymptomatic. Also, the majority of STIs were found amongst homosexual men aged 25 to 44 years, which is the largest

group in our database, and therefore, our findings cannot be generalized to the HIV-infected population as a whole.

However, these data may be an indication that a substantial number of HIV-infected patients are co-infected with STIs. Some STIs are known to facilitate HIV transmission, which may expose the HIV-uninfected sex partners of patients with HIV to an additional risk of transmission[199]. It has been suggested that co-infection with STIs are a cofactor in the sexual transmission of HCV amongst HIV-infected homosexual men. Indeed, the increase in newly diagnosed HCV infection amongst homosexual men being followed by SHM has coincided with reported outbreaks of LGV and syphilis in the Netherlands. Early detection and treatment of STIs may have an impact on controlling the HIV epidemic. Also, when STIs are the underlying mechanism for sexual transmission of HCV, the screening and treatment for these infections may have an impact in controlling the further spread of HCV.

To improve our knowledge of the interaction between STIs and HIV, more detailed information on the occurrence of STIs in the HIV-infected population is needed, such as the relation of the timing of acquisition of an STI to that of HIV infection. Also, studies regarding the clinical impact of STIs on HIV disease progression are needed to determine the impact of STIs on treatment outcomes and immune activation.

In the SHM database, a remarkable number of patients have been diagnosed with neurosyphilis. After World War 2, the rates of neurologic syphilis decreased significantly. Since 1980, a number of cases of neurosyphillis among HIV-infected persons have been reported[200]. Previous studies have found an increased risk of neurosyphilis in HIV-infected patients with low CD4 cell counts[201, 202]. Further studies in HIV-infected individuals are needed to determine the impact of STIs on progression of HIV disease and the HIV epidemic and to examine the development of neurosyphilis among HIV-infected individuals.

Jan Prins is greatly acknowledged for his contribution to the STI section of this chapter.

7. Treatment and prevention

Estimating the risk of HIV infection from homosexual men receiving treatment to their HIV-uninfected partners.

Colette Smit & Timothy Hallett

This chapter is a shortened version of a recently published paper in STI (*203*): http://sti.bmj.com/content/early/2010/07/18/sti.2010.042622.long.
Tim Hallett, Geoff Garnett and Frank de Wolf are gratefully acknowledged for their contributions.

The risk of HIV transmission from homosexual men on cART is related to patterns of patient monitoring and condom use. Using a mathematical model on viral load evolution, we estimated the HIV transmission risk for various patterns of condom use and patient monitoring. This model showed that the risk of transmitting HIV to a sexual partner is 22% when condoms are never used; with inconsistent condom use this risk is slightly reduced. However, the risk of HIV transmission decreases to 3% when men receiving treatment decide not to use condoms during the 6 month period following the last undetectable viral load measurement (following this 6 month period consistent condom use is resumed). This risk is reduced further if they decide not to use condoms for only a 3 month period following the last undetectable viral load measurement. Thus, when HIV-infected men receiving cART base condom use on the time since their last undetectable viral load measurement, the risk of transmission is much lower than with inconsistent condom use. The key message for patients is that although always using condoms is the best way to protect partners from the risk of HIV transmission, when such use cannot be achieved, the second best strategy is to use condoms whenever the last undetectable viral load was measured more than 3 months ago.

De kans op HIV overdracht van homoseksuele mannen die met cART worden behandeld naar hun HIV-negatieve sekspartner is gerelateerd aan de frequentie van virale load metingen en condoomgebruik. De kans op HIV overdracht bij verschillende scenario's van condoomgebruik en frequenties van HIV load metingen is geschat met een wiskundig model. De schattingen van dit model laten zien dat de kans op HIV transmissie 22% is wanneer condooms nooit worden gebruikt. Bij inconsistent condoomgebruik is er een geringe afname in deze kans. Terwijl de kans op HIV transmissie sterk afneemt, tot 3% bij concom gebruik wanneer een laatste virale load meting langer dan 6 maanden geleden is en een nog sterkere afname treedt op wanneer een periode van 3 maanden wordt aangehouden. Wordt het condoomgebruik afgestemd op de laatste ondetecteerbare virale load meting, dan is de HIV transmissiekans veel lager dan bij inconsistent condoom gebruik. De kernboodschap aan patiënten is dan ook dat condooms tijdens alle sekscontacten de beste bescherming biedt tegen HIV besmetting. Wanneer een 100% gebruik van condooms niet haalbaar is, dan is de beste strategie om dat wel te doen wanneer de laatst gemeten langer dan 3 maanden geleden is en ondetecteerbaar als uitslag had.

Background

As the HIV-infected population receiving antiretroviral treatment grows, its potential contribution to the HIV epidemic increases. Therefore, the infectiousness and the sexual behaviour of the population receiving treatment will play important roles in the trajectory of the Dutch (and global) HIV epidemic in the near future.

The rate of HIV transmission is closely tied to the plasma viral load levels of HIV-infected persons, which cART can greatly reduce[204]. On the basis of this evidence, the Swiss National AIDS commission (EKAF) suggested that there was effectively no risk of HIV transmission from patients receiving cART who followed the treatment guidelines strictly, who had no detectable viral load in the last 6 months, and who had no other sexually transmitted infections[205, 206]. The implication was that such patients do not need to use condoms with their sexual partners. Although the chance of HIV transmission is very low amongst patients receiving treatment who have an undetectable viral load, it is unlikely to be zero. Over time, with many sex acts amongst many individuals, a small rate of transmission could translate into a large number of new HIV infections[207, 208].

With a stochastic mathematical model, we estimated the risk of HIV transmission in the Netherlands from men who have sex with men (MSM) and determined how this is influenced by various patterns of condom use and schedules of viral load monitoring.

Mathematical model to estimate the chance of HIV transmission

This stochastic individual-based simulation model of viral trends, HIV transmission risk and patient monitoring amongst MSM in the Netherlands during first-line treatment was parameterised using data from the SHM observational database[13, 209] (Figure 1). The model incorporated different scenarios for the way in which condom use may depend on recent viral load measurements. The risk of HIV transmission was characterised as the probability that a man receiving treatment will infect his uninfected sexual partner during the course of first-line treatment[210]. We assumed that there were 100 sex acts per year in the partnership and that the efficacy of condoms in reducing transmission was 95%.

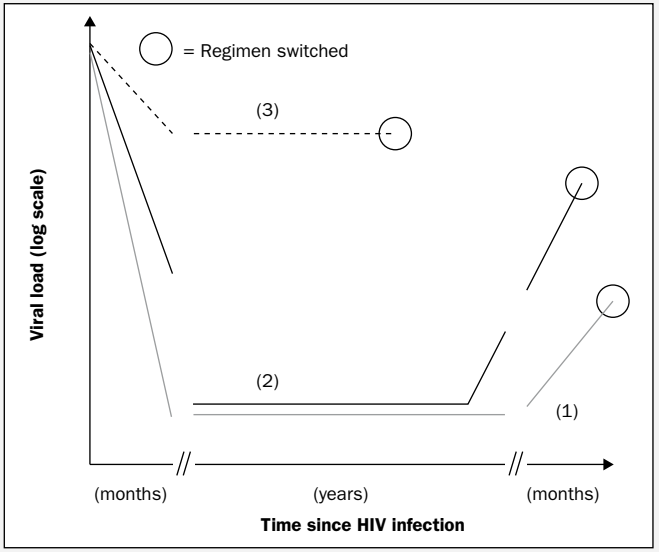


Figure 7.1: Schematic representation of the three assumed trajectories of (log) viral load following treatment initiation: (1) suppression achieved and adherence good (grey line); (2) suppression achieved but adherence poor (black line); and (3) suppression not achieved (dashed line).

Various scenarios for condom use in a partnership were considered: (1) never using condoms; (2) using condoms in 30% of the sex acts; (3) not using condoms if the last measurement of the viral load was both undetectable and obtained in the past 6 months; and (4) always using condoms. Scenario 3 corresponds to the way that the EKAF statement has been interpreted. In the model we considered two additional variants of this scenario whereby the decision not to use condoms was based either on the last measurement in the past 3 months or on the last viral load measurement ever taken (irrespective of time).

Risk of HIV transmission and different scenarios for condom use

We found that HIV-infected men receiving treatment pose a substantial risk of transmission (22%; 9-37% in the uncertainty analysis) to their uninfected partners if they do not use condoms (Figure 7.2).

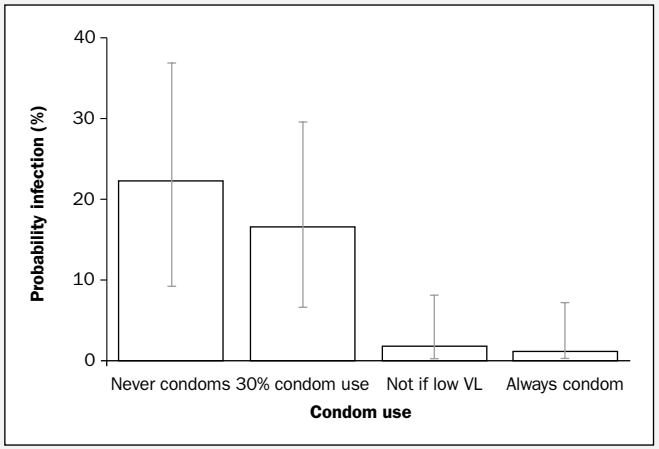


Figure 7.2: Probability of infection during first-line therapy, if (1) condoms are never used; (2) condoms are used 30% of the time; (3) condoms are used unless the last viral load measurement in last 6 months was undetectable versus (4) always using condoms (assuming the Fraser *et al.* relationship between viral load and infectiousness)[210]. Error bars show the uncertainty interval. It is assumed that the partnership is maintained over the entire course of first-line therapy.

This risk was generated in three ways: (1) the treatment is not sufficient to suppress viral load and transmission could occur, even if the regimen is quickly changed; (2) the HIV RNA level can rebound quickly and reach high levels before its detection and change of regimen; and (3) even with suppressed viral load, the risk of transmission is not zero, so with the many sex acts during treatment, the cumulative chance of transmission is not negligible.

Using condoms 30% of the time reduces the chance of HIV transmission, but only marginally, to 17% (7-29% in uncertainty analyses), since overall, a substantial number of unprotected sex acts remain.

In contrast, men who always used condoms, unless their viral load was undetectable at the last measurement in the past 6 months, were much less likely to transmit HIV to their partners (risk of transmission is 3%, 0.2-8% in the uncertainty analyses). This is because the risk generated in the first two ways, as mentioned above, was largely removed. Men following this strategy, on average, used condoms 10% of the time they were receiving first-line treatment. Nevertheless, the risk of HIV transmission with this strategy is greater than when condoms are always used, in which case the risk is 1% (0-7% in the uncertainty analyses). The risk is not zero, because condom efficacy is not perfect.

Frequency of patient monitoring

The frequency with which patients are monitored is a key determinant of the risk of HIV transmission (Figure 3A). Patients who are monitored frequently can be quickly switched to new regimens if first-line treatment fails, that is, before the patients have exposed their partners to an increased risk of transmission for a long period. The benefit of patient monitoring is influenced by the proportion of patients lost to follow-up. The probability of infecting a partner increases from 2%, when none of the patients are lost to follow-up, to 5%, when 20% of the patients do not return for care (Figure 3B). This results from undetected increases in viral load that exposes partners to a higher risk of infection.

Finally, we examined three ways in which condom use could be based on viral load measurements. The patient's decision not to use condoms could be based on having an undetectable viral load in the past 3 months, the past 6 months, or the last measurement ever. When the decision is based on a measurement in the past 3 months, there is a reduced transmission compared with a decision based on a measurement in the past 6 months, provided that patients are monitored at least every 3 to 12 months. However, when the decision is based only on the last measurement, regardless of time, the chance of transmission is higher, especially if the monitoring intervals are longer.

Conclusion

The debate over the EKAF statement regarding HIV transmission from patients receiving cART, as well as

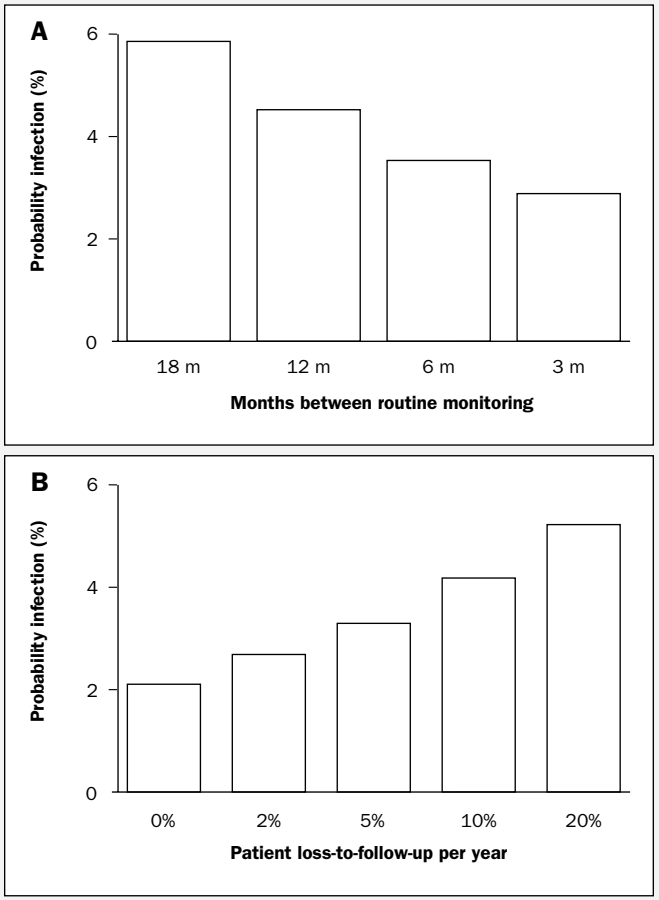


Figure 7.3: The influence of (A) monitoring frequency and (B) loss to follow-up on the probability of HIV transmission, assuming condom use unless the last viral load measurement in the previous 6 months was undetectable. It is also assumed that the partnership is maintained over the entire course of first-line therapy and that viral load is related to transmission rate, as described by Fraser *et al*[210].

earlier modelling work, did not take into consideration that the decision not to use condoms might be a condition of the last viral load measurement[207, 208]. There was also little focus on how HIV transmission is influenced by patterns of patient monitoring. The results of this model have shown that basing the decision to use condoms on viral load provides substantially better protection to partners than incomplete condom use, provided that the measurement is within the past 3 to 6 months. The implied key message to patients remains; always using condoms when receiving treatment is the best way to protect partners from the risk of HIV transmission. However, an additional message is that using condoms is most crucial when patients have not recently (within the past 3 months) had an undetectable viral load measurement, which could substantially improve protection for uninfected partners. This advice must be supported by frequent viral load monitoring of all patients receiving treatment, because frequent viral load measurement can maximise the potential for treatment to reduce HIV transmission.

special reports

8. The Amsterdam Cohort Studies on HIV infection - Annual Report 2009

Ineke Stolte, Maria Prins for the ACS

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS started shortly after the first cases of AIDS were diagnosed in the Netherlands. Since October 1984, men who have sex with men (MSM) have been enrolled in a prospective cohort study. A second cohort involving drug users (DU) was initiated in 1985. In 2009, the cohorts reached 25 years of follow-up. The initial aim of the ACS was to investigate the prevalence and incidence of, and risk factors for, HIV-1 infection and AIDS, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. During the past 25 years, these aims have remained mostly the same, although the emphasis of the studies has changed. Early on, the primary focus was to elucidate the epidemiology of HIV-1 infection, whilst more in-depth studies were performed later on to investigate the pathogenesis of HIV-1 infection. In recent years, the focus has shifted to also include the epidemiology and natural history of other blood-borne and sexually transmitted infections among the participants in the ACS.

From the beginning, research in the ACS has taken a multidisciplinary approach (epidemiology, social science, virology, immunology and clinical medicine). This unique collaboration has been very productive, significantly contributing to the knowledge and understanding of many different aspects of HIV-1 infection. This expertise has contributed directly to advances in prevention, diagnosis and management of HIV infection.

De Amsterdamse Cohort Studies (ACS) naar HIV en Aids zijn gestart kort nadat de eerste gevallen van Aids gediagnosticeerd werden in Nederland. Sinds oktober 1984 worden mannen die seks hebben met mannen (MSM) gevolgd in een prospectieve cohort studie. Een tweede cohort onderdruggebruikers startte in 1985. In 2009 bestonden de cohorten 25 jaar. Het oorspronkelijke doel van ACS was het onderzoeken van de prevalentie en incidentie van, en risicofactoren voor HIV-1 infectie en AIDS, het natuurlijk beloop van HIV-1 infectie en het evalueren van de effecten van interventies. De afgelopen 25 jaar zijn deze doelen min of meer gelijk gebleven maar is de nadruk van de studies wel veranderd. In het begin lag de focus vooral op het ophelderen van epidemiologie van HIV-1. Later zijn meer verdiepende studies uitgevoerd, met name naar de pathogenese van HIV-1. Afgelopen jaren worden eveneens de epidemiologie en het natuurlijke beloop van andere bloed-overdraagbare en seksueel overdraagbare (SOA's) aandoeningen bestudeerd.

Vanaf de beginfase heeft het onderzoek in de ACS zich onderscheiden door een multidisciplinaire aanpak (epidemiologie, sociale wetenschappen, virologie, immunologie en klinische geneeskunde). Deze unieke aanpak is erg productief gebleken en heeft inzicht gegeven in de verschillende aspecten van HIV-1. Deze expertise heeft direct bijgedragen aan de vooruitgang en verbetering in preventie, diagnose en behandeling van HIV infecties.

As of 31 December 2009, 2420 MSM and 1652 (injecting) DU were included in the ACS. Every 3 to 6 months, participants have completed a standardized questionnaire designed to obtain information regarding medical history, sexual and/or drug use behaviour, underlying cognitions, health care use, depression, psychological disorders, and

demographics. In addition, they undergo a medical examination (HIV-positive participants and, in the past, HIV-negative drug users as well), and blood is drawn for diagnostic tests and storage. The ACS have been conducted in accordance with the ethical principles set out in the declaration of Helsinki, and participation in the ACS is voluntary: written informed consent (the most recent version approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the DU cohort) is obtained for every participant.

Of the 2420 MSM, 585 were HIV-positive at study entry, and 216 seroconverted during follow-up. For the 1652 DU, 322 were HIV-positive at study entry, and 96 seroconverted during follow-up. By 31 December 2009, 342 MSM and 439 DU had died, and several other participants were asked to leave the study or left at their own request. About 90% of the participants who visited the ACS during a given calendar year returned for a follow-up visit the next year. In total, the Public Health Service of Amsterdam was visited 48,577 times by MSM and 25,791 times by DU.

Collaborating institutes and funding

Within the ACS, different institutes collaborate to bring together the data and biological sample collections. These are the Public Health Service of Amsterdam (PHSA) (Cluster Infectious Diseases, Department of Research), the Academic Medical Center (AMC) of the University of Amsterdam (Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine, and the International Antiviral Therapy Evaluation Center) and the Jan van Goyen Medical Center (Department of Internal Medicine). Until 2007, collection of blood cells was performed at the Sanquin Blood Supply Foundation, but this activity has since moved to the Department of Experimental Immunology at the AMC. However, the Sanquin Blood Supply Foundation is still affiliated with the ACS. Also, many collaborations exist between the ACS and other research groups both within and outside of the Netherlands.

The ACS is part of Stichting HIV Monitoring (the Netherlands HIV monitoring foundation) and is financially supported by the Centre for Infectious Disease Control of the Netherlands National Institute for Public Health and the Environment.

The ACS in 2009

The cohort of men having sex with men

In 2009, 525 MSM were followed at the PHSA of Amsterdam. Fourteen of them were newly recruited in 2009. From 2005, recruitment has been open for MSM of all ages with at least one sexual partner in the preceding 6 months. Of the MSM followed in 2009, 473 men were HIV-negative, and 53 men were HIV-positive. The HIV-positive men, of whom 39 were HIV seroconverters, were followed according to the 'HIV Onderzoek onder Positieven' (HOP) protocol, which was initiated in October 2003 for MSM who seroconverted or were HIV-positive at entry into the study cohort of young MSM after 1999. Since November 2008, all MSM followed at the PHSA have also been screened for STI.

In 2009, 21 HIV-positive men were included in the HOP, of whom 12 were exclusively followed in an HIV treatment centre outside the PHSA. By the end of 2009, 45 HIV-positive men were still in active follow-up in an HIV treatment centre outside the PHSA and were being followed according to the HOP protocol. From June 2006 onwards, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants have also been invited to participate in the ACS. By the end of 2009, 13 HIV discordant and 3 HIV-positive concordant couples were included in this partner study, of which 7 couples were still in active follow up.

In 2009, 258 HIV-positive MSM were seen at the Jan van Goyen Clinic or at one of the 22 other HIV treatment centres in the Netherlands. Ninety-one of them were HIV seroconverters. Plasma and cells from 60 of the 141 HIV-positive MSM in active follow-up at the Jan van Goyen clinic in 2009 were stored. Of these, 38 were HIV seroconverters, and the

remaining 22 were defined as (1) slow or non-progressor or matched fast progressor in 1996 or (2) were HIV-positive for more than 10 years and had a CD4 count greater than 400 cells/μl after 10 years of follow-up following an HIV-positive result without effective therapy.

The cohort of drug users

In 2009, 364 drug users were followed at the PHSA of Amsterdam. Forty-nine were young drug users aged 30 years or less, they were recruited after 2000 and had used cocaine, heroin, or amphetamines at least 3 times a week in the 2 months preceding enrolment. Of the 364 DU followed in 2009, 34 were HIV-positive at entry, 17 seroconverted for HIV during follow-up in the ACS, and 5 had their first study visit in 2009.

In 2005, a feasibility study (the Dutch-C project) was started within the DU cohort to evaluate the possibility of hepatitis C virus (HCV) testing and treatment combined with methadone programs. In 2009, as part of this project, 10 DU who were mono-infected with HCV initiated HCV therapy, resulting in a total group of 60 DU treated for HCV. This project is one of the first studies specifically designed as an intervention to increase HCV assessment and treatment in a well defined cohort of DU.

Substudies

The ACS Open project*

During the past 25 years vast amounts of data on social-scientific, demographic, clinical, and biomedical information have been obtained from the participants of the ACS by the various collaborating institutes. In 2005, the "ACS Open" project group, composed of data managers and scientists from all of the participating research groups, started to connect these data sets and build an easily accessible, multidisciplinary database that comprises all longitudinally obtained epidemiological, social-scientific and biomedical information, and contains data regarding the availability of stored samples in the repositories. In 2010 these data sets will be available to scientists in the collaborating institutes and their colleagues.

The ACS data are also very suitable for universities and research institutes to teach students in epidemiology, biomedicine and social science how to analyze longitudinal data sets. Therefore, a multidisciplinary data set with limited information has been made available for general use and launched on the Internet: www.amsterdamcohortstudies.org.

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

Primo-SHM study

In addition to the cohorts previously described, the ACS also includes patients who present with primary HIV-1 infection at the outpatient clinic of the AMC in the so-called "primo-SHM study". Some of these patients are seronegative men who seroconverted during follow-up in the MSM cohort at the PHSA. Some of them are also still followed with the HOP protocol of the ACS at the PHSA. The primo-SHM study is a national randomized study on the effect of early temporary quadruple antiviral therapy as compared to no therapy. As of December 2009, 238 patients were already included as patients with primary infection, of whom 173 participated in the randomized clinical trial (RCT). Inclusion in the RCT stopped in early 2010, and its results are expected in early 2011.

Blood is collected from all patients for storage of plasma and peripheral-blood mononuclear cells (PBMC), and sampling is more frequent early after entry into the study. Individuals are followed until they have to (re) start highly active antiretroviral therapy (HAART) because of a CD4+ T cell decline <350 cells/μl.

HIV-infected and HIV-exposed children

At the Emma Children's Hospital in the AMC, both HIV-infected and HIV-exposed children are in follow-up. Data from both groups are collected by the SHM, and collaborators in the Departments of Obstetrics and Gynecology and Experimental Immunology at the AMC study factors involved in neonatal HIV-1 transmission. Of the 59 HIV-infected children currently being followed, 58 were infected with HIV-1 and 1 with HIV-2. Two patients were co-infected with hepatitis B virus (HBV). The children infected with HIV-1 are included in the Pediatric Amsterdam Cohort on HIV-1 (PEACH). The HIV-exposed children are studied in the context of the European Collaborative Study on Mother-to-Child Transmission (MTCT) of HIV (ECS), an ongoing birth cohort study that recently merged with the Pediatric European Network for Treatment of AIDS (PENTA).

The HIV epidemic

HIV incidence

Nine MSM and no DU participating in the ACS at the PHSA had a first HIV-positive test in 2009 after a previous HIV-negative test. HIV incidence in 2009 was 2 per 100 person-years among MSM, and it has slowly increased since 1996, the year that combination antiretroviral therapy (cART) became generally available in high-income countries including the Netherlands, followed by a strong decrease in HIV-related morbidity and mortality rates.

The trend in HIV incidence among DU in the ACS differed from that observed among MSM; HIV incidence has substantially declined to less than 1 per 100 person-years in most recent years. Figures 8.1 and 8.2 show the yearly observed HIV incidence rates for MSM and drug users from the start of the ACS through 2009.

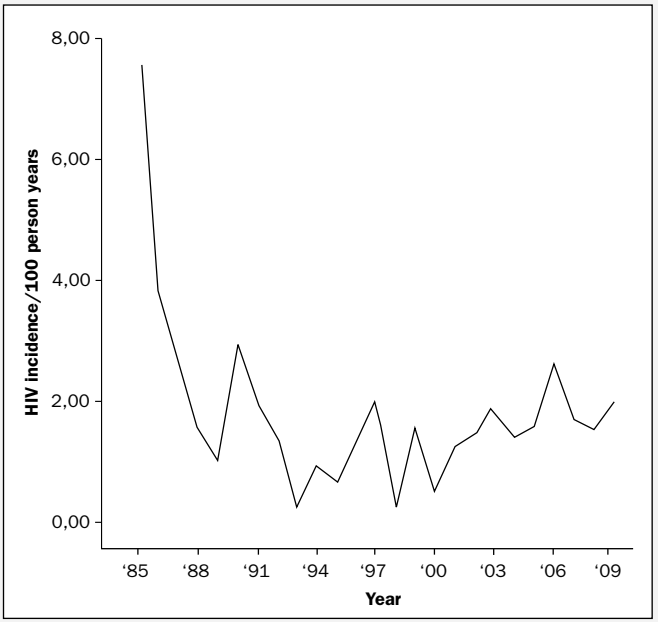


Figure 8.1: HIV incidence per calendar year among MSM in the ACS, 1984-2009

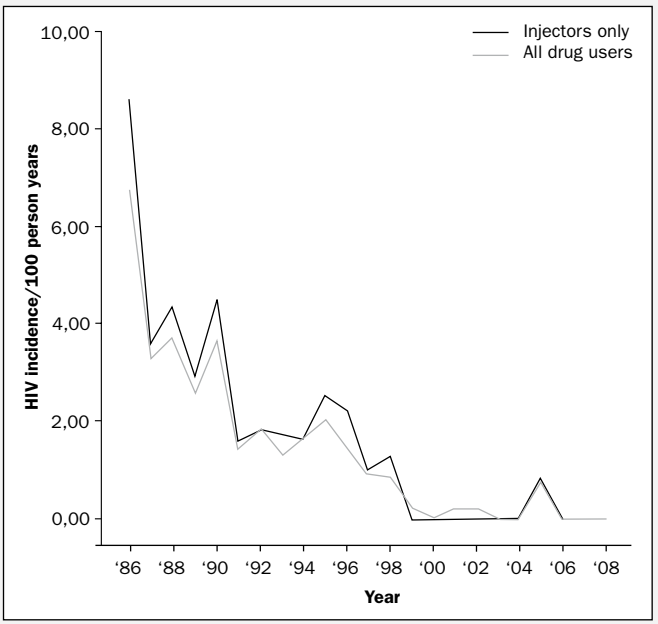


Figure 8.2: HIV incidence per calendar year among drug users in the ACS, 1986-2009

Transmission of therapy-resistant HIV strains

Surveillance of transmission of drug-resistant HIV-1 strains was performed for 9 MSM seroconverters and for 1 of 2 MSM seropositive at study entry in 2009. None of the individuals was infected with virus harbouring resistance-associated mutations; only a naturally occurring sequence variation was found in the predominant circulating virus populations. Phylogenetic analysis showed that 9 individuals harboured subtype B HIV-1 strains and 1 individual was infected with subtype CRF02-AG.

HAART uptake

Of all 258 HIV-positive MSM visiting the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands in 2009, 235 (91%) received some form of antiretroviral therapy. Of 258 MSM for whom viral load results were available in 2009, 228 (88%) had a viral load of less than 50 copies/ml (assay: M2000rt).

Of the 41 HIV-positive DU who visited the PHSA in 2009 and for whom treatment data were available, 35 (85%) received some combination of antiretroviral therapy. Of these 35, 33 (94%) had an undetectable viral load (less than or equal to 150 copies/ml [assay: M2000rt]) at their latest visit. Of 6 HIV-positive DU not receiving HAART, 3 (50%) had an undetectable viral load.

Risk behaviour of MSM

Among HIV-1-negative MSM practising anal sex the percentage of men practising unprotected anal intercourse (UAI) reached 55% in 2009. Similar to the HIV incidence, trends in UAI among HIV-negative MSM participating in the ACS have slowly increased since 1996.

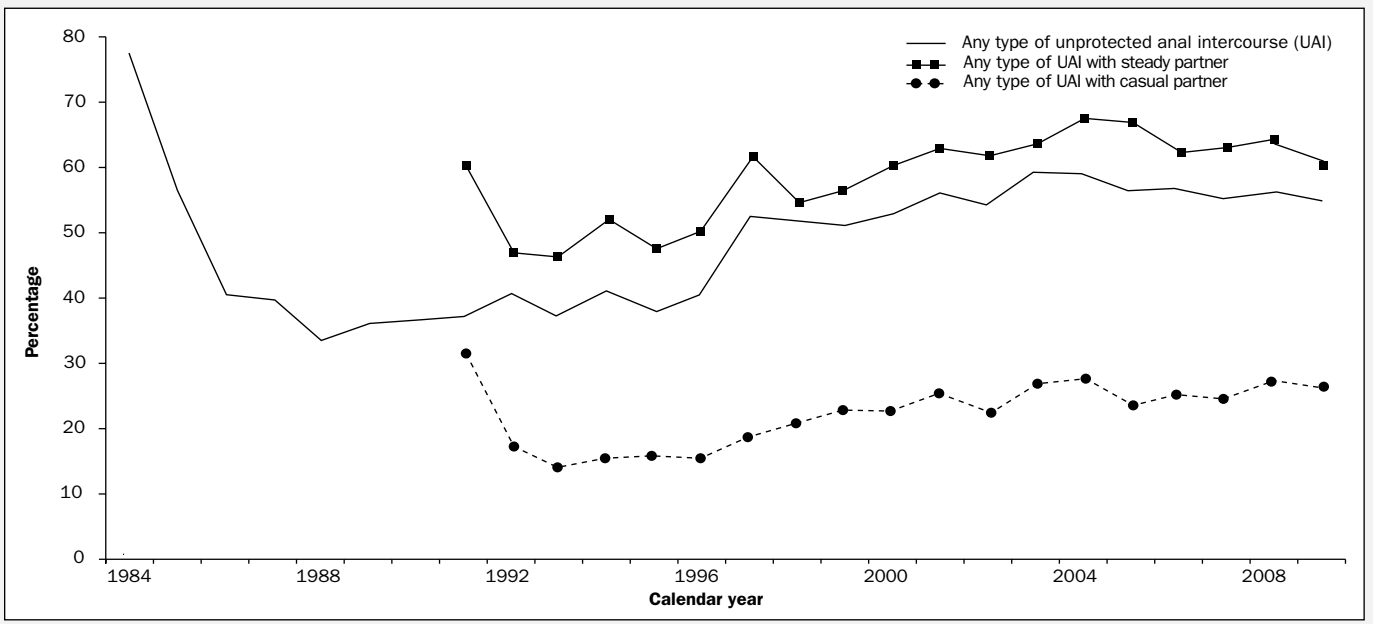


Figure 8.3: Trends in unprotected anal intercourse in the past 6 months amongst HIV-negative MSM who engaged in anal sex. ACS 1984-2009

Risk behaviour of DU

In HIV-negative DU, reports of both injection and borrowing needles significantly declined over the period 1985-2009. Reports of high risk sexual behaviour and sexually transmitted infections at follow-up visits decreased before 1996, but they remained relatively stable after 1996 at approximately 35% and 8% respectively (see Figure 8.4).

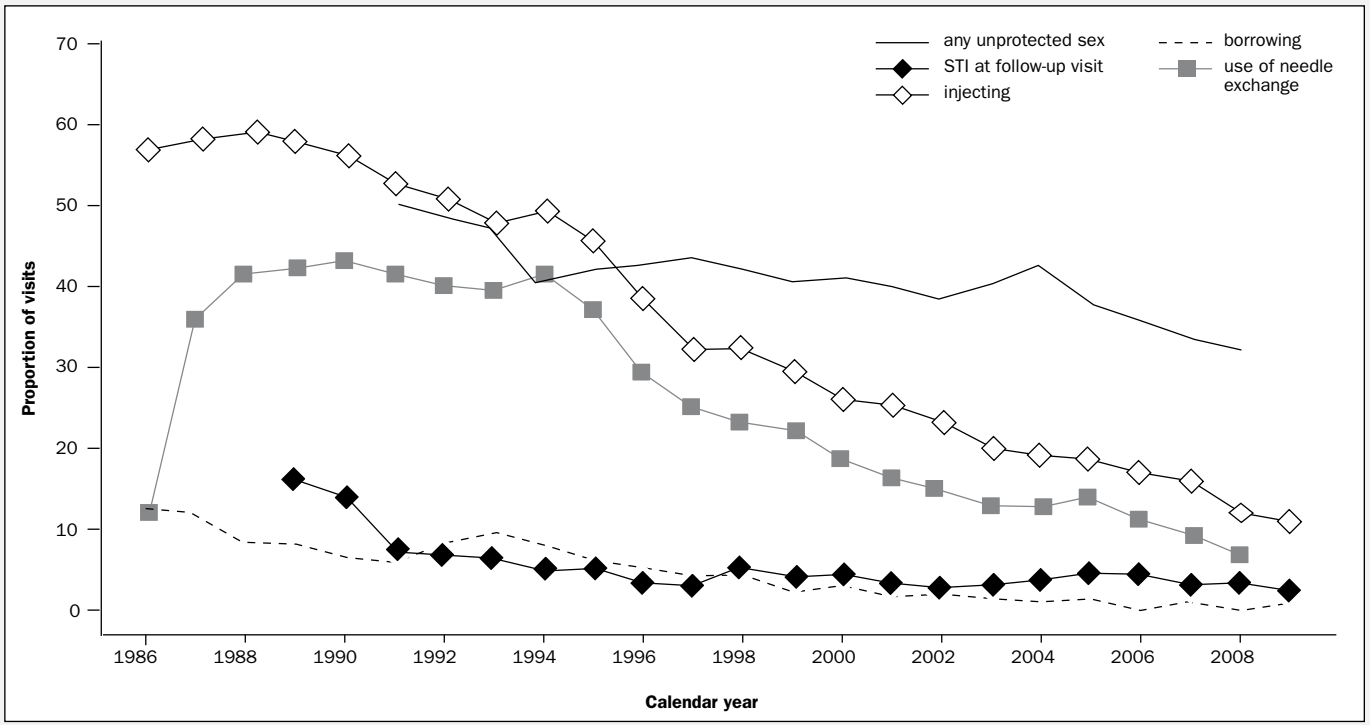


Figure 8.4: Proportion of visits per calendar year at which injecting and high risk sexual behaviour was reported amongst 1315 DU who were HIV-negative on ACS entry, 1986-2009. STI=sexually transmitted infection

Hepatitis B co-infections

The ACS has expanded in recent years to include studies of other blood-borne and sexually transmitted infections among the participants of the ACS, opening up new avenues for further research. In 2009, the first results on the retrospective longitudinal testing for HBV infections became available[211, 212]. Between 1984 and 2003, sera of MSM and DU in the ACS with a history of at least two visits were retrospectively screened for anti-hepatitis B core (HBc) antibodies. After 2003, most MSM and DU participating in the ACS were vaccinated against HBV, making further testing redundant.

After screening the sera of 1862 MSM, 1042 MSM proved to be negative for anti-HBc antibodies at study entry; 64 of the 1042 subsequently seroconverted during follow-up at a median age of 32 years. At the moment of seroconversion, 31 MSM were HIV-positive. HBV incidence declined dramatically in the first years and then remained stable throughout the study period. Although HBV is generally considered more infectious than HIV, this study shows that the trend and magnitude

in HBV and HIV incidence among MSM are similar. With the exception of 3 MSM, all were infected with an identical genotype A strain. This strain has been circulating not only amongst MSM of the ACS but also amongst the general MSM population in the Netherlands for at least 2 decades.

Sera of 1268 DU were screened for anti-HBc antibodies, and of the 598 participants who were anti-HBc–negative at entry, 83 subsequently seroconverted for anti-HBc antibodies. The incidence of HBV declined from 5.9 per 100 person-years between 1985 and 1993 to 0 per 100 person-years in 2002. Of the acutely infected injecting and non-injecting DU, 88% were infected with the same genotype D, serotype ayw3 strain. Current injecting was the most important risk factor for HBV infection. The decline in the incidence of HBV amongst DU in Amsterdam was probably caused by the decline in injecting behaviour. Injecting and non-injecting DU were infected with the same strain, indicating that DU infect one another, regardless of their risk behaviour. No reports of new cases among DU and the disappearance of the specific genotype D strain suggest that DU may no longer be a high-risk group for HBV infection in Amsterdam. However, trends in drug use need to be monitored in case injecting drug use regains popularity in the Netherlands, thereby increasing HBV transmission risk among DU.

ACS research highlights 2009

Since 2000, there has been a marked rise in acute hepatitis C virus (HCV) in HIV-positive MSM. We conducted an international phylogenetic study to investigate the existence of an HCV transmission network among MSM. This analysis revealed a large international network of HCV transmission. The rapid spread of HCV among neighbouring countries is supported by the large proportion (74%) of European MSM infected with an HCV strain co-circulating in multiple European countries, the low evolutionary distances among HCV isolates from different countries, and the trend toward increased country mixing with increasing cluster size. Temporally, this epidemic coincides with the introduction of HAART and associated increases in sexual risk behaviours. International collaborative public health efforts are needed to mitigate HCV transmission among this population[213].

Interestingly, we were able to study HCV-specific T cell responses during acute HCV infection in the presence of existing HIV-1 infection in four MSM infected with HIV-1. Three patients with near normal CD4+ T cell counts either resolved their HCV infection (n=1) or temporarily suppressed HCV RNA, and one patient with low CD4+ T cell had sustained high HCV RNA levels. All four patients had low HCV-specific CD8+ T cell responses and similar magnitudes of CD4+ T cell responses. Interestingly, individuals with resolved infection or temporary suppression of HCV-RNA had HCV-specific CD4+ T cell responses predominantly against nonstructural (NS) proteins[176].

HIV-infected participants of the ACS were screened for the presence of cross-reactive neutralizing activity in their serum. Cross-reactive neutralizing activity was observed in both rapid and slow progressors[214]. Longitudinal analysis revealed that the potency and breadth increased with duration of infection and correlated with CD4 counts at set point. In the first genome-wide association studies (GWA) on HIV-1 infection, single nucleotide polymorphisms (SNPs) in the HLA-C and the HCP-5 gene region have been described as major determinants in host control of HIV-1. We observed that the described SNPs were also associated with viral load and the clinical course in participants of the Amsterdam Cohort Studies[215].

The main clinical objective of cART is suppression of HIV-1 plasma viremia to below the lowest detection limit of commercial assays. In most patients on cART,

this objective is achieved and therefore, plasma viremia in these patients cannot predict the therapeutic outcome. Hence, additional markers have to be identified that are associated with the outcome of therapy in patients with fully suppressed plasma viremia. We demonstrated that the level of HIV-1 unspliced RNA in PBMC from such patients is predictive of subsequent virological rebound. So, a viral parameter measured in a patient receiving cART during a period of undetectable plasma viremia is predictive of the therapeutic outcome[216].

Steering committee: The politburo

In the 2009, the "politburo" met four times. Seventeen proposals for use of data and/or samples (serum/PBMC) were submitted to the politburo: 12 from AMC-Experimental Immunology, 1 from the AMC-Medical Microbiology, 3 from the UMCU, and 1 from researchers not affiliated with the ACS. Sixteen requests were approved, some after revision, and one request was denied.

To mark the 25th anniversary of the ACS, a successful and moving symposium for ACS participants and professionals affiliated with the ACS was held in Amsterdam, November 28, 2009.

Publications in 2009 that include ACS data

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Other publications:

The Amsterdam Cohort Studies on HIV infection and AIDS; A summary of the results 2001-2009. Heijnis & Schipper, Zaandijk, 2009; ISBN 978-90-9024893-6.

Theses in 2009 that include ACS data

Ingrid Schellens. *"Impact of HLA Class I restricted T cells on HIV-1 disease progression*". Promotor is prof dr F Miedema (UMCU), copromotores are dr J Borghans and dr D van Baarle.

M Navis. *"Cellular immunity driving HIV-1 evolution".* Promotor is prof dr H Schuitemaker (AMC). Copromotor is dr NA Kootstra (AMC).

Rogier van Gent. *"Lymphocyte dynamics in health and disease"*. Promoter is prof dr F Miedema (UMCU), copromotores are dr K Tesselaar and dr J Borghans (UMCU).

Jolanda Scherrenburg. *'T cell immunity to herpesviruses in immune disorders"*. Promoter is prof dr F Miedema (UMCU) and copromotor is dr D van Baarle (UMCU).

Maarten Rits. *"Cellular factors involved in HIV-1 replication"*. Promotor is prof dr H Schuitemaker (AMC). Copromotor is dr NA Kootstra (AMC).

Robin van Houdt. *"Molecular epidemiology of hepatitis B in the Netherlands"*. Promotor is prof dr RA Coutinho (RIVM/AMC). Copromotor is dr SM Bruisten (GGD Amsterdam).

Charlotte van den Berg. *"Hepatitis C virus epidemiology and immunology.* Promotor is prof dr RA Coutinho (RIVM/AMC). Copromotores are dr M Prins (AMC/GGD Amsterdam) and dr D van Baarle (UMCU).

Thijs van Montfort. *"Interaction of HIV-1 with dendritic cells: implications for pathogenesis"*. Promotor is prof dr B Berkhout (AMC). Copromotor is dr WA Paxton (AMC).

Daniela Bezemer. *"Impact of antiretroviral therapy on HIV-1 transmission dynamics"*. Promotores are prof dr RA Coutinho (AMC) and prof dr M Sabelis (AMC). Copromotores are dr M Prins (AMC/GGD Amsterdam) and dr F de Wolf (AMC).

K Kozaczynska. *"HIV-1 superinfection"*. Promotor is prof dr B Berkhout (AMC), copromotores are dr M Cornelissen (AMC) and dr T van der Kuyl (AMC).

9. Curaçao

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

Since 2005, Stichting HIV Monitoring (SHM) has collected data on HIV-infected patients in Curaçao. As of June 2010, a total of 673 patients had been registered; of those, 549 (82%) were still alive. Compared to last year, this is an increase of 87 patients, or 15%. Altogether, 421 (77%) patients were still in outpatient clinical care. The majority of the registered patients were men (62%) who were infected via heterosexual contact (63%) and originated from the Netherlands Antilles or Aruba (89%), where they were also infected (88%). Generally, patients were diagnosed at a late stage of infection, with a median CD4 count of 321 cells/mm^3, and thus, they started combination antiretroviral therapy (cART) below the currently recommended CD4 threshold. The frequency of monitoring, including outpatient clinical visits and measurements of CD4 counts and viral load, increased over calendar time. When starting cART, protease inhibitors appeared to be part of the majority of first-line treatment regimens, in contrast to the Netherlands, where use of protease inhibitors is usually postponed until treatment is begun with second-line regimens. Resistance patterns, however, were similar to those observed in patients treated in the Netherlands, except that resistance to non-nucleoside reverse transcriptase inhibitors was less common.

Vijf jaar geleden begon Stichting HIV Monitoring met het verzamelen van data van hiv-patiënten in Curaçao. Begin juni 2010 waren er 673 patiënten geregistreerd van wie er 594 (82%) nog in leven waren. Vergeleken met vorig jaar betekent dit een toename van 87 patiënten, oftewel 15%. In totaal waren er nog 421 (77%) patiënten in (poli-) klinische zorg. De meeste geregistreerde patiënten waren van het mannelijk geslacht (62%), waren geïnfecteerd door heteroseksueel contact (63%), waren afkomstig van de Nederlandse Antillen of Aruba (89%) en waren daar ook geïnfecteerd (88%). Over het algemeen werden patiënten pas laat in hun infectie gediagnosticeerd met een mediaan CD4-celaantal van 321 cellen/mm^3. Ook startten zij combinatietherapie onder de aanbevolen CD4-grens. De frequentie van monitoring, dat wil zeggen (poli-)klinische bezoeken en CD4- en virale-loadbepalingen, nam toe over de tijd. Proteaseremmers werden veel vaker dan in Nederland gebruikt in de eerstelijns behandelcombinatie. In Nederland wordt gebruik van proteaseremmers juist uitgesteld tot tweedelijns behandeling. Resistentiepatronen waren desondanks hetzelfde als in patiënten in Nederland, behalve dat er minder resistentie tegen non-nucleoside reverse-transcriptase remmers werd waargenomen.

Since 2005, Stichting HIV Monitoring (SHM) has collected demographic and clinical data on HIV-infected patients in follow-up at the St. Elisabeth Hospital or the Stichting Rode Kruis Bloedbank in Willemstad, the capital of Curaçao. Such an extensive monitoring and registration system is unique in a Caribbean setting. Not only has implementation of this system given more insight into the local HIV epidemic and the effect of clinical care, it has also led to an improvement in the organisation of clinical care. This special report contains a concise overview of the currently registered population. More in-depth analyses of the effect of treatment, the loss to follow-up, and the delay between testing for HIV and entering clinical care are ongoing, and first results are expected to be published soon.

HIV-infected population in care

As of June 2010, 673 HIV-infected patients were registered in Curaçao, including 549 (82%) who were still alive and 124 (18%) who had died. Compared to last year's report, in which 586 registered patients were reported, this is an increase of 87 patients, or 15%[37]. About half of the 87 newly registered patients were diagnosed before 2009.

The total follow-up since receipt of an HIV diagnosis was 4087 person-years. Of those who were assumed to still be alive because they were not registered as having died, 421, or 77%, were still being followed in clinical care and had at least one contact with the HIV health care worker on the island in the year prior to June 2010. Since the HIV prevalence in Curaçao is estimated to be 0.6% to 1.1% and since there are 140,000 inhabitants on the island, approximately 1000 individuals are currently infected with HIV, and about half of them are not in clinical care[217].

In total, 98 (15%) of the registered patients were diagnosed in or before 1995; 34 (35%) of these patients died before June 2010 (Web Appendix Table 9.1). Between 1996 and 2010, 516 patients were diagnosed, corresponding to an average of 34 patients per year (Figure 9.1).

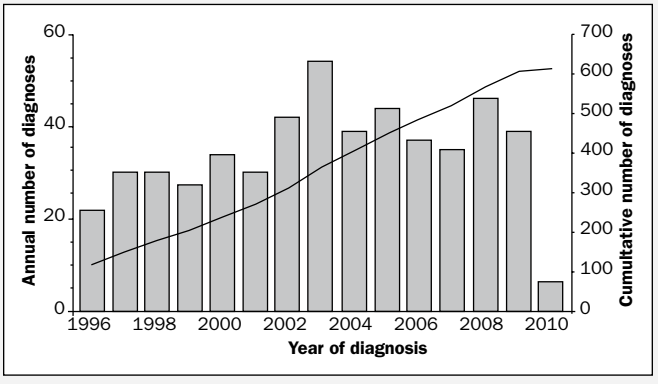

Figure 9.1: Annual and cumulative number of HIV diagnoses amongst 673 HIV-infected patients in Curaçao registered by Stichting HIV Monitoring as of June 2010. In total, 98 patients were diagnosed in or before 1995, whilst for 60 patients the year of diagnosis was unknown or not yet recorded. Bars: annual number of diagnoses; line: cumulative number of diagnoses since the start of the HIV epidemic.

The majority of the registered patients were men who originated from the Netherlands Antilles or Aruba and reported being infected via heterosexual contact (Table 9.1). The median age at diagnosis was 38 years, and at start of combination antiretroviral therapy (cART) it was 42 years.

Table 9.1: Characteristics of the HIV-infected population in Curaçao registered by Stichting HIV Monitoring as of June 2010.

	Alive, N=549		Deceased, N=124		Total, N=673	
	N/ median	**%/IQR**	**N/ median**	**%/IQR**	**N/ median**	**%/IQR**
Gender, male	330	60	90	73	420	62
Transmission						
MSM	103	19	14	11	117	17
Heterosexual	374	68	78	63	452	67
Other/unknown	72	13	32	26	104	15
Country of birth						
Antilles	394	72	110	89	504	75
Haiti	67	12	7	6	74	11
Dominican Republic	37	7	4	3	41	6
Treated with cART	377	69	72	58	449	67
Diagnosis						
CD4 (cells/mm^3)	335	119–520	97	40–329	321	98–499
RNA (log_{10} copies/ml)	4.4	3.8–5.1	4.9	3.5–5.6	4.4	3.7–5.1
Age (years)	38	30–46	40	32–53	38	31–47
AIDS	34	6	25	20	59	9
Time to cART	1.5	0.3–4.9	0.9	0.2–3.2	1.4	0.3–4.8
Follow-up (years)	5.3	1.8–10.3	2.5	0.3–6.3	4.8	1.4–9.6
Start of cART						
CD4 (cells/mm^3)	151	51–248	60	8–153	132	45–244
RNA (log_{10} copies/ml)	5.0	4.4–5.5	4.9	4.3–5.6	5.0	4.4–5.5
Age (years)	41	34–49	44	37–56	42	35–50
AIDS	58	11	37	30	95	14
Follow-up (years)	4.2	1.6–8.4	1.9	0.3–4.5	3.7	1.4–7.7
Present (June 2010)						
CD4 (cells/mm^3)	414	275–583	-	-	414	275–583
RNA <500 copies/ml	272	60[a]	-	-	272	60[a]
Age (years)	46	39–53	-	-	46	39–53

Legend: N=number; IQR=interquartile range; MSM=men having sex with men; cART=combination antiretroviral therapy; [a]percentage of 456 patients with a viral load measurements.

Children and adolescents

At the time of diagnosis, 11 patients were younger than 13 years of age ('children') and 12 were between 13 and 18 years ('adolescents'). Most of the children, 9 in total, were infected by mother-to-child transmission (MTCT), and 6 were diagnosed prior to 1995. In 1995, universal testing of pregnant women was introduced in Curaçao, and only 5 HIV-infected children were diagnosed afterwards, of whom 3 were infected by MTCT. In recent years, there have been approximately 5 pregnancies annually in HIV-infected women. Adolescents were mainly infected via heterosexual (8 patients) or homosexual (3 patients) contact. Over the years, 14 children and adolescents have aged and are now registered as adults. As of June 2010, there were still 4 children and 5 adolescent patients, but data were available in the preceding year for none of the children and for only 2 of the adolescents.

Country of infection

For 389 patients, or 58% of the registered population, the most likely country of infection was known. The majority, 341 patients, or 88% of those with a known country of infection, were infected in the Netherlands Antilles or Aruba. Eighteen (18) patients were reportedly infected in Haiti or the Dominican Republic and 16 patients in the Netherlands. Amongst the 311 patients born in the Netherlands Antilles or Aruba, 295 (95%) were also infected there. The mainly Caribbean and European origin of the HIV infection in Curaçao was apparent from the HIV-1 subtype distribution. The subtype was known for 186 (28%) patients, and all but 2 were infected with subtype B, which is the most prevalent subtype in the Caribbean and the Netherlands amongst patients of non-African origin.

Late presentation and start of treatment

Generally, patients were diagnosed at a rather late stage of the infection as was shown by the CD4 cell count at diagnosis, which was 321 cells/mm^3. At the start of cART, median CD4 cell counts were 132 cells/mm^3, which is well below the threshold of 200 cells/mm^3 at which treatment definitely should be started (Figure 9.2). However, only 14% of the patients had experienced an AIDS-defining disease by the time treatment was started.

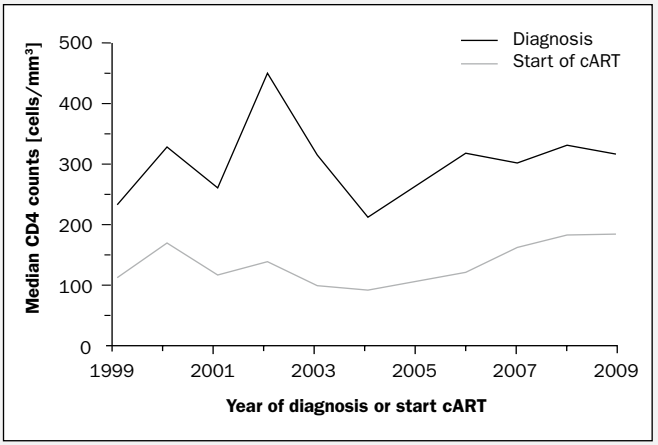

Figure 9.2: Median CD4 T-cell counts at HIV diagnosis and at the start of combination antiretroviral therapy (cART) amongst HIV-infected patients in Curaçao. At the time of diagnosis, median CD4 cell counts were 321 (interquartile range [IQR], 98-499) cells/mm^3, whilst at the start of cART, CD4 cell counts were 132 (IQR, 45–244) cells/mm^3. There were no statistically significant changes over time.

Late presentation was not the only cause of a late start of treatment. In 154 patients who had a CD4 count measured both at HIV diagnosis and at the start of treatment and who were diagnosed in 1996 or later, when cART was available and could have been started as the first treatment option, the median CD4 cell count was 228 (interquartile range [IQR], 64–433) cells/mm^3 at diagnosis and 138 (51–260) cells/mm^3 at the start of cART. Patients who presented with CD4 cell counts below 200 cells/mm^3 did not delay the start of treatment; 90% of these 74 patients started cART within 6 months of HIV diagnosis. However, of the 80 patients with more than 200 CD4 cells/mm^3 at diagnosis, 23 (29%) started with CD4 cell counts below the threshold level.

Patient monitoring

A possible reason for starting treatment at less than optimal CD4 counts may be infrequent patient monitoring. This, however, seems not to be the situation in Curaçao. Between 2002 and 2010, on average, 2.0 immunology measurements were performed annually per patient, with an increase from 1.8 in 2002 to 2.5 in 2009. During the same period, viral load was monitored 1.8 times per year, and it had increased from 1.6 in 2002 to 2.5 in 2009. Finally, the frequency of clinical visits was, on average, 2.3 per year, with 2.0 visits per year in 2002-2006 increasing to 3.2 in 2009. The increases are possibly related to the introduction of monitoring of local viral load and immunology. Previously, blood samples were sent to laboratories in the Netherlands, which may have negatively affected monitoring frequency.

Combination treatment

In total, 449 (67%) patients started cART. Of the 260 patients who did so between 2004 and 2010, 68% started with a combination of combivir and ritonavir-boosted lopinavir and 16% with a combination of truvada and efavirenz. The use of protease inhibitors in the first-line treatment regimen is remarkable, since patients in the Netherlands usually start with a protease inhibitor-sparing regimen. One reason for the more frequent use of lopinavir in Curaçao may be that lopinavir is available locally, whilst there are occasional disruptions in supply of some of the other antiretroviral drugs to the local pharmacy. However, over time, there have been clear shifts in the prescription of treatment regimens, and since 2008, the combination of truvada and efavirenz has become more popular (Figure 9.3).

Treatment outcome

Of the 415 patients who started cART when they were antiretroviral therapy-naive, CD4 cell counts for 51% increased by at least 150 cells/mm^3 during the first 6 months of treatment; after 2 years, this proportion had increased to 82% (Figure 9.4A). Eighty-one percent of the

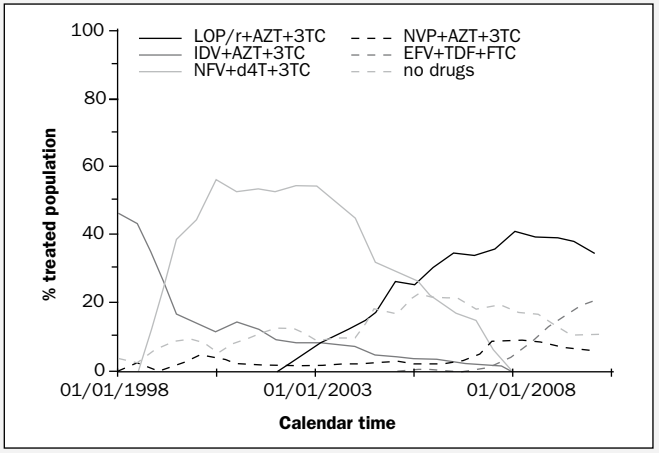

Figure 9.3: Percentage of patients treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. The proportion of patients using IDV+AZT+3TC decreased from 46% in 1998 to almost 0% after 2007. This decrease was counterbalanced by an increase in the proportion of patients treated with NFV+d4T+3TC. Since 2002, a combination of LOP/r+AZT+3TC has been used increasingly, and 35% of the patients on cART were on this regimen at the beginning of 2010. At that time, 6% of the patients used a combination of NVP+AZT+3TC, and 21% were on a combination of EFV+TDF+FTC. After 2004, 10 to 20% of the patients who ever started cART were (temporarily) not being treated.
Legend: AZT=zidovudine; 3TC=lamivudine; d4T=stavudine; IDV=indinavir; LOP/r=ritonavir-boosted lopinavir; NFV=nelfinavir; NVP=nevirapine; EFV=efavirenz; TDF=tenofovir; FTC=emtricitabine.

patients achieved a viral load level below 500 copies/ml within 6 months of starting treatment (Figure 9.4B). In a subgroup of 308 patients who were still in follow-up as of June 2010, CD4 counts appeared to plateau at approximately 400 cells/mm^3 after 2 years of cART (Figure 9.4C). The proportion of patients with a viral load below 500 copies/ml, however, decreased from 71% after 48 weeks to approximately 60% after 5 years of treatment, indicating a decreasing ability to suppress viral load (Figure 9.4D).

Mortality and survival

Of the group of 585 patients who were still alive as of 1 January 2005 or were diagnosed after that time, 48 patients had died by June 2010. Taking into account loss to follow-up, we found that the survival probability after 4 years of

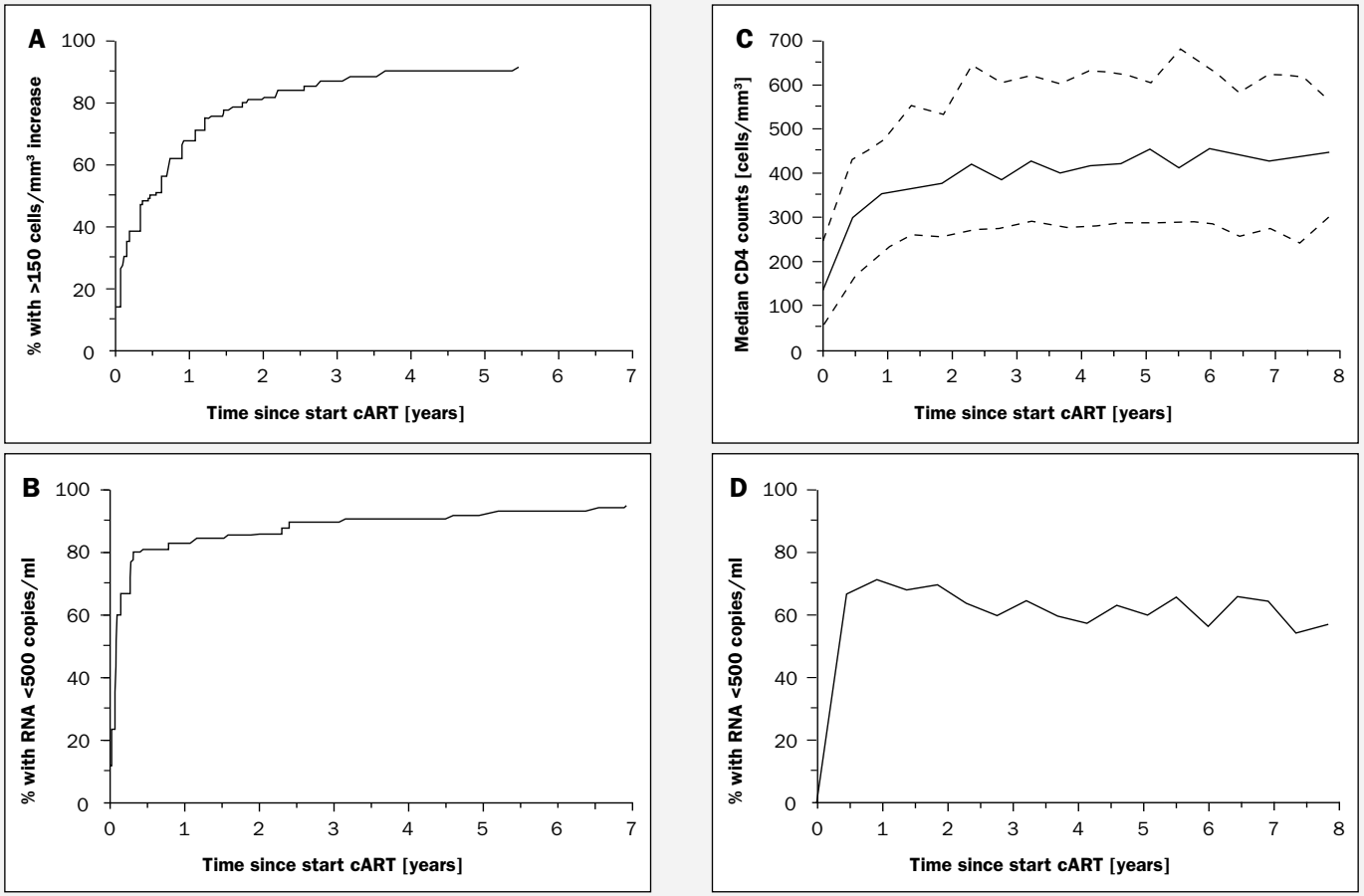

Figure 9.4: (A) The proportion of patients with a CD4 cell increase of more than 150 cells/mm^3 after the start of combination antiretroviral therapy (cART) was 51% after 6 months and increased to 82% after 2 years, whilst (B) 81% of patients reached, but did not necessarily maintain, HIV RNA levels below 500 copies/ml within 6 months. (C) Median CD4 cell counts (solid line; dotted line: IQR) increased from 151 (IQR, 55–247) cells/mm^3 at the start of cART to 299 (IQR, 161–241) cells/mm^3 after 24 weeks and stabilised at approximately 400 cells/mm^3 after 2 years. (D) The proportion of patients with HIV RNA <500 copies/ml was 67% after 24 weeks and 71% after 48 weeks, and it gradually declined to between 50% and 60% after 5 years. In all figures, only patients who were previously antiretroviral therapy-naive are considered; (A) and (B) represent time-to-event analyses; (C) and (D) include patients who were still in follow-up as of June 2010.

follow-up was 91%. Altogether, 226 patients started cART in or after 2005, and out of this group, 20 patients had died, corresponding to a 4-year survival probability of 87%.

Drug resistance

Since the proportion of patients with viral load suppression declined over time, it may be expected that resistance to one or more antiretroviral drugs developed in some patients. In total, 115 patients were examined for resistance by a genotypic characterisation of the RT and protease gene of the HIV virus. In 66 (57%) of these patients, high-level resistance to at least one antiretroviral drug was found, according to an interpretation algorithm developed by Stanford University[161]. In general, resistance patterns

were similar to those observed in patients treated in the Netherlands, except that resistance to non-nucleoside RT inhibitors found in less than 25% of patients was less common than in the Netherlands. Presumably, this is a consequence of the less widespread use of these drugs in Curaçao.

Infection with resistant virus

Transmission of resistant virus to uninfected individuals was examined in 52 patients who had a genotypic sequence within 1 year after diagnosis but before the start of treatment. Resistance-associated mutations were found in three patients, but for one patient the pre-treatment sample may have been confused with a sample having resistance mutations that was obtained after the start of treatment. Only one of the patients reported having been infected in the Netherlands Antilles. Hence, infection with a resistant virus strain and the consequent preclusion of certain drugs from the antiretroviral armoury does not seem to be a major problem currently.

Conclusion

In conclusion, the quality of monitoring and treatment of HIV-infected patients in Curaçao is improving, but it has not quite reached levels comparable to those in the Netherlands. This is due in part to limited financial resources and to the fact that there are no HIV nurses and only one HIV health care worker on the entire island. As a consequence, patients essentially have to manage the non-medical aspects of their infection alone or with their family or friends. There is still a taboo regarding HIV, however, and patient care is hampered by the stigma surrounding the disease. Presently, efforts are ongoing to appoint a designated HIV nurse, and the necessary resources will be reserved in the National Strategic Plan for the period 2010 to 2014.

list of tables & figures

Web Appendix list of tables and figures

An appendix containing tables and figures supplementary to this report can be found on the SHM website, www.hiv-monitoring.nl.

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The effect of combined antiretroviral therapy on the overall mortality of HIV-infected individuals.
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Life expectancy of recently diagnosed asymptomatic HIV-infected patients approaches that of uninfected individuals
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Antiretroviral treatment as a strategy for controlling the HIV epidemic amongst men who have sex with men
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Mission
Stichting HIV Monitoring (SHM) 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 HIV 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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