Monitoring Report 2011

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

HIV Monitoring

Contributing to the quality of HIV care

Stichting HIV Monitoring (SHM), the Dutch HIV monitoring foundation, was founded in 2001. Based in Amsterdam, SHM was 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:
To further the knowledge and understanding of the epidemiology and the course of the treated and untreated HIV infection.

www.hiv-monitoring.nl

HIV Monitoring

Colophon

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and Frank de Wolf
on behalf of
the Netherlands
collaborative
HIV treatment
centres

HIV Treatment Centres

The monitoring of HIV-infected adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 25 health institutes that are acknowledged by the Dutch Minister of Health, Welfare and Sport as HIV treatment centres or subcentres. In addition, HIV-infected children and adolescents are monitored in four institutes that are recognized as paediatric HIV treatment centres.

In 2011 the following health institutes were involved as (sub)centres for adult HIV care (in alphabetical order of town):

1. Medisch Centrum Alkmaar — Alkmaar
2. Flevoziekenhuis — Almere
3. Academic Medical Centre of the University of Amsterdam — Amsterdam
4. Onze Lieve Vrouwe Gasthuis — Amsterdam
5. Sint Lucas Andreas Ziekenhuis — Amsterdam
6. Slotervaart Ziekenhuis — Amsterdam
7. Stichting Medisch Centrum Jan van Goyen — Amsterdam
8. VU Medisch Centrum — Amsterdam
9. Ziekenhuis Rijnstate — Arnhem
10. HagaZiekenhuis (location Leyenburg) — Den Haag
11. Medisch Centrum Haaglanden (location Westeinde) — Den Haag
12. Catharina Ziekenhuis — Eindhoven
13. Medisch Spectrum Twente — Enschede
14. Universitair Medisch Centrum Groningen — Groningen
15. Kennemer Gasthuis — Haarlem
16. Medisch Centrum Leeuwarden — Leeuwarden
17. Leids Universitair Medisch Centrum — Leiden
18. Academisch Ziekenhuis Maastricht — Maastricht
19. Universitair Medisch Centrum Sint Radboud — Nijmegen
20. Erasmus Medisch Centrum — Rotterdam
21. Maasstad Ziekenhuis — Rotterdam
22. St Elisabeth Ziekenhuis — Tilburg
23. Universitair Medisch Centrum Utrecht — Utrecht
24. Admiraal De Ruyter Ziekenhuis — Vlissingen
25. Isala Klinieken (location Sophia) — Zwolle

Centres for the treatment and monitoring of paediatric HIV and AIDS were:

A. Emma Kinderziekenhuis, AMC-UvA — Amsterdam
B. Beatrix Kinderkliniek, UMCG — Groningen
C. Sophia Kinderziekenhuis, EMC — Rotterdam
D. Wilhelmina Kinderziekenhuis, UMCU — Utrecht


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Introduction

Each year Stichting HIV Monitoring (SHM) publishes a Monitoring Report on human immunodeficiency virus (HIV) infection in the Netherlands. This report provides a comprehensive review of trends over time in the HIV epidemic and the effect of treatment. Trends we report this year are best characterised as cautiously optimistic. A larger number of individuals registered with HIV is receiving combination antiretroviral treatment (cART), with a larger proportion reaching viral suppression to a level below the assay threshold for a longer period of time and experiencing CD4-cell increases higher than ever before. Moreover, it appears that there is no further increase in the annual number of new diagnoses. All in all, these are promising results achieved through the hard work of professionals in HIV care and prevention and in basic and applied HIV research.

However, the success of cART is a fragile balance; we do not know how long it will hold and at what expense. Although the proportion of patients with virologic failure is relatively low, a large proportion of those with failure have resistance to the drugs used. With the increasing number of individuals treated, this implies a substantial increase in the absolute number of cases showing resistance. cART strategies so far have not yielded annual mortality rates similar to those of age- and gender-matched uninfected individuals. AIDS is still diagnosed, although at a lower rate than in the past, and remains a primary cause of death. Serious non-AIDS-related diseases have become a major challenge in the clinical management of HIV-infected individuals and are now more frequently registered as a cause of death. The infected population not only has become older, but has perhaps continued to age faster than the uninfected population.

Since the last SHM monitoring report, the registered HIV-infected population has increased by 1408 cases. We estimate the number of new diagnoses in MSM at approximately 750 in 2009 and anticipate the same in 2010. In heterosexuals we estimate approximately 300 cases annually in the last few years. Between 2003 and 2008 we report a steady increase of new infections. The increase in the cases registered reflects the increase in the number of individuals tested and shows the success of new HIV testing policies. The increase of the number of new diagnoses over that same period is paralleled by reports on increasing transmission risk behaviour amongst homosexual men. It remains to be seen if a reversed relationship can be seen for the stabilisation we report this year for the number of new infections in 2009 and 2010.

This year marks the 10th anniversary of SHM, which was founded in 2001 as a result of the successful AIDS Therapy Evaluation in the Netherlands project (ATHENA). To mark our 10th anniversary and to emphasise the ongoing changes taking place at SHM, we have introduced a new logo and corporate identity this year. The Monitoring Report 2011 departs from the square shape of previous years and is now presented in a more compact, reader-friendly format. For the first time this year, we are also publishing a Dutch summary of the report. This summary is available in hard copy and can also be downloaded from the SHM website, www.hiv-monitoring.nl.

As of 2002, SHM was officially charged by the Dutch Minister of Health, Welfare and Sport to monitor the HIV epidemic and the quality of HIV care in the Netherlands. Through the collection and maintenance of anonymous data from HIV patients throughout the country, our work contributes significantly to the knowledge of HIV and enables treating physicians to assess and improve patient care. As such, our target groups are primarily the HIV-treating physicians who work in the 25 hospitals throughout the country officially acknowledged as HIV treatment centres. Treating physicians have access to the data provided by their treatment centre to SHM, and when research proposals are approved, they can access all data from all centres. Other HIV research groups can also access the data on approval of research proposals. Research conducted by SHM in collaboration with national or international research groups results in tangible advice geared to medical professionals, patients, government and healthcare at large.

The Monitoring Report, after the summary and recommendations, includes a section on the HIV monitoring programme, with detailed descriptions of the findings on the number of newly registered HIV diagnoses, the changes over time in the characteristics of the infected population at the time of diagnosis, morbidity and mortality in the HIV-infected population, the effects of cART, and the development of resistance to antiretroviral drugs. Also in this section is information on HIV infection amongst pregnant women and children, as well as co-infection with hepatitis B and hepatitis C virus.

The Special Reports section includes a chapter on the results from the Amsterdam Cohort Studies and one on HIV in Curaçao. A web-based Appendix with supplementary tables and figures can be found on our website, www.hiv-monitoring.nl.

I would like to thank the HIV-treating physicians, HIV nurse-consultants and the staffs of the diagnostic laboratories and facilities in the HIV treatment centres, along with the data collecting and monitoring staff both within and outside SHM, for their ongoing efforts and contribution. I would also like to thank the HIV patients who provide data to SHM for their help and contribution. Through the contributions of professionals and patients, we continue to gain insight into HIV and HIV treatment that ultimately leads to improved care for people with HIV living in the Netherlands.

Prof. Frank de Wolf MD

Director, Stichting HIV Monitoring

Summary & recommendations

Frank de Wolf

Earlier diagnosis, earlier start of treatment

Of the 18,735 patients with an HIV-1 infection and a known date of diagnosis registered by Stichting HIV Monitoring (SHM) as per mid 2011, 14,874 started cART between January 1995 and December 2010 and had follow-up available after therapy initiation. In recent years, diagnosis and antiretroviral treatment of HIV has entered a new phase reflected in several trends. Over time, patients with HIV are being diagnosed at an earlier stage of infection with higher CD4-cell counts, indicating a less impaired immune system. Half of the population in 1996 had CD4-cell counts of 250 cells/mm^3 or higher at the time of diagnosis, whereas half the population in 2010 had 350 cells/mm^3 or higher.

Patients are starting combination antiretroviral therapy (cART) earlier, as is confirmed by the increase in median CD4-cell numbers amongst the 14,874 patients who started cART between January 1995 and December 2010. Half of the patients who started cART between 1995 and 2000 had CD4 counts of 200 cells/mm^3 or higher, and similar counts (i.e., 190 cells/mm^3) were measured for those who started cART between 2000 and 2005. Thereafter, median counts at the start of cART rose to 240 cells/mm^3 between 2005 and 2009 and then to 300 cells/mm^3 in 2010.

High levels of HIV suppression

Suppression of HIV production occurred in 58.3% of patients within 6 months after commencing therapy, for 72.3% within 9 months and for 80.0% within 12 months. Over calendar time, suppression of HIV to below 50 copies/ml after 9 months of cART was achieved in 67.8% of patients starting between 1999 and 2001; it increased to 73.5% for those starting between 2002 and 2004 and to 75.2% for those starting between 2005 and 2007. Between 2008 and 2010 the response seemingly declined to 72.3%, due to the introduction of a new laboratory assay for HIV RNA determination. When the results of those tested with this new assay were excluded, 83.3% of the patients reached the threshold of 50 copies/ml after nine months of cART.

Sustained suppression measured from 36 weeks up to a maximum of nine years of cART, was achieved for 82% to 84%. In cases of uninterrupted cART, figures rose between 88% and 90%. According to model estimates, nearly normal CD4-cell counts are reached after virologically successful cART. For those starting cART with 50, 50-200, 200-350 and 350-500 CD4-cells/mm^3, the mean CD4-cell count eight years later were 485 (95% confidence interval [CI], 457-516), 551 (95% CI, 530-574), 665 (95% CI, 637-694) and 800 cells/mm^3 (95% CI, 746-856), respectively.

Declining HIV-related disease and death

HIV-related illness and AIDS are less frequent and HIV/AIDS-related death has fallen significantly. The overall mortality rate in the registered population is 12.9 (95% CI, 12.3-13.5) per 1000 person-years, and it declined over time to 8.9 (95% CI, 7.3-10.6) in 2010. The incidence of AIDS has decreased sharply to between 10 and 20 cases per 1000 patients per year in recent years, although the incidence in 2010 will be approximately 10% higher, when we take the backlog in the registration of AIDS into account.

The mortality rate after the start of cART substantially decreased over calendar time to 9.8 (95% CI, 8.1-11.8) per 1000 person-years in 2010. Also, the incidence of AIDS decreased dramatically to 8.9 per 1000 person-years in 2010.

Despite its decline, the mortality rate is still well above that which would be expected in the same group of individuals if they were not infected with HIV. The excess mortality rate can be explained in part by patients who already had AIDS at the time of their HIV diagnosis. In addition, it may be due to the effects of HIV infection and the use of cART, as well as to factors related to family and lifestyle. However, a subgroup of recently diagnosed, effectively treated patients had a life expectancy similar to the HIV-negative population of the Netherlands. This suggests that effective cART strategies may enable HIV-positive patients to achieve low levels of mortality similar to those in the general population.

The median time between HIV-1 diagnosis and death in patients who died after the start of cART increased over calendar time from 3.9 years (interquartile range [IQR], 2.7–7.4) in 1996 to 8.6 years (IQR, 5.1–15.1) in 2010. Also, the median time between the start of cART and death increased from 0.3 years (IQR, 0.2–0.4) in 1996 to 6.6 years (IQR, 2.1–11.0) in 2010, as did the median age at death from 43 years (IQR, 37–50) in 1996 to 52 years (IQR, 45–63) in 2010. In addition, last CD4 counts before death rose from 30 cells/mm^3 (IQR, 10–80) in 1996 to 298 cells/mm^3 (IQR, 150–489) in 2010. In other words, HIV-1-positive patients are living longer with HIV and are using cART longer.

Changing causes of death

Causes of death in the HIV-infected population are changing. Amongst 249 patients who died before the start of cART, AIDS was the most common cause of death. Causes of death registered after the start of cART were AIDS in 34% of cases, non-AIDS-defining malignancy in 14%, cardiovascular diseases in 7%, non-natural causes in 5% and other or unknown causes in 40%. Hence, approximately two-thirds of people who were HIV-1-positive and died after starting cART did not die of AIDS, but of other causes. A total of 114 patients died in 2010. Of these, 12 (11%) died of AIDS, 24 (21%) of a non-AIDS-defining malignancy, 8 (7%) of a non-AIDS-defining infection, 5 (4%) of liver failure, 3 (3%) of pulmonary-related causes, 3 (3%) non-natural death, 2 (2%) of cardiovascular disease, 2 (2%) of substance abuse and 64 (56%) of other, unknown or unclassifiable causes.

The median last known CD4 counts are low for all groups of patients, but particularly for those who died of AIDS-defining causes. This implies that HIV infection may play a role in mortality, even if AIDS is not the immediate cause of death. It confirms findings by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study, in which death due to liver disease, non-AIDS malignancies, cardiovascular disease and other non-AIDS-related causes were all associated with lower last known CD4-cell counts, albeit less strongly than death due to AIDS.

Declining AIDS, increasing non-AIDS disease

In total, 2087 of the 14,874 patients experienced at least one AIDS-defining event during 86,990 person-years of follow-up after starting cART, resulting in an incidence of first AIDS-defining events after the start of cART of 24.0 (95% CI, 23.0–25.0) per 1000 person-years of follow-up. This incidence fell significantly from 175.4 in 1996 to 14.2 in 2010 ($p<0.0001$), declining rapidly between 1996 and 1998 and more slowly between 1998 and 2011.

Serious non-AIDS-defining disease has been registered for a total of 1658 patients during 67,211 person-years of follow-up. Hence, the incidence of serious non-AIDS-defining diseases after the start of cART was 23.5 (95% CI, 23.5–25.9) per 1000 person-years of follow-up. This incidence rose significantly from 21.1 in 2002 to 29.9 in 2010 ($p=0.01$). A heightened incidence of serious non-AIDS-defining diseases is associated with patients being older ($p<0.0001$), being antiretroviral-therapy experienced at the start of cART ($p<0.0001$), having a lower CD4 count ($p<0.0001$), being positive for hepatitis B ($p=0.0019$) or C ($p<0.0001$) virus, having a longer time between HIV-1 diagnosis and the start of cART ($p=0.0047$) and being either less than a year or more than 11 years in follow-up ($p<0.0001$).

When each individual serious non-AIDS-related disease registered in the population after start of cART was considered, it appeared that the incidence of renal disease, osteoporosis and non-AIDS malignancy rose over calendar time between the start of monitoring, which varied from 1998 to 2002, and 2010. The incidence, however, of liver disease, diabetes mellitus, myocardial infarction and stroke did not rise. All serious non-AIDS-related diseases are associated with older age. Independently, low CD4-cell counts are associated with renal disease, liver disease, diabetes mellitus, stroke and non-AIDS-related malignancy, but not with myocardial infarction and osteoporosis. A positive test for HBV or HCV is independently associated with liver disease, as is a longer time of exposure to HIV before starting cART. Gender is associated with only myocardial infarction (males) and osteoporosis (females).

According to age and gender, the incidence of diabetes mellitus, myocardial infarction, osteoporosis and stroke in patients on cART is higher than in the general population of the Netherlands. This is also true for non-AIDS-related malignancies, although the difference with these cancers is restricted to the male HIV-infected population on cART. Research has begun to further detail the possible association with HIV-infection itself, the use of cART and patient immune status, as well as differences in lifestyle factors reported in association with these diseases.

In a study of the possible direct effect of HIV on non-AIDS-related diseases, we found that the cumulative number of years spent with periods of HIV RNA levels of 1000 copies/ml or higher was associated only with non-AIDS-related mortality, independent of latest CD4-cell counts. However, when we excluded the viral load measurements taken less than six months prior to the end of follow-up from the calculation of exposure time, the effect of the cumulative number of years of exposure to plasma levels of 1000 HIV RNA copies/ml or more disappeared, indicating that the effect of exposure time to HIV RNA levels of 1000 copies/ml or higher may be partly driven by patients stopping antiretroviral medication during end-stage disease.

The time between HIV diagnosis and cumulative time after the start of cART with periods of viraemia, when taken together, can be seen as a marker of the cumulative exposure to HIV viraemia; albeit, an imperfect one, because the true moment of infection cannot be reliably estimated for most patients. Viraemia copy-years may be a more refined measure of cumulative plasma HIV RNA exposure than exposure time to plasma levels of more than 1000 HIV RNA copies/ml. Viraemia copy-years have been associated with time to all-cause mortality, also independent of CD4-cell counts. More research is needed to study the independent effects of long-term viraemia, exposure to antiretroviral therapy medication, biomarkers of inflammation and immune activation on non-AIDS-related morbidity and mortality.

HBV/HCV co-infections

Chronic hepatitis B (HBV) and hepatitis C (HCV) infections are associated with progression to chronic liver disease. Amongst the HIV-infected individuals screened for viral hepatitis, the prevalence was 8% for HBV and 12% for HCV co-infection. The majority of co-infected patients were homosexual men, and amongst them, the number of new HCV diagnoses has significantly increased over time. Homosexual men are currently the largest group of individuals co-infected with HCV.

Of the co-infected patients, 59% of patients with HIV/HBV and 27% of patients with HIV/HCV received treatment for the co-infection. Anti-HBV treatment is available as part of anti-HIV treatment, and 48% to 65% of the co-infected patients showed a reduction of HBV DNA. Patients with HCV were treated with peg-IFN in combination with ribavirin, resulting in an overall sustained virologic response in 45%. Compared to HIV mono-infected patients, the risk of death was not increased amongst those with co-infection. However, both HBV and HCV co-infection were strongly associated with progression to severe chronic liver disease.

Treatment of HBV, and especially HCV, co-infections is not yet optimal, although direct-acting antiviral drugs exist for HBV and have recently become available for HCV. Hence, prevention of progression to severe chronic liver disease may become feasible, and monitoring of chronic HBV and HCV infection is currently performed by SHM for the HIV co-infected population.

Limited virological failure and resistance

Although a high percentage of patients on cART currently achieve sustained suppression of HIV viral load, a small group achieve only incomplete suppression, which may be a marker of inadequate adherence to therapy and may herald the presence of drug resistance. Incomplete suppression, or virologic failure, is observed in 5% of the treated patients annually.

In approximately 50% to 80% of patients experiencing virologic failure, resistance to non-nucleoside reverse transcriptase (RT) inhibitors and to the nucleoside RT inhibitors lamivudine and emtricitabine has been found. Resistance to other nucleoside RT inhibitors and protease inhibitors has been found in only a substantial proportion of patients previously treated with non-cART regimens. Altogether, 10% of patients currently in follow-up are resistant to at least one antiretroviral drug. This proportion is probably an underestimation, since results of genotypic resistance measurements are obtained in less than one third of patients with virologic failure.

Evidence of transmission of resistant virus is found in less than 5% of patients, indicating that infections from the reservoir of treated patients with resistance are relatively rare and that new infections occur mainly via untreated HIV-infected individuals who may not yet be aware of their infection.

cART and the HIV epidemic

Since the 1990s, the annual number of diagnoses amongst MSM steadily increased to just above 800 in 2008. The registered number of diagnoses in 2009 and 2010 was, however, considerably lower than in 2008. In part, this lower number is the result of a backlog in the registration of HIV cases due to the visit-based data collection by SHM. However, even when this backlog is taken into account, the expected number of diagnoses in these years would be approximately only 750, which is lower than in 2008, but comparable to that in 2007.

In the heterosexual population, the annual number of diagnoses reached a maximum around 2004 and then has declined to approximately 300 cases annually in recent years. When a backlog in registration was considered, the number of diagnoses appeared not to decrease any further in 2009 and 2010.

Injecting drug use is rarely reported any longer as the most probable mode of transmission, which reflects the decreasing popularity of injecting drugs since the 1980s. Also, needle exchange programmes and easily accessible dispensing of methadone has contributed greatly to a reduction in the number of new infections in this group.

Hence, evidence is accumulating that the increasing trend in the number of new diagnoses amongst men who have sex with men (MSM) has halted. Alternatively, 2007 and 2008 may be years with an excess of new diagnoses, which caused a rise above the long-term trend because of the introduction of opt-out testing for HIV at major sexually transmitted infection (STI) clinics at about that time. It is of interest that the proportion of recent infections amongst the new diagnoses has increased.

The increase in CD4 counts at diagnosis and the ensuing decrease in proportion of late diagnoses suggests that patients are testing positive for HIV increasingly earlier in the course of their infection. This earlier diagnosis is also apparent in the observed increase from 10% in 1996 to 37% in 2010 in the proportion of MSM who were diagnosed with a recent infection (defined as 1.5 years, at most, between the last negative HIV test and the first positive test). Diagnosis with a recent infection was less common in older MSM. Amongst the homosexuals diagnosed in 2008 or later, 48% of the diagnosed HIV infections were classified as recent amongst those aged 18 to 24 years, but only 24% were recent infections in those aged 55 years or older. Also, the proportion of recent infections amongst heterosexuals appeared to increase, but to a more moderate extent (5% in 1996 to 10% in 2010).

As may be expected, median CD4 counts in those diagnosed with a recent infection were high, 500 (370-670) cells/mm^3 in homosexual men, and they were slightly lower, 450 (284-650) cells/mm^3, in heterosexual men and women.

Since the proportion of recent infections, as well as CD4 counts at diagnosis, has increased amongst those diagnosed with HIV, testing for HIV has apparently become more common.

Decreasing late presenters and start of treatment

Overall, 56% of the patients were late presenters, i.e., individuals either presenting for care with a CD4-cell count below 350 cells/mm^3 or presenting with an AIDS-defining event regardless of the CD4 count. In recent years, between 10% and 15% of the patients already had AIDS at the time of diagnosis.

Although the proportion of late presenters has decreased over time, in 2010 44% of MSM, 68% of heterosexual men, and 62% of heterosexual women were still diagnosed late in the course of their infection. Moreover, in 2010, amongst homosexuals and possibly heterosexual men, there appeared to be an upswing in the proportion with late presentation. Similar patterns were observed in the proportion of patients presenting for care with advanced HIV disease.

Amongst heterosexuals who had an HIV diagnosis in 2008 or later, patients of sub-Saharan African origin more often presented with a late-stage infection (73%) compared to those of Dutch origin (56%). Late presentation was also more common in patients diagnosed at older ages.

Late presentation was in part responsible for the late start of treatment. In patients who were diagnosed in 2009 or later with CD4 counts below 350 cells/mm^3 and who were thus eligible for treatment, there was almost no delay between their HIV diagnosis and start of treatment. Within three months of their HIV diagnosis, 75% of these patients had started treatment, and after one year, 93% had done so. For those who had more than 350 CD4-cells/mm^3 at diagnosis, CD4 counts at the start of treatment were 370 (IQR, 310-480) cells/mm^3, with 62% of the patients starting in time.

In recent years, cART has been started increasingly earlier in the course of HIV infection as evidenced by higher CD4 counts at the start of treatment since the mid-2000s. In 2010, median CD4 counts at the start of treatment were 290 (IQR, 173-360) cells/mm^3. Hence, more than 25% of the HIV-infected patients started treatment according to the current guidelines, which recommend starting before CD4 counts cross the threshold of 350 cells/mm^3. However, a large group of patients still began treatment with CD4 counts below 200 cells/mm^3, which is considered a late start.

Current first-line cART combinations

In 2010 and 2011, 73% of all first-line cART regimens for therapy-naive patients included a combination of tenofovir/emtricitabine and efavirenz, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir. This is in accordance with the current guidelines. An additional 10% of the regimens were a combination of tenofovir/emtricitabine and nevirapine; 17% of the patients started other, most likely individual-based, combinations.

Dutch guidelines do not recommend raltegravir as part of the first-line regimen, because potential long-term side-effects of raltegravir have been unexplored. More importantly, raltegravir is a twice-daily drug, whereas national guidelines favour once-daily regimens. Consequently, only 1% of those starting cART, or 14 patients in total, started this combination.

Conclusion & Recommendations

The health and life expectancy of individuals infected with HIV have improved substantially. That is largely the result of highly effective cART, which enables improved levels of suppression of HIV production for a prolonged period of time.

Improved testing policies now give people at risk the opportunity to be regularly checked for HIV, and an increasing number are being tested. Consequently, when testing is positive, people are still in an early phase of infection and can be treated earlier. This year's report shows the continuing increase in the number of infected individuals who start treatment early.

People with HIV being treated early on have an improved long-term immune response to cART, reaching higher and more often nearly normal CD4-cell counts.

Current guidelines for the start of cART have resulted in a high level of evidence-based standardised combinations of first-line antiretroviral drugs. Once therapy is begun, individuals remain on their first-line regimen for a longer time, which indicates fewer side effects and less drug toxicity. It also points to the regular and well managed follow-up of patients on therapy. A relatively low annual percentage (5%) of the individuals on cART experience virologic failure. A high percentage of these, however, have HIV resistant to one or more of the drugs used. Hence, transmission of resistant HIV is limited. However, figures are less reliable since systematic resistance measurement is in urgent need of improvement.

As of mid-2011, 18,735 patients were registered in the Netherlands, with a total follow-up time since diagnosis of 150,816 person-years. Compared to last year, the registered population has increased by 1408 patients, or 8.1%. The majority were diagnosed with HIV in 2010 and 2011, but 17% were diagnosed in or prior to 2009.

From 2009 to 2011, the increase in the annual number of new HIV diagnoses amongst MSM has stabilised to an estimated 750. This is a promising result, as it may reflect an improved awareness of the risk of infection and the need for regular HIV testing.

Despite these impressive figures showing the importance of large-scale anti-HIV treatment in combination with effective HIV testing strategies, AIDS is still an important cause of death amongst HIV-infected individuals. Too many infected individuals are tested late, with a late start of cART. In addition, the mortality rate is still higher amongst HIV-infected individuals than amongst those who are not infected.

Large-scale treatment also has changed the morbidity and causes of death in the HIV-infected population. Serious non-AIDS-related diseases occurring after the start of cART include renal disease, osteoporosis and non-AIDS-related malignancy, and incidences have risen since the introduction of cART. Liver disease, diabetes mellitus, myocardial infarction and stroke are diagnosed in the HIV-infected population, as well. All non-AIDS-related diseases are associated with older age, indicating that cART has increased the life expectancy of HIV-infected people.

However, the incidence of diabetes mellitus, myocardial infarction, osteoporosis and stroke is higher in the HIV-infected cART-treated population than in the general population of the Netherlands, as is true for males with non-AIDS-related malignancies. A direct effect of HIV or effects of long-term cART may play a role, and further research will be carried out as part of the HIV aging project.

Liver disease is associated with chronic HBV or HCV infections, which are prevalent in the HIV-infected population. Antiviral treatment of HBV and HCV is expected to substantially change the pattern of liver-related disease. However, follow-up of patients treated with anti-HBV drugs is still relatively short, and antiviral treatment of HCV has started only very recently. Data management and data collection are currently being adapted to enable proper follow-up of HBV and HCV.

Large-scale cART, because of its HIV suppressive efficacy, may help contain the spread of HIV, especially when adherence is high and it is combined with an HIV testing policy that aims at finding infected individuals early in the course of disease and providing early treatment. In that way, the window of opportunity of transmission is diminished, and together with other means of primary prevention, it is probably the only way until a protective vaccine is available.

However, since cART does not eradicate HIV from the body, large-scale adoption of an early start of lifelong cART is not without risks. HIV resistance will inevitably grow, albeit perhaps slowly, along with transmission of resistant HIV. Together with uncertainties regarding adherence to lifelong cART and its toxicity and the role of cART and HIV in the early aging process of those infected, such a large-scale adoption of early cART stresses the need for continuing high quality standards of HIV care and monitoring.

Monitoring programme report

1. The HIV epidemic in the Netherlands

Ard van Sighem, Colette Smit

As of June 2011, 14,610 HIV-infected patients, including 14,455 adults and 155 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. In recent years, approximately 1100 new HIV infections have been diagnosed each year, and, in contrast to previous years, there appeared to be no further increase in the annual number of diagnoses amongst men who have sex with men (MSM). Over the years, testing for HIV has become more common, as exemplified by increasing $CD4^+$ T cell counts at the time of diagnosis and a greater proportion of patients diagnosed with a recent infection. Nevertheless, approximately 40% of MSM and more than 60% of heterosexual men and women were diagnosed with CD4 counts below 350 cells/mm^3, which currently is the CD4 threshold for starting treatment.

In HIV-infected women in the Netherlands there is an ongoing decrease in pregnancy rates. This is apparent in HIV-infected women from all geographic regions and is a result of the increasing age of women currently in follow-up. Furthermore, the number of children born in the Netherlands and infected through MTCT has declined over time, most likely because of the HIV screening amongst pregnant women introduced in 2004.

Medio 2011 waren er 14.610 HIV-geïnfecteerde patiënten in follow-up in een van de 25 HIV-behandelcentra in Nederland; 14.455 volwassenen en 155 kinderen. Bijna een derde van deze groep was 50 jaar of ouder. Het jaarlijks aantal nieuwe HIV-diagnoses was ongeveer 1100 in de laatste paar jaar en leek – in tegenstelling tot de jaren daarvoor – onder mannen die seks hebben met mannen (MSM) niet verder te stijgen.
Sinds een aantal jaar wordt steeds vaker op HIV getest. Dit blijkt uit hogere CD4-celaantallen op het moment van diagnose en een naar verhouding steeds grotere groep patiënten bij wie een recente HIV-infectie wordt vastgesteld. Desondanks wordt bij 40% van de MSM en bij meer dan 60% van de heteromannen en -vrouwen HIV pas vastgesteld wanneer het CD4-aantal lager is dan 350 cellen/mm^3, de grenswaarde voor het starten van behandeling.

De toenemende leeftijd van de HIV-geïnfecteerde vrouwen in follow-up heeft tot gevolg dat het aantal zwangerschappen afneemt. Daarnaast zien we ook een afname in het aantal kinderen dat in Nederland met HIV wordt geboren. Dit is heel waarschijnlijk het gevolg van de nationale hiv-screening onder zwangere vrouwen.

For 10 years, Stichting HIV Monitoring (SHM) has collected demographic and clinical information from almost all HIV-infected patients who have been followed in one of the 25 HIV treatment centres in the Netherlands. One of the main results of this assiduous monitoring is a detailed knowledge of the characteristics of the HIV-infected population. This chapter will present an overview of the population in clinical care as of June 2011. Also, changes in characteristics of the infected populations over time will be shown, focussing on adults, children and adolescents, and pregnant women.

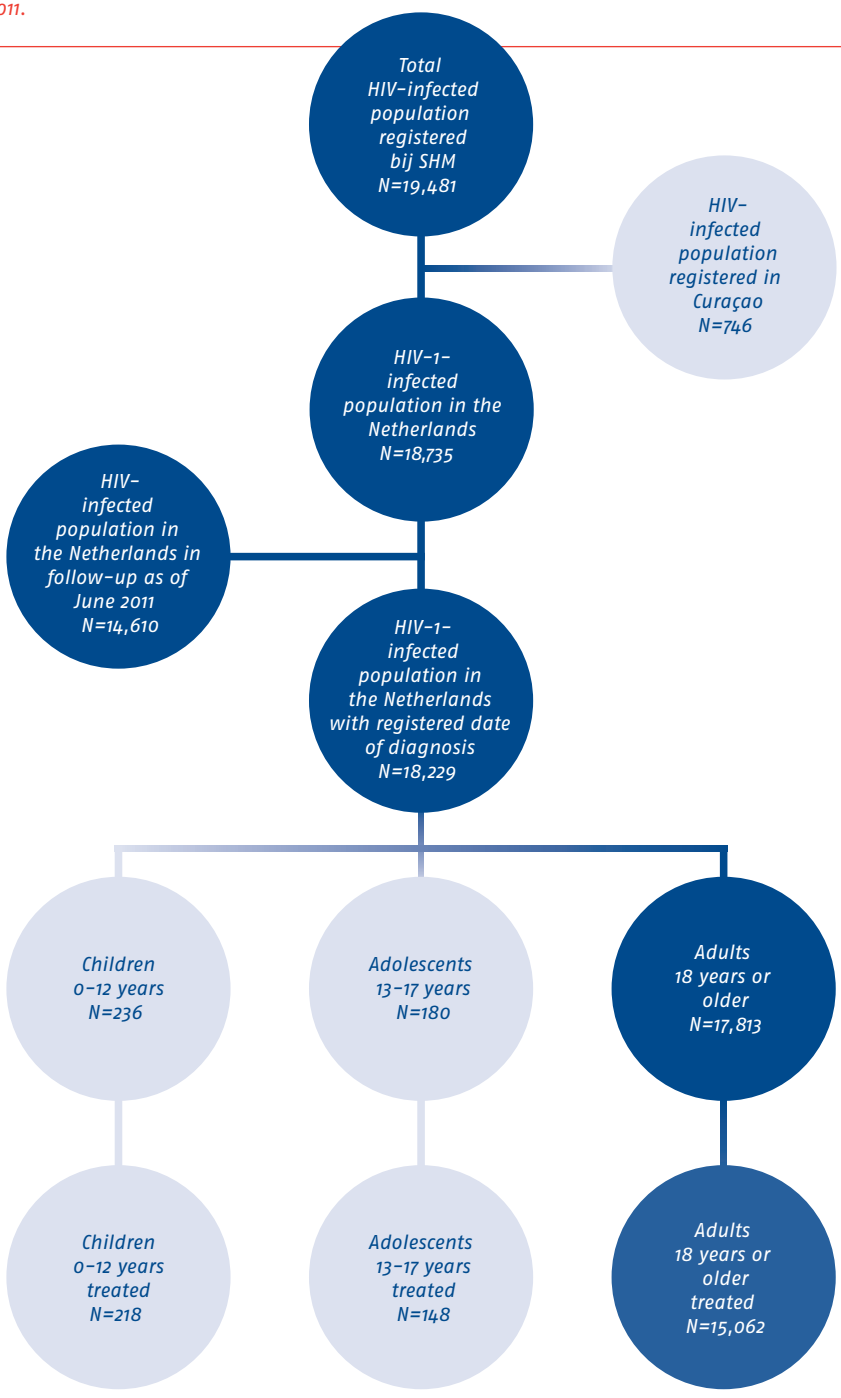
Total population

As of June 2011, 19,481 HIV-infected patients were registered by SHM. Here we focus on demographic and clinical characteristics of the 18,735 patients who are registered in one of the 25 HIV treatment centres in the Netherlands. The remaining 746 patients are registered in the St. Elisabeth Hospital in Willemstad, Curaçao, and are discussed in more detail in Chapter 7 (*Figure 1.1*).

Of the 18,735 patients, the majority were infected with HIV-1 (18,229; 97%), whilst 84 patients were infected with HIV-2, and 55 patients had antibodies against both HIV-1 and HIV-2. For 313 patients, serologic results were not yet available. The total follow-up time since diagnosis was 150,816 person-years.

Last year, we reported 17,327 patients registered in the Netherlands, which means that since that time the registered population has increased by 1408 patients, or 8.1% [1]. Although the majority of the newly registered patients were diagnosed with HIV in 2010 and 2011, 17% of those newly registered were diagnosed in or prior to 2009.

Figure 1.1: Overview of the HIV-infected population as registered by Stichting HIV Monitoring (SHM) as of June 2011.



Population in follow-up as of June 2011

Patients in clinical care

In total, 14,610 of the 18,735 registered patients, including 14,455 adults and 155 children and adolescents, were still under clinical observation (*Figure 1.1; Table 1.1; Web Appendix Table 1.1*). The remaining 4125 patients had either died or were lost to follow-up. Patients were considered lost to follow-up if no data were available after June 2010. Most likely, the number of 14,610 patients is an underestimation. For some patients there may have been a backlog in data collection of more than one year, whilst other patients may not have even been registered by SHM.

Table 1.1: *Characteristics of the 14,610 patients in follow-up as of June 2011. An extended version of this table is available on the website (Web Appendix Table 1.1).*

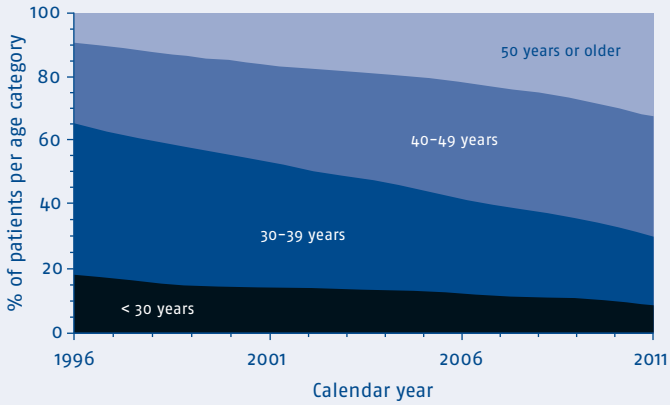
	Men (N=11,614 80%)		Women (N= 2996, 20%)		Total (N=14,610)	
	N	%	N	%	N	%
Transmission						
MSM	8523	73	–	–	8523	58
Heterosexual	1902	16	2589	86	4491	31
IDU	240	2	102	3	342	2
Blood (products)	111	1	71	2	182	1
Other/unknown	838	7	234	8	1072	7
Age category (years)						
0–12	51	0	43	1	94	1
13–17	27	0	34	1	61	0
18–24	224	2	90	3	314	2
25–34	1423	12	695	23	2118	14
35–44	3367	29	1089	36	4456	30
45–54	4154	36	727	24	4881	33
55–64	1810	16	237	8	2047	14
≥65	558	5	81	3	639	4
Region of origin						
The Netherlands	7763	67	860	29	8623	59
Sub-Saharan Africa	938	8	1300	43	2238	15
Western Europe	723	6	122	4	845	6
Latin America	773	7	258	9	1031	7
Caribbean	394	3	162	5	556	4
Years aware of HIV infection						
<1	640	6	119	4	759	5
1–2	1716	15	298	10	2014	14
3–4	1650	14	382	13	2032	14
5–10	3133	27	1016	34	4149	28
>10	4246	37	1121	37	5367	37
Unknown	229	2	60	2	289	2

Legend: *MSM=men who have sex with men; IDU=injecting drug use.*

Ageing population

The majority of the population in clinical care was infected via sexual contact and originated from the Netherlands or sub-Saharan Africa. The median age of the population was 45 years (interquartile range [IQR], 38-52) and has been increasing since 1996 (*Figure 1.2*). This increase in age is mainly a consequence of the 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, almost one third of the patients currently in clinical care, 32%, are 50 years or older, including 36% of the men and 20% of the women (*Web Appendix Table 1.1*).

Figure 1.2: *The age of the HIV-infected population in follow-up has increased over calendar time. In 1996, 18% of the patients in follow-up were younger than 30 years of age, whereas 9% were 50 years or older. In 2011, these proportions were 9% and 32%, respectively. 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 is shown.*



Duration of infection

On average, patients in follow-up as of June 2011 received their HIV diagnosis 8.9 years before. However, this number obscures the fact that a large group of patients, 37% of those in care, have managed to live with a diagnosed HIV infection for more than 10 years, whilst 6% have done so for more than 20 years. Although the average time since diagnosis was similar between homosexual men (8.8 years) and heterosexual men and women (8.3 years), a larger proportion of homosexual men than heterosexual patients, 37% compared to 30%, were diagnosed less than 5 years previously. The majority of injecting drug users, 77%, received their HIV diagnosis more than 10 years ago, which reflects the decreasing number of infections in this group.

Treatment combinations

The majority of the patients in care, 85%, had started cART, whilst 15% were not yet treated, probably because there was no indication to do so. The most frequently prescribed regimens, which accounted for 43% of all treatment combinations, were a combination of tenofovir/emtricitabine and either efavirenz or nevirapine. In 2010, these 2 combinations accounted for 41% of all regimens. Tenofovir as part of any treatment combination was used by 73% of the patients, whilst emtricitabine was used by 64%, efavirenz by 35%, and nevirapine by 25%.

Clinical condition

Partly as a result of treatment, the median CD4-cell counts were relatively high, 510 (IQR, 370-69) cells/mm^3. Of all patients in care, 80% had an HIV viral load below 500 copies/ml. Almost a quarter of the patients, 23%, had been diagnosed with an AIDS-defining event; about half of these patients were diagnosed with AIDS concurrently with their HIV diagnosis.

Trends over time – diagnosis

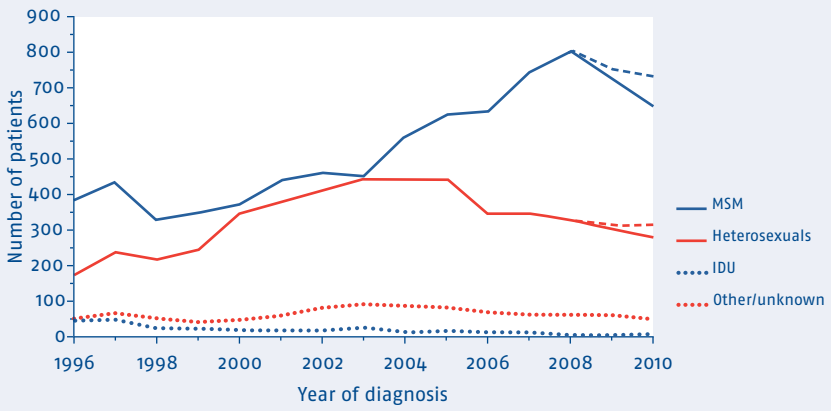
HIV-1-infected individuals

We now shift our focus to the 17,813 (98%) adults out of the 18,229 HIV-1-infected patients for whom the date of diagnosis was recorded. The majority of these patients were men who have sex with men (MSM) (10,244, 58%); otherwise, they were men (2499, 14%) or women (3110, 17%) infected via heterosexual contact. For 699 (4%) patients, including 513 men and 186 women, the reported mode of transmission was injecting drug use, whilst 197 (1%) patients were infected by contact with contaminated blood. Other and unknown modes of transmission accounted for the remaining 1064 (6%) infections.

No further increase in annual number of diagnoses

Since the 1990s, the annual number of diagnoses amongst MSM has steadily increased to just above 800 in 2008. The registered number of diagnoses in 2009 and 2010 was, however, considerably lower than in 2008 (*Figure 1.3*). In part, this lower number is the result of a backlog in the registration of HIV cases due to the visit-based data collection by SHM. However, even when this backlog is taken into account, the expected number of diagnoses in these years would only be around 750, which is still lower than in 2008, but comparable to 2007. Hence, evidence is accumulating that the increasing trend in the number of diagnoses has halted. Alternatively, 2007 and 2008 may be years with an excess of new diagnoses causing a rise above the long-term trend because of the introduction of opt-out testing for HIV at major STI clinics at about that time [2].

Figure 1.3: Annual number of HIV-1 diagnoses per transmission risk group. In 2010, men who have sex with men (MSM) accounted for 65% of the diagnoses, infections via heterosexual contact for 29%, infections via injecting drug use (IDU) for 1%, and infections via other or unknown routes for 5% of the annual tally. The dashed lines indicate the projected number of diagnoses when a backlog in registration of HIV cases (4% in 2009, 13% in 2010) is taken into account.

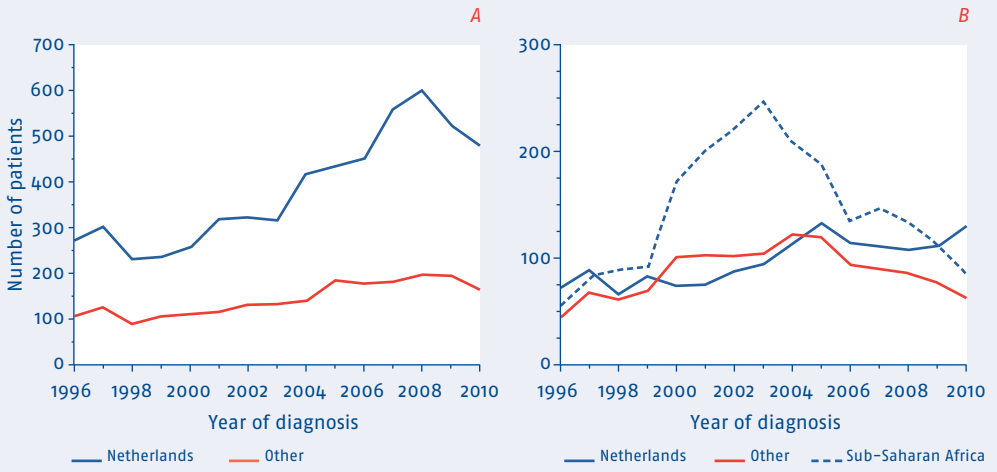


In the heterosexual population, the annual number of diagnoses reached a maximum around 2004 and then has declined to approximately 300 cases annually in the last few years. When a backlog in registration was considered, the number of diagnoses seemed not to decrease any further in 2009 and 2010. Injecting drug use is rarely reported any longer as the most probable mode of transmission, which reflects the decreasing popularity of injecting drugs since the 1980s. Also, needle exchange programmes and easily accessible methadone dispensing has contributed greatly to a reduction in the number of new infections in this group.

Region of origin

Amongst patients infected via homosexual contact, 72% originated from the Netherlands, 10% from other European countries, and 7% from Latin America (*Figure 1.4A*). Between 1996 and 2010, there were no significant changes in these proportions. In the past five years, however, the proportion of MSM from Central and Eastern Europe has increased, whereas diagnoses amongst MSM from Latin America has decreased. More specifically, in 2005, 2% of MSM were from Central and Eastern Europe and 8% from Latin America, whilst in 2010 these proportions were 5% for both groups. Patients originating from Central European countries that recently joined the European Union, in particular Poland and Romania, were responsible for the largest share of the increase in diagnoses, but even so, their absolute number was relatively small (15 in 2005 and 30 in 2010). Likewise, the number of diagnoses amongst Latin Americans decreased owing to fewer diagnoses amongst Surinamese patients (30 diagnoses in 2005 and 18 in 2010).

Figure 1.4: Annual number of diagnoses amongst (A) men who have sex with men (MSM) and (B) patients infected via heterosexual contact stratified by country of birth. Of the 10,244 MSM, 7402 (72%) originated from the Netherlands, 1015 (10%) from other European countries, and 667 (7%) from Latin America. Amongst the 5609 heterosexual patients, 2335 (42%) originated from sub-Saharan Africa and 1775 (32%) from the Netherlands. Note: data collection for 2009 and 2010 is not yet finalised.



In the heterosexual population, only 32% originated from the Netherlands, whilst 42% originated from sub-Saharan Africa (*Figure 1.4B*). However, the number of diagnoses amongst sub-Saharan Africans and, to a lesser extent, amongst patients from other regions dropped sharply after 2003, probably as a result of stricter immigration laws that came into effect in the Netherlands at approximately that time. Of note, the number of diagnoses amongst Dutch heterosexuals increased from 111 in 2009 to 131 in 2010, which is 47% of the annual tally amongst patients infected via heterosexual contact. It is unclear, however, if this increase represents a true rise in the number of infections or if it is a mere fluctuation. Similar trends in diagnoses amongst patients from Central and Europe and Latin America were observed as in the homosexual population, but the absolute number of diagnoses in these groups was just as small.

Country of infection

For 13,727 (77%) of the diagnosed patients, the most likely country of infection was reported. The majority of the patients born in the Netherlands, 93%, also reported to have been infected in the Netherlands (*Figure 1.5*). Patients born in sub-Saharan Africa were mostly infected in that region (83%), whereas 15% of them were infected in the Netherlands. In patients from other regions, except South and Southeast Asia, the majority were infected in the Netherlands.

Figure 1.5: Proportion of HIV-1-infected adults per region of origin who were infected in their own region of origin, in the Netherlands, or elsewhere.

Legend: EU-W=Western Europe; EU-E/C=Eastern and Central Europe; Lat=Latin America; Car=Caribbean; sSA=sub-Saharan Africa; SA=South and Southeast Asia; NL=the Netherlands; Other=other regions of origin.

Unsurprisingly, there were major differences in the region of infection between the major risk groups. The majority of the homosexual men, 88%, were infected in the Netherlands. Also, the majority of the patients infected via injecting drug use, 82%, were infected in the Netherlands, whilst 10% of them reported to have been infected in other Western European countries. Amongst heterosexual patients, 45% were infected in the Netherlands, whilst 38% reported having been infected in sub-Saharan Africa. Altogether, 79% of all Dutch heterosexual 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.

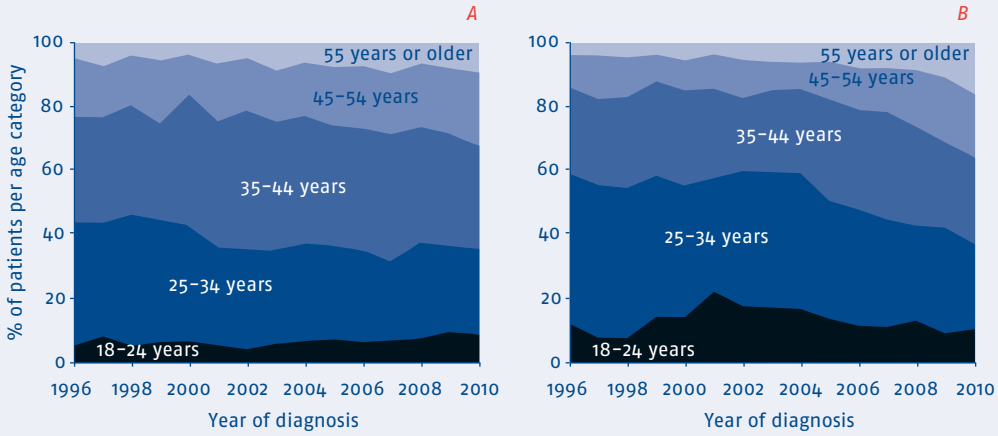
Increasing age at diagnosis

The age at which patients were diagnosed with HIV has been slowly increasing over time. In 1996, the average age at the time of diagnosis was 37 years; in 2010, it was 40 years. One fifth (21%) of the adults who received their HIV diagnosis in 2010 was 50 years or older, whilst this proportion was 13% over the entire period since 1996. There were, however, considerable differences between MSM and heterosexual men and women. MSM born in the Netherlands were diagnosed at a mean age of 40 years, whilst those of foreign origin were diagnosed at 35 years. Heterosexual women were on average five years younger at the time of diagnosis than men, and patients of Dutch origin were nine years older than patients born in sub-Saharan Africa and four years older than heterosexuals born elsewhere.

For MSM, the age distribution at diagnosis gradually changed over time, whilst amongst heterosexuals there were no notable changes up to 2004 (*Figure 1.6*). Thereafter, the age at diagnosis started to increase concomitantly with the decreasing number of

diagnoses amongst patients from sub-Saharan Africa, who are generally younger than heterosexuals of other origin as indicated before.

Figure 1.6: Age distribution at the time of diagnosis amongst HIV-1-infected men who have sex with men (A) and heterosexual men and women (B). Between 1996 and 2010, the proportion of men who have sex with men (MSM) aged 45 years or older at the time of diagnosis increased from 23% to 32%, whilst these proportions were 38% and 27% for heterosexuals. During the same period, the proportion of patients between 35 and 44 years of age decreased from 38% to 27% for MSM and from 47% to 27% in heterosexuals.



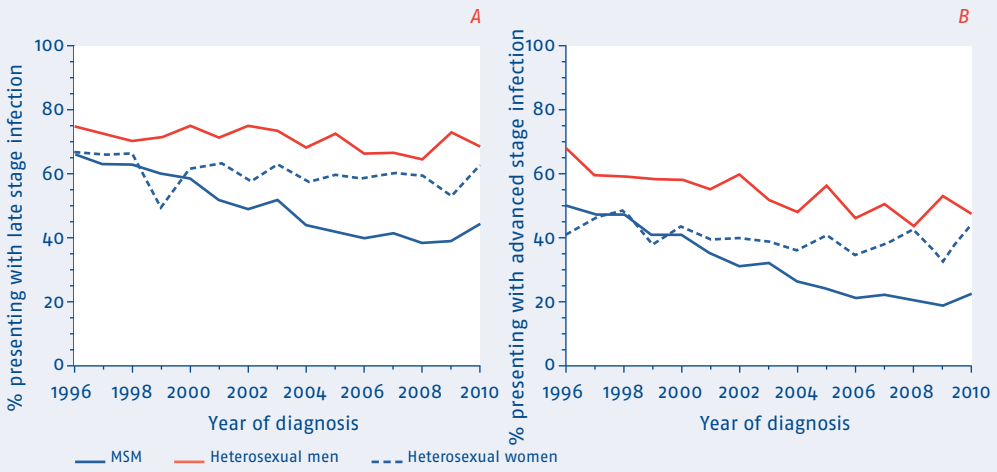
Young adults

The number of diagnoses amongst young adults less than 25 years of age infected via heterosexual contact was approximately 70 in the mid-2000s and decreased to 28 in 2009 and 29 in 2010. Amongst MSM, both the number and the proportion of diagnoses of young adults increased over time. In 2009, there were 70 diagnoses amongst young MSM, accounting for 10% of the annual tally, whilst for 2010, 58 diagnoses, or 9%, have been recorded so far.

Late presentation

Overall, 56% of the patients were late presenters, i.e., individuals either presenting for care with a CD4-cell count below 350 cells/mm^3 or presenting with an AIDS-defining event regardless of the CD4 count. In recent years, between 10% and 15% of the patients already had AIDS at the time of diagnosis. Although the proportion of late presenters has decreased over time, in 2010 44% of MSM, 68% of heterosexual men, and 62% of heterosexual women were still diagnosed late in their infection (*Figure 1.7*). Moreover, in 2010, there appeared to be an upswing in the proportion of patients with late presentation amongst homosexuals and possibly also amongst heterosexual men. Similar patterns were observed in the proportion of patients presenting for care with advanced HIV disease.

Figure 1.7: Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection. Between 1996 and 2010, 56% presented with late HIV disease: men who have sex with men (MSM) 47%, heterosexual men 71%, heterosexual women 60%, injecting drug users (IDU) 65%. Overall, 37% were advanced presenters: MSM 29%, heterosexual men 53%, heterosexual women 40%, and IDU 48%. Late disease: presenting for care with CD4-cell counts below 350 cells/mm³ or presenting with AIDS, regardless of CD4 count. Advanced disease: presenting for care with CD4 counts below 200 cells/mm³ or with AIDS, regardless of CD4 count.

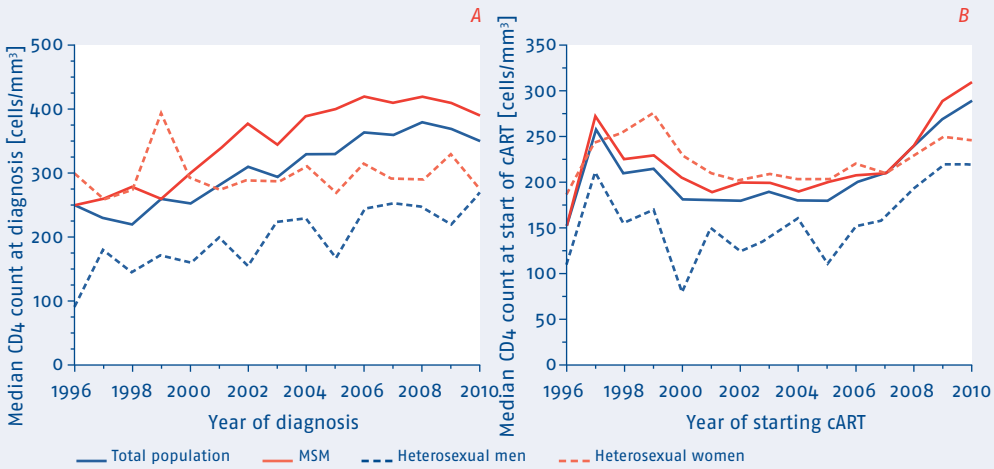


Amongst heterosexuals who had an HIV diagnosis in 2008 or later, patients of sub-Saharan African origin more often presented with a late-stage infection (73%) compared to those of Dutch origin (56%). Late presentation was also more common in patients diagnosed at older ages. Amongst those diagnosed at 45 years of age or older, 46% of MSM and 70% of heterosexuals were late presenters. In contrast, the proportion of late presenters was 26% amongst MSM and 29% amongst heterosexuals diagnosed at ages younger than 25 years. It should be noted, however, that such young persons, because of their relatively short sexual lives, are inclined to be diagnosed in an early stage of the infection.

Increasing CD4-cell counts

Between 1996 and 2010, median CD4-cell counts at the time of diagnosis for the total population increased from 250 to 540 cells/mm³ (*Figure 1.8*). This overall increase was mainly the result of an increase in CD4 counts in both homosexual and heterosexual men, whereas such counts in women remained virtually unchanged. In the last few years, CD4 counts in homosexual men seem to have reached a plateau.

Figure 1.8: Changes over time in median CD4 counts (A) at diagnosis and (B) at the start of combination antiretroviral therapy (cART). (A) Between 1996 and 2010, CD4-cell counts at diagnosis increased from 250 (interquartile range [IQR], 80-434) to 350 (IQR, 180-540) cells/mm³ in the total diagnosed population. The increase was most apparent for men who have sex with men (MSM): 250 (IQR, 80-430) in 1996 and 390 (IQR, 230-560) cells/mm³ in 2010. During the same period, CD4 counts in heterosexual men increased from 90 (IQR, 21-380) to 270 (IQR, 60-522) cells/mm³, whereas CD4 counts in heterosexual women were 290 (IQR, 120-490) cells/mm³ and did not change over time. (B) In the total population, CD4 counts at the start of cART rose to 260 (IQR, 220-392) cells/mm³ shortly after cART became available, decreased to a plateau around 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2010, CD4 counts were 290 (IQR, 173-550) cells/mm³ in the total population, 310 (IQR, 220-580) for MSM, 220 (IQR, 50-320) in heterosexual men, and 247 (IQR, 90-343) cells/mm³ in heterosexual women.



Earlier diagnosis

The increase in CD4 counts at diagnosis and the ensuing decreasing proportion of late diagnoses suggests that patients are testing positive for HIV increasingly earlier in the course of their infection. This earlier diagnosis was also apparent from the observed increase from 10% in 1996 to 37% in 2010 in the proportion of MSM who were diagnosed with a recent infection, defined as 1.5 years, at most, between the last negative HIV test and the first positive test. Diagnosis with a recent infection was less common in older MSM. Amongst the homosexuals diagnosed in 2008 or later, 48% of the diagnosed HIV infections were classified as recent amongst those aged 18 to 24 years, but this was true for only 24% of those aged 55 years or older. Also amongst heterosexuals, the proportion of recent infections appeared to increase but at a more moderate level (5% in 1996 to 10% in 2010).

As may be expected, median CD4 counts in those diagnosed with a recent infection were high, 500 (370-670) cells/mm^3 in homosexual men and slightly lower, 450 (284-650) cells/mm^3, in heterosexual men and women. Although CD4 counts at diagnosis were generally lower in those diagnosed with a non-recent infection, there was a trend over time towards higher CD4 counts. In MSM, CD4 counts were 210 (80-395) cells/mm^3 in 1996 and 320 (160-490) cells/mm^3 in 2010, whilst in heterosexuals, CD4 counts increased from 180 (50-390) cells/mm^3 to 240 (60-460) cells/mm^3 during the same period.

Increasing frequency of testing

Apparently, since the proportion of recent infections, as well as CD4 counts at diagnosis, have increased amongst those diagnosed with HIV, testing for HIV has become more common. An extra indication for this is provided by the proportion of diagnosed patients with a previous HIV-negative test. Whereas 22% of MSM diagnosed in 1996 had a previous HIV-negative test, this proportion rose to 68% by 2010. Amongst heterosexuals, the proportion of patients who previously tested negative was confined to a range between 10% and 20% between 1996 and 2007, but from 2008 onwards the proportion of patients with a negative test increased and was 30% in 2010, or, more specifically, 27% in heterosexual men and 35% in heterosexual women. These numbers can be compared with those amongst patients who were diagnosed with HIV at STI clinics for whom the proportion reporting an earlier HIV-negative test was markedly higher, 80% amongst MSM and approximately 50% amongst heterosexual men and women [3].

Trends over time – start of cART

Treated population

Amongst the 17,813 adult patients with an HIV-1 diagnosis, 15,062 patients started cART. The majority of these patients, 83%, started cART whilst being antiretroviral therapy-naive. The total follow-up time since start of cART was 102,342 person-years.

Treatment combinations

According to the current guidelines, the recommended first-line antiretroviral regimens in therapy-naive patients include a combination of tenofovir/emtricitabine and efavirenz, ritonavir-boosted atazanavir, or ritonavir-boosted darunavir [4]. In 2010 and 2011, these regimens accounted for 73% of all first-line regimens, whilst a further 10% of the administered regimens were a combination of tenofovir/emtricitabine and nevirapine. The remaining patients, 17%, started other, most likely individual-based, combinations.

Although the American guidelines also include the combination of tenofovir/emtricitabine and raltegravir amongst their recommended first-line regimens, the Dutch guidelines do not because potential long-term side-effects of raltegravir have been unexplored. More importantly, raltegravir is a twice-daily drug, whereas national guidelines favour once-daily regimens. Consequently, only 1% of those starting cART, or 14 patients in total, started this combination.

Earlier start of treatment

In the past few years, cART has been started increasingly earlier in the HIV infection as evidenced by higher CD4 counts at the start of treatment since the mid-2000s (*Figure 1.8*). In 2010, median CD4 counts at the start of treatment were 290 (IQR, 173-360) cells/mm^3. Hence, more than 25% of the HIV-infected patients started treatment according to the current guidelines, which recommend starting before CD4 counts cross the threshold of 350 cells/mm^3. On the other hand, a large group of patients still began treatment with CD4 counts below 200 cells/mm^3, which is considered a late start.

Late presentation, late start

Late presentation was in part responsible for the late start of treatment. In patients who were diagnosed in 2009 or later with CD4 counts below 350 cells/mm^3 and who were thus eligible for treatment, there was almost no delay between their HIV diagnosis and start of treatment. Within three months after their HIV diagnosis, 75% of these patients had started treatment and after one year, 93% had done so. For those with more than 350 CD4-cells/mm^3 at diagnosis, CD4-cells at the start of treatment were 370 (IQR, 310-480) cells/mm^3 with 62% of the patients starting in time.

Short-term treatment outcome

In the entire group who started cART, median CD4 counts increased from 215 cells/mm^3 at the start of cART to 350 cells/mm^3 after 24 weeks. An increase similar in magnitude, albeit at higher CD4 counts, was observed in those starting in 2009 or later: 280 cells/mm^3 at the start of cART and 424 cells/mm^3 after 24 weeks. Suppression of HIV RNA levels to below 500 copies/ml was achieved by 86% of the patients. A more exhaustive overview of treatment outcome is presented in Chapter 3.

HIV-infected children and adolescents

Health care for HIV-infected children (infected at <13 years of age) and adolescents (infected from 13 to 18 years of age) living in the Netherlands is provided in four paediatric HIV treatment centres and, as with adult patients, diagnosis, treatment and follow-up of these children are monitored by Stichting HIV Monitoring (SHM). During the past ten years up until June 2011, 238 children and 180 adolescents had been registered by SHM with the diagnosis of HIV (*Table 1.2*).

Children

The main route of HIV transmission amongst children in care in the Netherlands is mother-to-child transmission (MTCT). The median age at HIV diagnosis was 2.7 years. Although almost half of the children were born in the Netherlands, both parents of only 5% of the children originated from the Netherlands, whilst one or both parents of 61% of the children originated from sub-Saharan Africa.

Combination antiretroviral therapy (cART) was initiated in 218 out of the 236 (92%) HIV-infected children. Treatment and treatment responses amongst the HIV-infected children and adolescents are described in more detail in Chapter 3.

Of the patients who were diagnosed with HIV as children, three patients died. Overall mortality amongst patients who were diagnosed with HIV as children was 0.12/100 person-years of follow-up. Two of these patients were more than 18 years of age at the time of death. One patient died from an AIDS-defining event, and in the other patient the cause of death was renal failure. One patient died at the age of 12 years from an AIDS-defining event.

Adolescents

Demographic characteristics differed between HIV-infected children and adolescents. Adolescents were much older (median age 17.0 years, interquartile range [IQR]: 16.2-17.6) when diagnosed with HIV compared to the children (median age 2.7 years, IQR: 0.6-6.6) (*Table 1.2*). Of the 180 adolescents, 117 were female; 107 were born in sub-Saharan Africa. Heterosexual contact was the route of HIV transmission amongst 120 adolescents. These figures reflect the HIV epidemic in sub-Saharan Africa, with 76% of the young HIV–infected individuals being female [5]. Overall mortality amongst patients who were diagnosed with HIV as adolescents was 0.56/100 person-years of follow-up, with a total of 9 deaths at a median age of 29 years (IQR: 19-30 years). Causes of death were an AIDS-defining event (n=6), sepsis (n=1) and suicide (n=1); for one patient the cause of death was unknown.

Table 1.2: Demographic characteristics of HIV-1 infected children (aged 0–12 years at time of HIV diagnosis) and adolescents (aged 13–18 years at time of HIV diagnosis) registered up to 1 June 2011 in the SHM observational database.

	Children		Adolescents	
	Number	%	Number	%
Total	236		180	
Gender				
Boy	132	56	63	35
Girl	104	44	117	65
Route of transmission				
MTCT	198	83	4	2
Blood contact	22	9	17	9
Unknown	14	6	10	6
Heterosexual contact	1	4	120	67
Homosexual contact	1	4	23	13
IDU	0	0	6	3
Region of origin				
Netherlands	116	49	43	24
Sub-Saharan Africa	88	37	107	59
Caribbean/Latin America	12	5	13	7
Other	20	8	17	9
Region of the parents				
Both the Netherlands	11	5	2	1
One or both sub-Saharan Africa	145	61	25	14
One or two other regions or unknown	80	34	153	85
Median age at diagnosis (IQR)				
Years	2.7 (0.6–6.6)		17.0 (16.2–17.6)	
Deaths	3	1	9	5

***Legend:** MTCT=mother to child transmission; IDU=injecting drug use*

Vertical transmission of HIV in the Netherlands

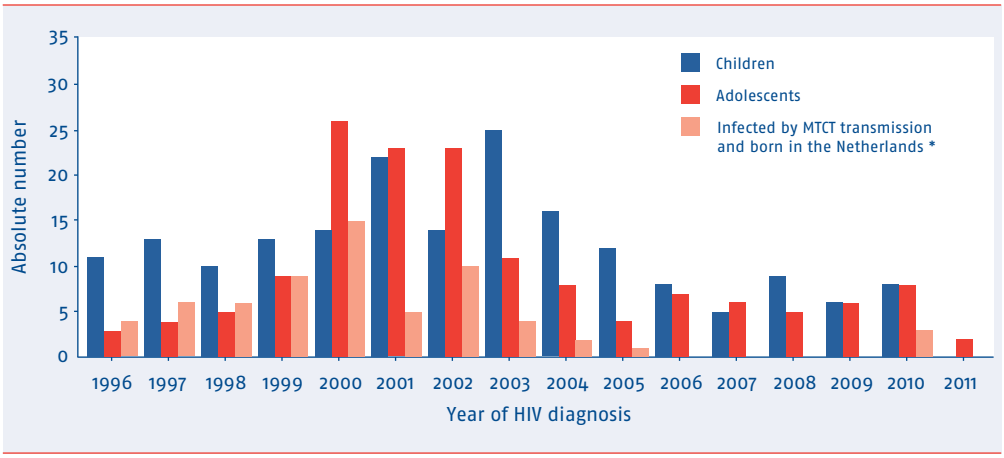
The number of children born in the Netherlands and infected through MTCT has declined over time (*Figure 1.9*), most likely because of the HIV screening amongst pregnant women introduced in 2004 [6]. The proportion of pregnant women refusing an HIV test in the first trimester is extremely low (0.2%) [7]. In addition, when testing is positive for HIV, treatment is offered, and breastfeeding after delivery is discouraged.

Despite these measures, vertical HIV transmissions still occurred in the Netherlands, albeit at low numbers. Since 1 January 2004, six HIV-infected newborns were reported to SHM. Two were born in 2004 to mothers who became pregnant in 2003, before the screening of pregnant women had started. One MTCT case happened in 2005, with the mother having been negative on initial screening and probably infected later during pregnancy. Three children were born with HIV in 2010. One was born to a mother who had tested negative during the screening in the first trimester of the pregnancy. For the remaining two children, it is still unknown if their mothers were screened during pregnancy.

Our results of the monitoring of HIV-infected children show a substantial decline in MTCT since the introduction of a national screening programme of pregnant women in 2004 and a yearly number of HIV-infected children born in the Netherlands that is close to zero. However, screening of pregnant women for HIV during only the first trimester is not always a sure measure because infection can occur during the second and third trimester. When testing occurs very early in infection, i.e., during or shortly after primary infection, results may be negative.

Since the prevalence of HIV amongst pregnant women in the Netherlands is between 0.04 and 0.08% [7], a nationwide second pregnancy screening is not very likely to be effective. Nevertheless, such a test may be beneficial in the sub-population of pregnant women who originate from countries with a generalised HIV epidemic.

Figure 1.9: *Number of HIV-infected children and adolescents according to their year of HIV diagnosis and the number of children infected with HIV by mother-to-child transmission (MTCT) and born in the Netherlands. None of the adolescents born in the Netherlands were vertically infected with HIV.*



Legend: *MTCT= mother-to-child transmission*

** According to year of birth*

Pregnant women

Transmission of HIV from an HIV-infected mother to her child is the most common route of HIV transmission amongst children aged 0-15 years worldwide [8]. Combination antiretroviral therapy (cART) has been shown to be beneficial in the prevention of mother-to-child transmission (MTCT), which has been reduced dramatically since the treatment of pregnant women with cART [9].

Since January 2004, pregnant women have been screened for HIV antibodies as part of the national prenatal screening programme [10, 11], and 171 women who were unaware of their HIV infection were diagnosed during their pregnancy and reported to Stichting HIV Monitoring (SHM).

Total number of pregnancies

By June 2011, a total of 1295 pregnancies were registered amongst 3550 HIV-infected women and monitored by SHM. Of the total of 940 women with a pregnancy, 468 (52%) were pregnant at HIV diagnosis, and 454 (48%) became pregnant after HIV diagnosis. In addition, 243 women became pregnant for a second or more time (*Table 1.3*).

Characteristics

Characteristics of the HIV-infected women with a registered pregnancy are presented in *Table 1.3*. Most pregnant women originated from sub-Saharan Africa (60%), whilst a minority was born in the Netherlands (15%). Significant differences were found between women of different origins. Dutch women became pregnant whilst knowing their HIV status more often (74%) compared to women originating from sub-Saharan Africa (48%) and Latin America/Caribbean (48%) ($p<0.0001$). The median age at first pregnancy significantly increased over time ($P=0.0012$) from 28 years in 1998 to 31 years in 2009. The median age of women born in the Netherlands at the start of their first pregnancy was 30 years (interquartile range [IQR]: 26-35). Women of Dutch origin were significantly older during their first pregnancy compared to women originating from sub-Saharan Africa (median age: 28 years, IQR: 24-33) and from Latin America/Caribbean (median age: 27 years, IQR: 23-33). Heterosexual contact was the most important route of HIV transmission amongst the mothers. Fourteen mothers (1%) were infected with HIV through injecting drug use; eight of them were of Dutch origin, and six originated from Eastern or Central Europe. Ninety-six percent of the women of sub-Saharan origin were infected through heterosexual contact, whilst 4% were infected through contaminated blood products.

Overall median CD4-cell counts at the start of the first pregnancy were 390 cells/mm^3 (IQR: 250-540). CD4-cell counts were significantly higher amongst women with an HIV diagnosis before becoming pregnant, 414 cells/mm^3 (IQR: 296-559), compared to women who were diagnosed with HIV during their pregnancy with a median CD4-cell count of 340 cells/mm^3 (IQR: 210-520) ($P<0.0001$). Of the women with a known HIV infection before becoming

pregnant, 62% received treatment before the start of the pregnancy, resulting in higher CD4-cell counts at the start of the pregnancy. An HIV RNA plasma level shortly before delivery was available for 731 pregnant women (78%). Amongst women with a known HIV RNA plasma level before delivery, 80% had an undetectable viral load. Reponses to cART in pregnant women are described in detail in Chapter 3.

In total, 980 (76%) newborns resulted from 1295 pregnancies; 270 (21%) pregnancies ended in abortion, of which 129 were an induced abortion. Induced abortion was frequent before cART became available [12]. Increased awareness of HIV infection through screening, in combination with the effectiveness of cART in preventing MTCT, have reduced the proportion of induced abortion [13] to a stable low 4% of the pregnancies in recent years. Perinatal death accounted for 3% of all pregnancies (n=37); 20 deaths were stillbirths, three deaths occurred during childbirth, and 14 deaths were in the first seven days after delivery.

In total, more than half of the newborns with a known delivery method were delivered vaginally. Elective caesarean delivery is known to reduce the risk of MTCT if there is a detectable maternal viral load, but it is less beneficial if sufficient viral suppression is achieved in the mother following successful treatment with cART [14, 15]. The proportion of elective caesarean deliveries has decreased over time from 51% in 2000 to 21% of the pregnancies in recent calendar years (p=0.002)

Table 1.3: *Characteristics of HIV-infected pregnant women, 1 January 1988 – 1 June 2011.*

		Total
	Women	Pregnancies
	N=940	N=1295
	N (%)	N (%)
HIV diagnosis before pregnancy (%)	468(52)	
Number of pregnancies after HIV diagnosis		
1		940 (73%)
2		243 (19%)
3		76 (6%)
4		21 (2%)
5		9 (0.7%)
6		4 (0.3%)
7		2 (0.1%)
Age at start of first pregnancy occurring in HIV infection		
Years (Median (IQR))	29(24-33)	
HIV Transmission route		
Heterosexual (%)	880 (94)	
Other (%)	60 (6)	

	Women N=940 N (%)	Total Pregnancies N=1295 N (%)
Region of origin		
Netherlands (%)	142 (15)	
Sub-Saharan Africa (%)	563 (60)	
Latin America/Caribbean (%)	136 (14)	
Other (%)	99 (11)	
Pregnancy outcome		
Partus (%)		980 (76)
Abortion (%)		270 (21)
Unknown (%)		45 (3)
Mode of delivery		
Vaginal delivery (%)		573 (44)
Caesarean delivery (%)		406 (31)
Unknown (%)		315 (24)
Perinatal deaths		37 (3%)
Number of pregnancies per calendar year:		
<1997 or unknown		103 (8%)
1997-1999		122 (9%)
2000-2001		187 (14%)
2002-2003		272 (21%)
2004-2005		276 (21%)
2006-2007		197 (15%)
2008-2010		138* (11%)
CD4-cell counts (cells/mm^3) at time of start of first pregnancy (median, IQR):		
All pregnant women	390 (250-540)	
HIV diagnosis before pregnancy	414 (296-559)	
HIV diagnosis during pregnancy	340 (210-520)	
Start cART		
Before pregnancy	309 (32%)	
During pregnancy	489 (51%)	
No cART during pregnancy	55 (6%)	
Pregnancy before cART availability	87 (9%)	
HIV RNA plasma levels before delivery		
Undetectable	582 (62%)	
Detectable	149 (16%)	
Unknown	209 (22%)	
Ever CDC-c event	154 (16%)	

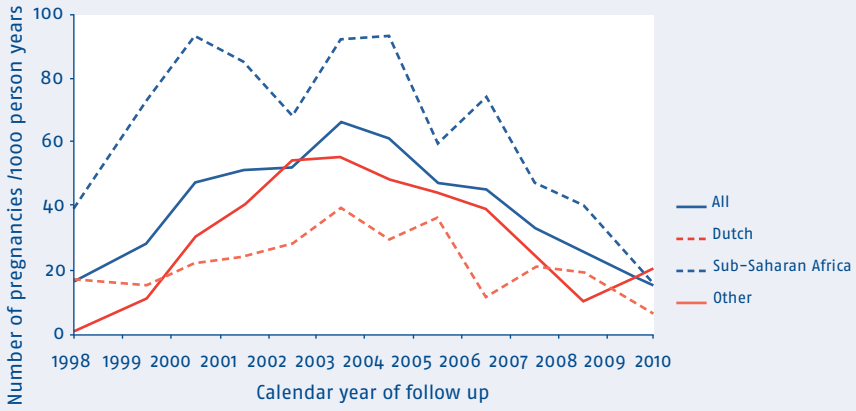
Legend: *IQR=Interquartile range; cART=combination antiretroviral therapy; CDC-c=Centers for Disease Control and Prevention C classification*

** Data collection for calendar year 2010 not yet completed, as the term date is after 31 December 2010.*

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

Overall, the occurrence of a first pregnancy during or after HIV diagnosis amongst HIV-infected women aged between 16 and 45 years was 36 pregnancies per 1000 person-years (PY) (95% confidence interval (CI): 33-39). The incidences in the total group of women and those according to geographic origin are presented in *Figure 1.10*.

Figure 1.10: *Incidence of pregnancies per 1000 person-years 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 person-years (PY). All women aged between 16 and 45 years were considered to be "at risk" for pregnancy. Person-years were calculated from the time of HIV diagnosis until the last visit, death, the point at which the patient was lost to follow-up or reached the age of 45 years, or 1 January 2010.



In the total group, the incidence increased from 20 (95% CI: 11-33) in 1998 to 66 (95% CI: 54-81) in 2003 and then gradually decreased between 2003 and 2008 to 25 (95% CI: 18-33) pregnancies per 1000 PY. In women of all different origins, the incidence of pregnancy declined over calendar time. The highest pregnancy rates were found amongst women originating from sub-Saharan Africa. Differences in the incidence of pregnancies amongst women of different geographic origin have also been found in earlier studies, and incidence rates have been reported to be highest in women originating from sub-Saharan Africa [16]. An HIV-infected woman's decision to become pregnant has been found to be socially and culturally related [12]. The incidence of pregnancy amongst women originating from sub-Saharan Africa who are monitored by SHM has declined over time. In the Dutch HIV epidemic a substantial proportion of the heterosexually infected women originate from sub-Saharan African countries (49%). The number of HIV diagnoses amongst sub-Saharan African patients has dropped sharply since 2003 (*Figure 1.4*), probably as a result of stricter

immigration laws in the Netherlands that came into effect at approximately the same time. The number of HIV diagnoses amongst women originating from sub-Saharan Africa decreased from 173 diagnoses in 2003 to 62 diagnoses in 2010. The age of women from sub-Saharan countries currently in follow-up has become older and is now 40 years (IQR: 32-46). The group of women of sub-Saharan African origin of childbearing age has diminished, with fewer pregnancies occurring in this group.

In conclusion, the decrease in pregnancy rates amongst HIV-infected women in the Netherlands continues in those from all the geographic regions. Although most pregnancies occur in women originating from sub-Saharan Africa, the number of pregnancies in this group is also decreasing, which might be a result of the drop in newly diagnosed heterosexually infected patients from sub-Saharan countries since 2003 and the increasing age of sub-Saharan African women currently in follow-up.

2. Death, AIDS and serious non-AIDS-related diseases

Rebecca Holman, Luuk Gras, Ard van Sighem

Mortality rates and the incidence of AIDS amongst HIV-infected individuals have declined steadily since the introduction of combination antiretroviral treatment (cART). The proportion of patients who die of AIDS has decreased steadily as well, but the incidence of death from other causes is rising. The incidence of AIDS continues to decline substantially, but the incidence of renal disease, osteoporosis and non-AIDS malignancies is increasing. The decreasing incidence of AIDS over time is largely the result of successful treatment of HIV-positive patients that has led to an increasing proportion of patients with high CD4-cell counts. A range of demographic features, as well as those of HIV and antiretroviral treatment, contribute to the incidence of individual non-AIDS-defining serious diseases. The incidence of non-AIDS-defining malignancies, diabetes mellitus, myocardial infarction, osteoporosis and stroke was higher in HIV-positive patients on cART than in age- and gender-matched individuals in the general population of the Netherlands. As the mean age in the HIV population increases and serious non-AIDS-defining diseases in the general population occur at a higher rate with increasing age, it is to be expected that the incidence of certain non-AIDS-defining diseases will continue to increase in the future. The results presented in this section highlight the need for regular and careful monitoring of many aspects of the health of HIV-positive patients. This is particularly true as more patients live with HIV and take antiretroviral medication in the long term. The extent to which exposure to long-term antiretroviral therapy, HIV viraemia, inflammatory responses and immune system activation contribute to non-AIDS-related morbidity and mortality needs further study.

Sinds de introductie van combinatie antiretrovirale therapie (cART) zijn de mortaliteit en incidentie van AIDS bij HIV-geïnfecteerden geleidelijk gedaald. Het percentage patiënten dat sterft ten gevolge van AIDS is ook gedaald, maar de incidentie van sterftegevallen wegens andere oorzaken stijgt. Hoewel de AIDS-incidentie daalt, stijgt de incidentie van nierziekten, osteoporose en niet-AIDS-gerelateerde maligniteiten. De afname in de AIDS incidentie over tijd wordt grotendeels veroorzaakt door de succesvolle behandeling van HIV-positieve patiënten; dit resulteert in een steeds grotere groep patiënten met een hoog CD4-celaantal. Verschillende demografische, HIV- en antiretrovirale behandelingsfactoren dragen bij aan de incidentie van de verschillende niet-AIDS-definiërende ernstige ziekten. De incidentie van niet-AIDS-definiërende maligniteiten, diabetes mellitus, myocardinfarct, osteoporose en CVA

was hoger bij HIV-positieve patiënten die cART gebruikten dan bij personen in de algemene Nederlandse bevolking van hetzelfde geslacht en dezelfde leeftijd. Met het stijgen van de gemiddelde leeftijd van de HIV-populatie en de hogere prevalentie van ouderdom ziekten in de algemeen ouder wordende bevolking, valt te verwachten dat de incidentie van bepaalde niet-AIDS-definiërende ziekten in de toekomst zal blijven stijgen. De in dit hoofdstuk gepresenteerde resultaten benadrukken de noodzaak voor het regelmatig en zorgvuldig controleren van een groot aantal gezondheidsaspecten bij HIV-positieve patiënten. Dit is vooral van belang nu steeds meer HIV-patiënten langer leven op antiretrovirale therapie. De mate waarin blootstelling aan langdurige antiretrovirale therapie, de hoeveelheid virus in het bloed, ontstekingsreacties, en activering van het immuunsysteem bijdragen aan niet aan AIDS gerelateerde ziekte en sterfte behoeft nader onderzoek.

The widespread introduction and continuing improvement of combination antiretroviral treatment (cART) means that life expectancy amongst HIV-1-infected adults is currently much higher than before cART was widely available [17]. However, the life expectancy for HIV-1-infected patients on cART is still below that of individuals of the same gender and age in the general population of the Netherlands [18] and other developed countries [17], and it is even lower for patients who start cART late in the disease course [19]. Since the introduction of cART, the risk that the cause of death in patients with HIV-1 will be AIDS has decreased; however, the risk that these patients will die of non-AIDS-related causes or have serious non-AIDS-defining diseases has increased in both the United States [20] and various European countries [21]. It is unclear whether the excess mortality is due to the effects of HIV infection, the use of cART or factors related to family and lifestyle [22]. In contrast, a subgroup of recently diagnosed, effectively treated patients has been found to have a similar life expectancy to the HIV-negative population of the Netherlands [23]. This suggests that effective cART strategies may enable HIV-positive patients to achieve low levels of mortality similar to those in the general population.

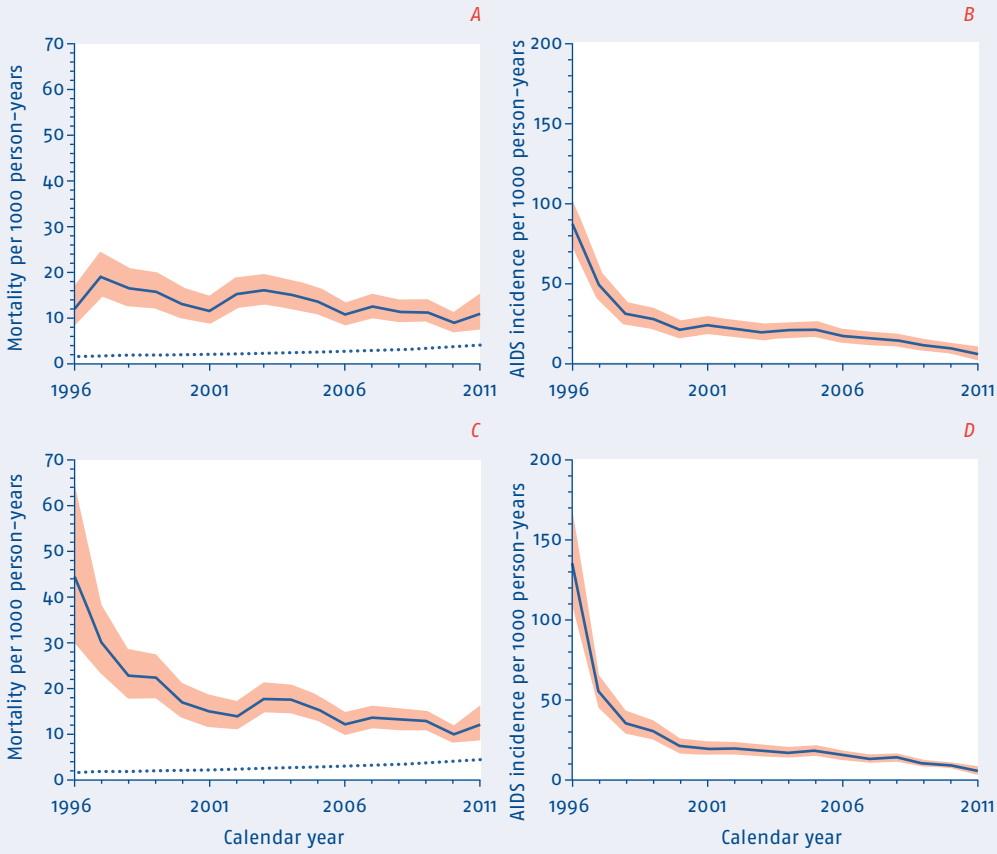
Reporting on the effect of cART on clinical outcomes is an important part of monitoring the HIV epidemic in the Netherlands. Therefore, in this chapter, we report on trends in mortality, causes of death, AIDS and serious non-AIDS-defining morbidity amongst HIV-1-infected patients before and after the start of cART. The serious non-AIDS-defining diseases we examine are: renal insufficiency, liver disease, diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies. Furthermore, loss to follow-up may have a negative impact on an individual patient's prognosis, as regular follow-up is needed to recognize clinical signs and symptoms at an early stage. A high rate of loss to follow-up makes the evaluation of the effect of cART on mortality and morbidity in the population more difficult. We therefore also report on the loss to follow-up amongst the members of our cohort. We also provide recommendations on maintaining the quality of care for HIV-1-positive patients in the Netherlands.

Mortality and incidence of AIDS

The overall mortality rate in the group of 18,229 HIV-1-infected patients with a registered date of diagnosis was 12.9 (95% confidence interval [CI], 12.3-13.5) per 1000 person-years, and it declined over time to 8.9 (7.3-10.6) in 2010 (*Figure 2.1A; Web Appendix Table 2.1*). Despite this decline, the mortality rate was well above the rate that would be expected in the same group of individuals if they were not infected with HIV. The excess mortality rate could be explained in part by patients who already had AIDS at the time of their HIV diagnosis. When these patients were excluded, the average mortality rate decreased to 11.1 per 1000 person-years. The mortality rate was even lower (10.1) in patients who were diagnosed with HIV in 1996 or later. 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 18,229 patients, the incidence of AIDS decreased sharply to between 10 and 20 cases per 1000 patients per year in the last years (*Figure 2.1B*). As there is some backlog in the reporting of AIDS events, we expect that eventually the incidence in 2010 will be approximately 10% higher.

Likewise, the mortality rate after the start of cART substantially decreased over calendar time to 9.8 (95% CI, 8.1-11.8) per 1000 person-years in 2010. This decrease should, however, be interpreted with caution since it is in part due to a survival effect. Also, the incidence of AIDS decreased dramatically to 8.9 per 1000 person-years in 2010 (*Figure 2.1D*). These patterns are similar to those seen in data from various European countries [24], including Switzerland [25, 26] and Denmark [26]. In Switzerland, people on cART have a level of mortality similar to people successfully treated for cancer [27]. It is unclear whether the higher mortality in comparison to the general population is due to the effects of HIV infection, the use of cART or factors related to family and lifestyle [22]. However, a subgroup of recently diagnosed, effectively treated patients had a life expectancy similar to the HIV-negative population of the Netherlands [23]. This suggests that effective cART strategies may enable HIV-positive patients to achieve low levels of mortality similar to those in the general population.

Figure 2.1: *Annual mortality (A, C) and incidence of AIDS (B, D) in 18,229 HIV-1-infected patients in the Netherlands after HIV diagnosis (upper plots) and in a subpopulation of 15,342 treated patients after the start of combination antiretroviral therapy (lower plots). Solid lines represent the incidence, whilst the shaded 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: 1756 deaths, 136,532 person-years of follow-up; B: 2415 AIDS cases after six weeks after HIV diagnosis, 117,452 person-years; C: 1529 deaths, 101,798 person-years; D: 1637 AIDS cases after 4 weeks after start of combination antiretroviral therapy, 93,597 person-years.*



Mortality before the start of cART

A total of 18,688 patients with a known date of HIV-1 diagnosis and who were aged more than 16 years at the time of HIV-1 diagnosis had been registered by Stichting HIV Monitoring (SHM) by 31 May 2011.

Of these patients, 249 died between 1 January 1995 and 31 May 2011, and SHM was notified of their deaths before 31 May 2011. Of the remaining patients, 15,676 started cART, and 2763 were not known to have died or to have started cART during 30,856 person-years of follow-up. We defined follow-up for these patients as the time between HIV-1 diagnosis and the date of death or the start of cART, whichever occurred first. Hence, there were 8.1 deaths (95% CI, 7.1–9.1) per 1000 person-years of follow-up.

Of the 249 patients who died before starting cART, 199 (80%) were male, and 129 (52%) were born in the Netherlands. In addition, 91 (37%) had probably contracted HIV via homosexual contact, 71 (29%) via heterosexual contact and 37 (15%) via intravenous drug use. The median time between diagnosis and death was 18.4 months (interquartile range [IQR], 1.6–69.2) and the median age at death was 44 years (IQR, 37–54). The number of patients who died of AIDS in the period 1995–2000 was 33 (59%); in the period 2001–05 this was 45 (41%), and in the period 2006–11, 17 (21%) died from AIDS.

The cause of death and the last known CD4 count of these patients are presented in *Table 2.1*. AIDS was the most common cause of death. At least one CD4 count was available for 197 patients. The median CD4 count for these patients was 170 cells (IQR, 30–415). The median last known number of CD4-cells was lowest in patients dying of AIDS, but it was also well below the normal range for death from all causes except "non-natural causes or substance abuse".

Table 2.1: *The cause of death and last known CD4 count of the 249 patients who died without starting combined antiretroviral therapy.*

Cause of death	Number of deaths	Percentage of deaths*	Median last known CD4 count (cells/mm³)	Median number of months between HIV diagnosis and death
AIDS	95	38%	22	10
Non-AIDS defining malignancy	27	11%	265	5
Non-natural causes or substance abuse	26	10%	490	41
Non-AIDS defining infection	18	7%	216	44
Other, unclassifiable or unknown causes	83	33%	310	26

**Percentages may not sum to 100 due to rounding.*

A total of 105 (42%) patients died after 1 July 1996; they had a CD4 count lower than 200 cells/mm^3 and died at least a month after the diagnosis of HIV-1, implying that they would have been eligible for cART. In addition, 50 (53%) of the 95 patients who died of AIDS were diagnosed with AIDS within a month of HIV diagnosis. This, in conjunction with the low CD4 counts, shows that most patients with AIDS as the cause of death who had never started cART were diagnosed with HIV-1 late in the disease.

These results show that not all deaths before cART were due to late HIV-1 diagnosis. HIV may have been diagnosed in end-stage critical non-HIV disease. Further insight into the unknown causes of death and the reasons why cART was not prescribed may help prevent deaths in the future. It remains important to identify HIV-positive patients early in the course of their infection, to monitor CD4-cell counts regularly and to prescribe cART according to current guidelines [28].

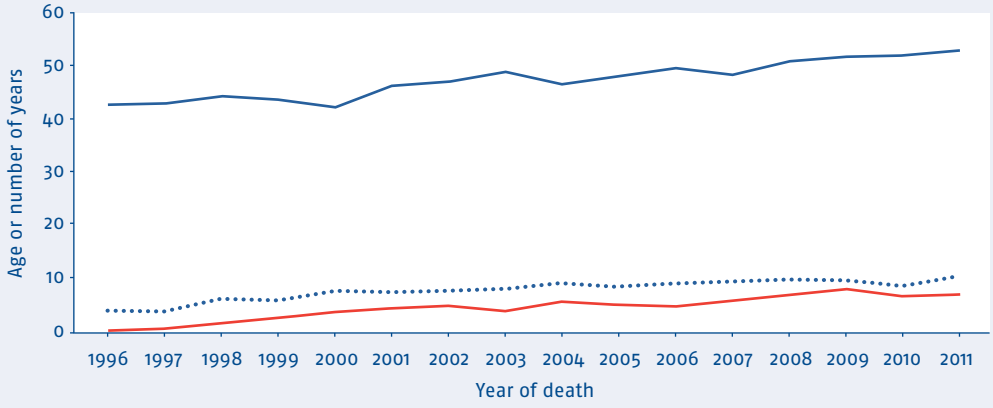
Mortality after the start of cART

The number of patients who died after starting cART in each calendar year and their demographic characteristics and cause of death are presented in *Web Appendix Table 2.2*. In summary, a total of 14,874 HIV-1-positive patients aged 16 years or more started cART between 1 January 1995 and 31 December 2010. The death of 1530 (10%) of these patients was reported to SHM before 31 May 2011 and occurred between 1 January 1996 and 31 May 2011. There were 97,358 person-years of follow up between 1 January 1996 and 31 May 2011. Hence, there were 15.7 deaths (95% CI, 14.9 – 16.5) per 1000 person-years of follow-up.

The characteristics of the 1530 patients who died after starting cART are presented in detail in *Web Appendix Table 2.1*. A total of 1317 (86%) patients were male, 1072 (70%) were born in the Netherlands, and 809 (53%) had probably become infected with HIV-1 as a result of homosexual contact. The median age at death was 48 years (IQR, 41–56), the median time between HIV-1 diagnosis and death was 7.9 years (IQR, 3.4–12.7) and the median time between the start of cART and death was 3.8 years (IQR, 1.1-7.4). The median last CD4-cell count was 180 cells/mm^3 (IQR, 60-370).

Figure 2.2 shows the median age at the patient's death, median number of years the patient was HIV-1 positive, and median number of years the patient was on cART. Each of these values has risen steadily between 1996 and 2011. The median time between HIV-1 diagnosis and death was 3.9 years (IQR, 2.7–7.4) in 1996 and 8.6 years (IQR, 5.1–15.1) in 2010. The median time between the start of cART and death was 0.3 years (IQR, 0.2–0.4) in 1996 and 6.6 years (IQR, 2.1–11.0) in 2010. The median age at death was 43 years (IQR, 37–50) in 1996 and 52 years (IQR, 45–63) in 2010. This indicates that HIV-1-positive patients are living to an older age, living longer with HIV and using cART longer. The last CD4 count before death rose from 30 cells/mm^3 (IQR, 10–80) in 1996 to 298 cells/mm^3 (IQR, 150–489) in 2010. The interquartile range of the last CD4-cell counts increased in later calendar years because the causes of death were more varied in later calendar years and the level of the last CD4 count is associated with the cause of death as shown in *Table 2.2*.

Figure 2.2: *The median age at death (blue solid line), median number of years positive for HIV (dotted blue line) and median number of years on cART (red line) for patients who died after starting cART in each calendar year.*



The causes of death of the 1530 patients who died after starting cART are summarised in *Table 2.2* and presented in more detail in *Web Appendix Table 2.1*. A total of 521 (34%) patients died of AIDS, 214 (14%) of a non-AIDS-defining malignancy, 109 (7%) of cardiovascular diseases, 74 (5%) of non-natural causes and 612 (40%) of other or unknown causes. Hence, approximately two-thirds of people who were HIV-1 positive and died after starting cART did not die of AIDS, but of other causes. A total of 114 patients died in 2010. Of these, 12 (11%) died of AIDS, 24 (21%) of a non-AIDS-defining malignancy, 8 (7%) of a non-AIDS-defining infection, 5 (4%) of liver failure, 3 (3%) of pulmonary-related causes, 3 (3%) non-natural death, 2 (2%) of cardiovascular disease, 2 (2%) of substance abuse and 64 (56%) of other, unknown or unclassifiable causes.

Table 2.2: Cause of death and last known CD4 counts of the 1530 patients who died after starting combined antiretroviral therapy.

Cause of death	Number	Percentage*	Median last CD4 count (cells/mm³)
All AIDS defining causes**	521	34%	60
Infection	172	11%	
Malignancy	180	12%	
Not specified	169	11%	
Non-AIDS-defining malignancy	214	14%	220
All cardiovascular diseases	109	7%	307
Myocardial infarction	42	3%	
Stroke	15	1%	
Other ischemic heart disease	3	0%	
Other cardiovascular diseases	15	1%	
Non-AIDS defining infection	96	6%	140
Liver failure, cirrhosis and hepatitis B virus or hepatitis C virus co-infection at death	71	5%	250
Lung-related***	41	3%	210
Non-natural death	74	5%	331
Accident or other violent death	26	2%	
Suicide	35	2%	
Euthanasia	13	1%	
Substance abuse	32	2%	235
Other causes****	84	5%	285
Unknown or unclassifiable causes	288	19%	271
Total	**1530**	**100%**	**180**

* *Percentages may not sum to totals due to rounding.*

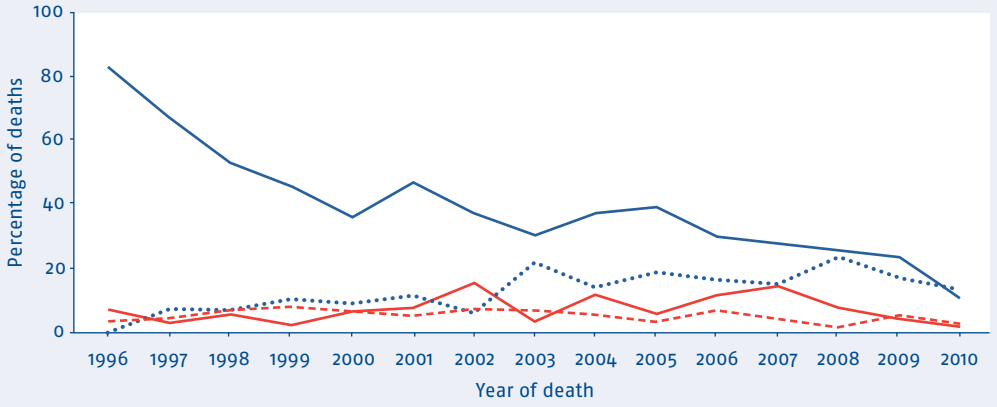
** *According to the clinical part of the 1993 revised classification system of the U.S. Centres for Disease Control and Prevention.*

*** *Includes: primary pulmonary hypertension, lung embolus, chronic obstructive lung disease and other types of respiratory diseases.*

**** *Includes but is not limited to: complications of diabetes mellitus; pancreatitis; lactic acidosis; liver failure without hepatitis B or C virus at death; renal failure; haematological, endocrine and psychiatric diseases; and diseases of the central nervous system, digestive system, skin and motor system, and urogenital disease.*

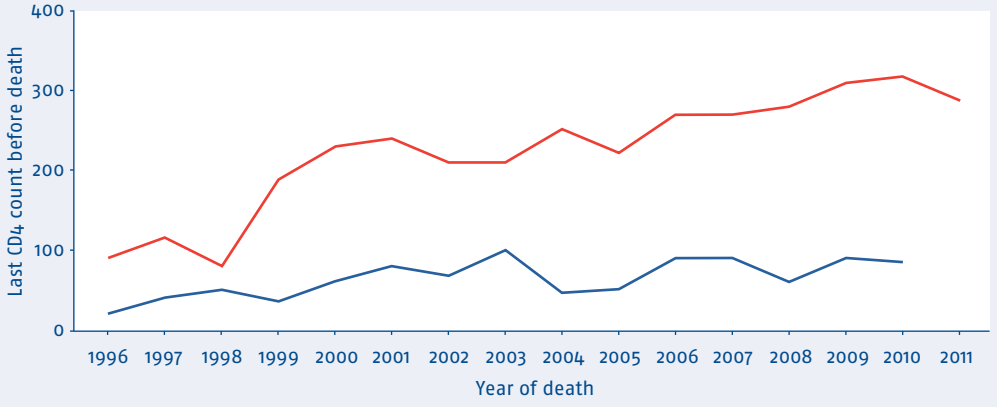
The percentage of deaths caused by AIDS, non-AIDS-defining malignancies, cardiovascular events, non-natural causes, and other or undefined causes according to the year of death are presented in *Figure 2.3*. The percentage of deaths caused by AIDS dropped sharply from 83% in 1996 to 11% in 2010. This is similar to patterns seen in the USA [20] and various European countries [21]. The percentage of deaths caused by non-natural causes and cardiovascular events has remained similar.

Figure 2.3: The percentage of deaths caused by AIDS (blue solid line), non-AIDS-defining malignancies (blue dotted line), cardiovascular events (red solid line) and non-natural causes (red dashed line).



The last known CD4 counts of patients according to cause of death are given in *Table 2.2* and presented for each calendar year in *Figure 2.4*. The median last known CD4 counts are low for all groups of patients, but particularly for those who died of AIDS-defining causes. This implies that HIV infection may play a role in mortality, even if AIDS is not the immediate cause of death. This can also be concluded from results of the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study [29], in which death due to liver disease, non-AIDS malignancies, cardiovascular disease and other non-AIDS-related causes were all associated with lower last known CD4-cell counts, albeit less strongly than death due to AIDS.

Figure 2.4: The last known CD4 counts of patients whose deaths were caused by AIDS (blue line) or other causes (red line) according to the year of death.



These results indicate that there have been no substantial changes in the baseline demographic characteristics of HIV-positive patients who die, because they are a reflection of the general HIV-1-infected population who are aging, living longer with HIV infection and spending more time on cART than in the past. In addition, patients have higher CD4 counts shortly before death than in the past. However, although there has been a shift from AIDS to non-AIDS-related causes of death, deaths from AIDS are still occurring in the Netherlands, and HIV-1-positive patients still have a higher rate of mortality than the general population [18].

AIDS and serious non-AIDS-defining diseases

Serious non-AIDS-defining diseases, such as renal insufficiency, liver disease, diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies, are similar in both HIV-infected and uninfected subjects. However, the incidence of these diseases may be higher amongst infected than uninfected subjects [30-36]. Researchers have suggested that, in addition to the usual disease-specific factors and the use of certain antiretroviral combinations [37, 38], HIV infection itself may be associated with a higher incidence of non-AIDS-defining diseases [31, 39, 40] or a marker for behavioural or family-related risk factors [22, 41].

We report on the incidence of AIDS, grouped serious non-AIDS-defining diseases and individual serious AIDS-defining diseases amongst patients on cART. To accomplish this we followed the following methodology: we defined AIDS as any Centers for Disease Control (CDC) category C condition [42]; we defined grouped serious non-AIDS diseases as acute and chronic renal insufficiency, liver disease (cirrhosis, fibrosis and hepatocellular carcinoma), diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS malignancies; and we also looked at these diseases individually. We also examined the first event for each patient in each category; we defined the start of the time at risk as the date on which the patient started cART or the start of routine collection of data for the event concerned, whichever was later; and we defined the end of the time at risk as the date on which the event occurred, the date of the last contact with the patient or the date of death. We report on the incidence of grouped non-AIDS-defining diseases from July 2002, as routine data collection for some of these conditions did not start until this date.

We modelled the incidences using a logistic regression model and the following covariates: gender, time updated age, whether a patient was antiretroviral-therapy experienced at the start of cART, the region of birth, total time in years spent with a viral load of more than 1000 cells per millilitre after starting cART, the probable route of HIV-1 transmission, current hepatitis B virus status, current hepatitis C virus status, the interval between HIV-1 diagnosis and the start of cART and total time in follow-up after the start of cART. The interval between HIV-1 diagnosis and the start of cART is a surrogate for the length of HIV-1 infection. In addition, we compared the incidences of diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies to age- and gender-matched groups from the general population of the Netherlands.

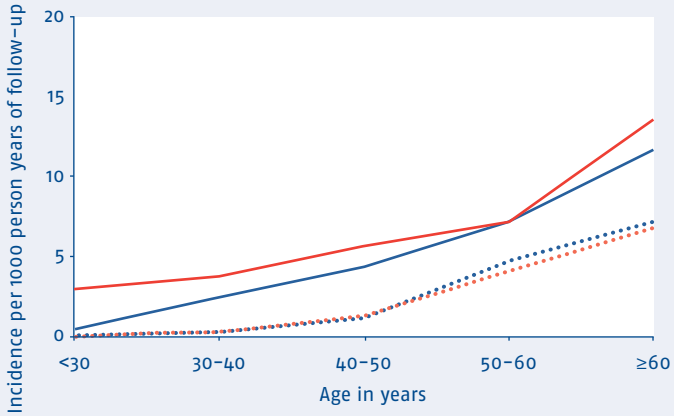
The number of cases of AIDS, grouped serious non-AIDS-defining diseases and individual serious non-AIDS-defining diseases per calendar year are presented in *Web Appendix Table 2.3* and the incidences per 1,000 years of person follow-up per calendar year are presented in *Web Appendix Table 2.4*. In summary, a total of 2087 of the 14,874 patients experienced at least one AIDS-defining event during 86,990 person-years of follow-up. Hence, the incidence of first AIDS-defining events after the start of cART was 24.0 (95% CI, 23.0–25.0) per 1000 person-years of follow-up. The incidence according to calendar year is presented in *Figure 2.1 A* and fell significantly from 175.4 in 1996 to 14.2 in 2010 (test for trend p-value < 0.0001). The incidence of AIDS fell rapidly between 1996 and 1998 and more slowly between 1998 and 2011. The slower decline in later calendar years may be attributable to the increasing proportion of patients in later calendar years with higher CD4 counts and, hence, a lower risk of the development of AIDS-defining events [43]. An overview of the incidence of AIDS and serious non-AIDS-defining diseases by age group, gender and latest CD4-cell count is presented in Web Appendix Tables 2.5 and 2.6.

A total of 1658 patients experienced at least one serious non-AIDS-defining disease during 67,211 person-years of follow-up. Hence, the incidence of grouped serious non-AIDS-defining diseases after the start of cART was 23.5 (95% CI, 23.5–25.9) per 1000 person-years of follow-up. This incidence rose significantly from 21.1 in 2002 to 29.9 in 2010 (test for trend p-value = 0.01). The increase in incidence might be due to the increasing mean age of the HIV-infected population, but it might also be due to the effects of living longer with HIV and the use of cART for many years [44, 45]. In a multivariate logistic regression model, increasing age (p-value < 0.0001), being antiretroviral-therapy experienced at the start of cART (p-value < 0.0001), having a lower CD4 count (p-value < 0.0001), being positive for hepatitis B (p-value = 0.002) and/or C (p-value < 0.0001) virus, having a longer time between HIV-1 diagnosis and the start of cART (p-value = 0.005) and being either less than a year or more than 11 years in follow-up (p-value < 0.0001) were associated with a raised incidence of grouped serious non-AIDS-defining diseases.

The incidence of renal insufficiency rose significantly from 1.7 cases per 1000 person-years of follow-up in 2002 to 7.4 cases in 2010 (test for trend p-value = 0.0006). In a multivariate logistic regression model, increasing age (p-value < 0.0001), lower CD4-cell count (p-value < 0.0001), positive for hepatitis C virus (p-value = 0.003) and either less than a year or more than 11 years in follow-up (p-value = 0.002) were associated with a raised incidence of renal insufficiency. There are no published data on the incidence of renal insufficiency as defined in SHM's database in the general population of the Netherlands. However, exposure to HIV and antiretroviral drugs has been associated with changes in renal function [31, 37]. In addition, the incidence of renal insufficiency has been linked to lower CD4 counts [46].

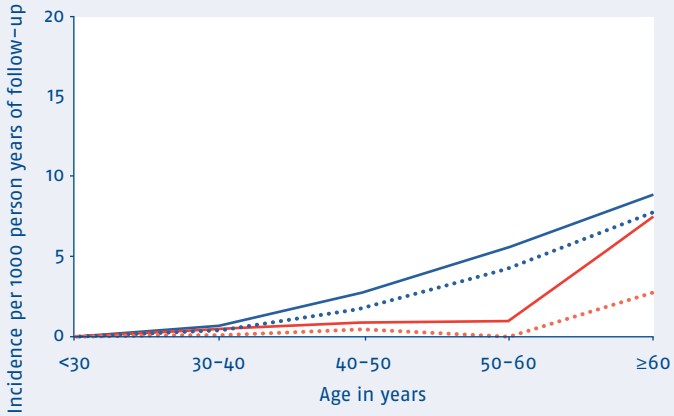
The incidence of liver disease was 5.4 cases per 1000 person-years of follow-up in 1998 and 6.2 cases in 2010. The incidence remained fairly stable between 1998 and 2010 (test for trend p-value = 0.61). In a multivariate logistic regression model, lower CD4 count (p-value = 0.001), being born in a country in Europe, North America or Southeast Asia (p-value = 0.04), positive for hepatitis B (p-value < 0.0001) and C (p-value < 0.0001) virus, the time between HIV-1 diagnosis and the start of cART (p-value = 0.002), and either less than a year or more than 11 years in follow-up (p-value = 0.009) were associated with a higher incidence of liver disease. There are no published data on the incidence of liver disease as defined in SHM's database in the general population of the Netherlands.

Figure 2.5: *The incidence of diabetes mellitus for men (blue lines) and women (red lines), for HIV-positive patients on cART (solid lines) and the general population of the Netherlands (dotted lines) according to age.*



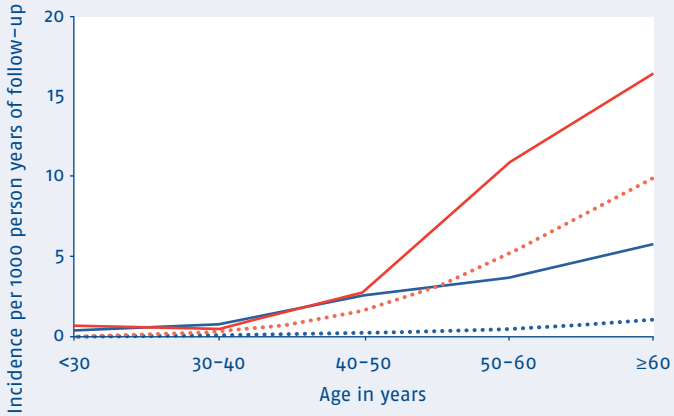
The incidence of diabetes mellitus was 6.3 cases per 1000 person-years of follow-up in 1998 and 4.3 cases in 2010. The incidence fell slightly between 1998 and 2010 (test for trend p-value = 0.008). In a multivariate logistic regression model, older age (p-value < 0.0001), being antiretroviral-therapy experienced at the start of cART (p-value < 0.0001), having a lower CD4-cell count (p-value = 0.04) and being born in a country outside of Europe or North America (p-value < 0.0001) were associated with the incidence of diabetes mellitus. Older age, lower last CD4 counts, being antiretroviral-therapy experienced at the start of cART and being born in a country outside of Europe or North America were associated with a higher incidence of diabetes mellitus. The incidence of diabetes mellitus according to age and gender for patients on cART and the general population [47] of the Netherlands are presented in *Figure 2.5*. The incidence is higher amongst patients on cART than in the general population. Higher incidences of diabetes mellitus have also been reported in other HIV-1-positive populations [30,48]. The incidence of diabetes mellitus may be increased amongst patients who have used protease inhibitors [49] or nucleoside reverse transcriptase inhibitors [50,51].

Figure 2.6: The incidence of myocardial infarction for men (blue lines) and women (red lines), for HIV-positive patients on cART (solid lines) and the general population of the Netherlands (dotted lines) according to age.



The incidence of myocardial infarction was 3.4 cases per 1000 years of person-years of follow-up in 2000 and 2.0 cases in 2010. The incidence fell slightly between 1998 and 2010 (test for trend p-value = 0.02). In a multivariate logistic regression model, being male (p-value = 0.009), increasing age (p-value < 0.0001), being antiretroviral-therapy experienced at the start of cART (p-value < 0.0001) and being born in a country in Southeast Asia (p-value < 0.0001) were associated with an increased incidence of myocardial infarction. The incidences of myocardial infarction according to age and gender for patients on cART and for the general population [52] of the Netherlands are presented in *Figure 2.6*. The incidence for patients on cART is higher than for the general population. The increased risk of myocardial infarction in patients with HIV may be related to HIV infection itself [53, 54], lifestyle factors [53] or complications resulting from use of antiretroviral drugs [55-57].

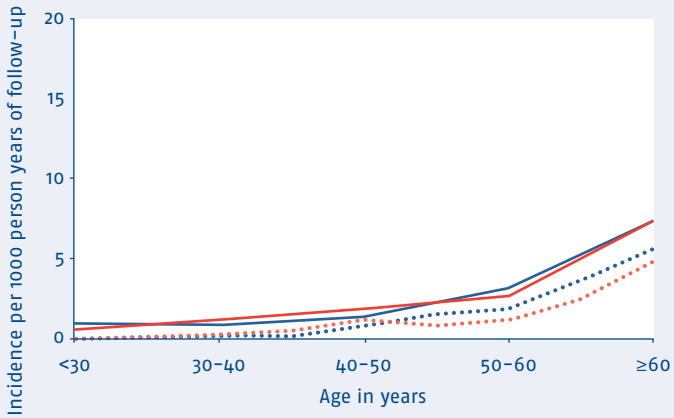
Figure 2.7: The incidence of osteoporosis for men (blue lines) and women (red lines), for HIV-positive patients on cART (solid lines) and the general population of the Netherlands (dotted lines) according to age.



The incidence of osteoporosis was 1.0 case per 1000 person-years of follow-up in 2002 and 4.3 cases in 2010. The incidence rose between 2002 and 2010 (test for trend p-value <0.0001). In a multivariate logistic regression model, being female (p-value = 0.005), increasing age (p-value < 0.0001), being born in the Netherlands (p-value = 0.03) and being either less than a year or more than 11 years in follow-up (p-value = 0.008) were associated with a higher incidence of osteoporosis. The incidence of osteoporosis according to age and gender for patients on cART and for the general population [58] of the Netherlands are presented in *Figure 2.7*. The incidence for both men and women is clearly higher for patients on cART aged more than 40 years. A higher incidence of osteoporosis has also been reported in other populations of HIV-infected patients [59]. It is thought that the cause of HIV-related osteoporosis is complex and may include features related to the HIV infection, antiretroviral treatment and traditional risk factors [60].

The incidence of stroke was 2.1 cases per 1000 person-years of follow-up in 2000 and 2.3 cases in 2010. The incidence was fairly stable between 2000 and 2010 (test for trend p-value = 0.63). In a multivariate logistic regression model, increasing age (p-value < 0.0001) and lower CD4 count (p-value < 0.0001) were associated with the incidence of stroke. The incidences of stroke according to age and gender for patients on cART and the general population [61] of the Netherlands are presented in *Figure 2.8*. The incidence in patients on cART is higher for both men and women and across age groups. Other studies have shown that the incidence of stroke may be higher amongst HIV-infected patients than amongst the general population [23] and that traditional risk factors, HIV infection itself and the use of antiretroviral medications may play a role in the occurrence of the condition. Accelerated atherosclerosis and vasculopathy associated with the use of antiretroviral medications may play an important role in stroke in HIV-patients [60].

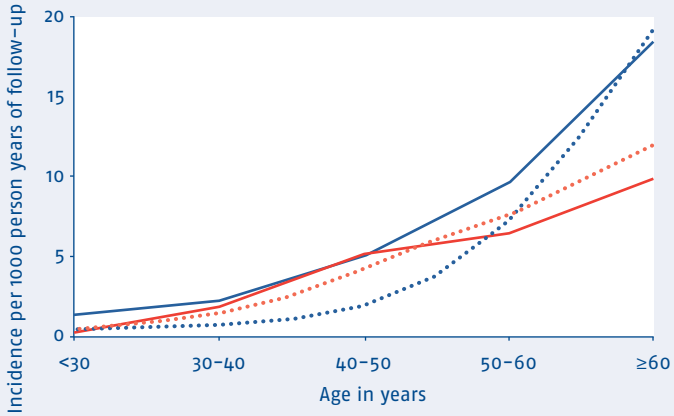
Figure 2.8: The incidence of stroke for men (blue lines) and women (red lines), for HIV-positive patients on cART (solid lines) and the general population of the Netherlands (dotted lines) according to age.



The incidence of non-AIDS-defining malignancies was 3.5 cases per 1000 person-years of follow-up in 1998 and 6.2 cases in 2010. The incidence rose between 1998 and 2010 (test for trend p-value = 0.003). In a multivariate logistic regression model, increasing age (p-value < 0.0001), being antiretroviral-therapy experienced at the start of cART (p-value = 0.01), having a lower CD4 count (p-value < 0.0001) and being born in the Netherlands, North America or Europe (p-value < 0.0001) were associated with a higher incidence of non-AIDS-defining malignancies. The incidence of non-AIDS-defining malignancies according to age and gender for patients on cART and for the general population of the Netherlands are presented in *Figure 2.9*. The incidence for women on cART is similar to the general population

of the Netherlands, but the incidence for men is consistently higher than the general population. An increased incidence of non-AIDS-defining malignancies has been reported in cohorts in Denmark [54], the United Kingdom [62] and the United States [63,64], although studies of individual types of cancer have not always shown this pattern [65]. Increased incidences of non-AIDS-defining malignancies may be the result of classic risk factors such as HIV infection and the use of cART [62], and are associated with exposure to low CD4 counts [66]. However, HIV may be a marker of behavioural [54] or family-related risk factors that increase the incidence of cancer in HIV patients [22, 41].

Figure 2.9: *The incidence of non-AIDS-defining malignancies for men (blue lines) and women (red lines), for HIV-positive patients on cART (solid lines) and the general population of the Netherlands (dotted lines) according to age.*



The increased incidence of diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies in patients on cART may be the result of traditional or family risk factors. The higher incidences may also be observed because the health of patients on cART is monitored regularly, meaning that morbidity may be noticed earlier than in the general population. However, there is increasing evidence that the ageing process may occur faster in HIV-positive patients, leading to increased frailty at earlier ages than in the general population [39, 67]. Immunosenescence, or changes in the immune system in older, uninfected individuals, resemble changes seen in untreated HIV-infected patients [68, 69]. The degree to which long-term cART can reverse these changes is the subject of ongoing investigations. Many of the factors associated with immunosenescence including thymus dysfunction and T-cell activation are more common amongst patients without a robust increase in CD4-cell counts after the start of cART than in those with a normal CD4-

cell count [70, 71]. Because low CD4-cell counts increase the risk of serious non-AIDS-defining diseases, HIV-associated immunosenescence may contribute to persistent immunodeficiency and early onset of age-associated illnesses [72]. We therefore explored the role of low CD4-cell counts, ageing, exposure time to HIV and other factors on the risk of non-AIDS-related mortality and morbidity in adjusted logistic models.

Web Appendix Table 2.7 shows that older age, lower CD4-cell counts, the use of mono- or dual antiretroviral therapy before the start of cART, and co-infection with hepatitis C virus were all associated with non-AIDS-related morbidity and mortality. Hepatitis B virus co-infection was associated with non-AIDS-related morbidity, but not mortality. The effect of a longer time between HIV diagnosis and the start of cART was also associated with both non-AIDS-related morbidity and mortality, but was stronger for mortality. The cumulative number of years spent with periods of HIV RNA levels of 1000 copies/ml or higher was associated only with non-AIDS-related mortality, independent of latest CD4-cell counts. Some patients in end-stage disease stop antiretroviral medication. We therefore excluded from the calculation of exposure time the viral load measurements taken less than six months prior to the end of follow-up. The effect of the cumulative number of years of exposure to plasma levels of 1000 or more HIV RNA copies/ml diminished to an odds ratio (OR) of 1.04 (95% CI, 0.96-1.12, p=0.32). Therefore, the effect of exposure time to HIV RNA levels of 1000 copies/ml or higher may be partly driven by patients stopping antiretroviral medication during end-stage disease.

The time between HIV diagnosis and cumulative time after starting cART with periods of viraemia, when taken together, can be seen as a marker of the cumulative exposure to HIV viraemia, albeit an imperfect one because the true moment of infection cannot be reliably estimated for most patients. Viraemia copy-years may be a more refined measure of cumulative plasma HIV RNA exposure than exposure time to plasma levels of more than 1000 HIV RNA copies/ml. Viraemia copy-years have been associated with time to all-cause mortality, also independent of CD4-cell counts [73], but this effect may also be partly due to patients stopping antiretroviral therapy during end-stage disease. More research is needed to study the independent effects of long-term viraemia, exposure to antiretroviral therapy medication, biomarkers of inflammation and immune activation on non-AIDS-related morbidity and mortality.

Loss to follow-up

The *Nederlandse Vereniging van HIV Behandelaren* [Dutch Association of HIV-treating Physicians] (NVHB) recommends that all HIV-positive patients who are not on antiviral therapy should have CD4 counts performed at least twice each year and HIV viral load determined at least once each year. In addition, the NVHB also recommends that all HIV-positive patients who are on antiviral therapy should have CD4 counts performed at least once each year and HIV viral load determined at least twice each year. The NVHB also recommends that certain groups of patients should have CD4 counts performed and viral load determined more often [28].

These recommendations imply that to receive optimal care, patients should visit their HIV treatment centre at least twice a year. However, personal circumstances may mean that a particular patient visits his or her treatment centre less often. Hence, in this report we define a patient as lost to follow-up if he or she has not visited an HIV treatment centre or had a CD4 count or HIV viral load determination for at least 12 months. This definition is similar to those used in many published studies carried out in Belgium [74], France [75, 76], the United Kingdom [77] and a range of European countries [78].

We examined data from 12,366 HIV-1-positive patients who started cART between 1 January 1996 and 1 January 2009 and followed them for a maximum of ten years after starting cART. We regarded patients who were not known to have died and whose last known contact with their HIV physician was before 1 January 2010 as lost to follow-up. A total of 1037 patients were lost to follow-up, and there were 82,741 person-years of follow-up.

Hence, 12.5 patients (95% CI, 11.8–13.3) became lost to follow-up per 1000 person-years of follow-up. This was lower than the 26.8 patients per 1000 person-years of follow-up found in a sample of patients from eight northern European countries [78], the 35 per 1000 person-years of follow-up in a cohort in France [75] and the 5.5% during the nine years of a study in Belgium [74]. Kaplan–Meier analyses of the time from the patient's start of cART to when he or she became lost to follow-up show that 11.6% of patients became lost to follow-up within 10 years of starting cART. This is slightly lower than the 13.4% found in a similar study in France [75].

Cox regression models show that gender, probable method of transmission of HIV-1, country of birth, CD4 count at the start of cART and age at start of cART are significantly associated with the time to a patient becoming lost to follow-up. Patients were less likely to become lost to follow-up if: they were female (hazard ratio (HR)=0.82, 95% CI=0.69 to 0.96, p-value=0.02); they had probably become infected with HIV-1 via homosexual contact (HR, 0.79; 95% CI, 0.64 to 0.96; p-value=0.02); they were born outside the Netherlands (HR, 0.25; 95% CI=0.21 to 0.30; p-value < 0.0001); they had a CD4 count under the median level in the population (HR, 0.87; 95% CI=0.76 to 0.99; p-value=0.048); and they were aged more than 30 years at the start of cART (HR, 0.81; 95% CI=0.70 to 0.94; p-value = 0.006). These results are similar to those found in longitudinal cohort studies in Belgium [74], France [76], the United Kingdom [77] and a range of European countries [78].

These results show that the current system of HIV treatment centres in the Netherlands is working to keep the percentage of patients lost to follow-up at a level lower than in surrounding countries. Monitoring of all HIV-positive patients at all HIV treatment centres by a single organisation helps avoid the "churn effect" [79], where patients who move between hospitals become repeatedly lost to follow-up. The results presented in this section also highlight the importance of informing and reminding HIV-positive patients of the importance of regular health care follow-up, even in the Netherlands. In addition, the results

also suggest that HIV treatment centres should continue to provide support to enable patients to surmount any obstacles they see to attending regular appointments with their treatment team and actively seek contact with patients who miss or delay appointments.

Conclusion

Before the introduction of antiretroviral therapy, HIV-1 infection was considered to be an acute illness with a mortality rate close to 100%. However, the widespread introduction of cART and its continuous improvements mean that HIV-1-positive patients are living longer and their risk of death from AIDS has decreased dramatically. However, at the same time, HIV-positive patients are ageing and have spent more time exposed to both HIV-1 itself and antiretroviral drugs. These factors may each contribute to a higher incidence of non-AIDS-defining diseases over time, such as renal disease, osteoporosis and non-AIDS-defining malignancies. In addition, there is substantial evidence that HIV-1-positive patients have a higher incidence of non-AIDS-defining diseases and that they are ageing faster and becoming frail more quickly than a gender- and aged-matched general population [39, 67].

The results presented in this chapter highlight the need for regular and careful monitoring of many aspects of the health of HIV-positive patients. This is particularly true as more patients live with HIV and take antiretroviral medication for the long term. These results also show that HIV-1 treatment in the Netherlands is generally good, but efforts to provide optimal treatment of HIV-1 should not be reduced. Thus, the need is highlighted for all physicians to remain aware of the symptoms of HIV infection and AIDS-defining conditions and to know how such symptoms may present in their patient population. In addition, physicians treating HIV-positive patients must remain aware of the increased incidence of serious morbidities and general frailty amongst these patients and develop the tools to balance antiretroviral medication with treatment for a variety of other chronic conditions.

3. Response to cART

Luuk Gras, Colette Smit, Ard van Sighem

cART in adults

In 2010, 1157 HIV-1-infected patients started combination antiretroviral therapy (cART); 30% of them started with CD4-cell counts at or above the currently recommended threshold of 350 cells/mm^3. Amongst patients from the Netherlands there was a lower percentage starting below this threshold (68%) than amongst those from sub-Saharan Africa (81%) or South America and the Caribbean (77%). Late HIV-1 diagnosis (defined as CD4-cell counts below 350/mm^3 at the time of diagnosis) was the major reason for a late start of cART. Within nine months of starting cART, 72% of the patients currently achieve HIV RNA plasma concentrations below 50 copies/ml. The viral load is lower amongst men and younger patients and those starting with CD4-cell counts of 350 cells/mm^3 or higher possibly because of poorer adherence to therapy. Although the time to initial virologic suppression may be longer in patients who start cART with CD4-cell counts of 350 cells/mm^3 or higher, there is a low probability of virologic failure in all three classes of antiretroviral drugs used in the initial regimen (nucleoside reverse transcriptase inhibitors, non-nucleoside reverse transcriptase inhibitors and protease inhibitors). Overall, we found that the risk of triple-class failure was low (3.4% at 5 years after starting cART). The level of risk was higher for patients from regions outside the Netherlands and those starting at lower CD4-cell counts, which may be due to different health-seeking behaviours between these two patient groups.

When cART has been started at CD4-cell counts between 350 and 500 cells/mm^3, eight years of therapy has induced viral suppression to below 50 HIV-1 RNA copies/ml, resulting in an increased mean of 800 CD4-cells/mm^3. This level is comparable to normal values seen in uninfected individuals. Increases were smaller when cART was started at lower CD4-cell counts and when viral load during cART was higher than 50 copies/ml. The increase in CD4-cell numbers was less with a lower HIV RNA plasma concentration in all patients at the start of cART, men, older patients and those from sub-Saharan Africa as compared to those from Western Europe and North America.

Of patients starting cART since, 50% continued their first-line regimen for more than three years. Toxicity remained the main reason for therapy discontinuation, although the incidence of toxicity-driven therapy changes has more than halved since the introduction of cART in 1996. Of all patients starting in 2007 and 2008, 18% changed the first regimen within two years because of toxicity. Patients with high CD4-cell counts at the start of cART, women and older patients had a higher risk for a toxicity-driven therapy change.

From our monitoring results on the effect of cART in the infected adult population, we conclude that improvement in HIV-testing rates is still needed to make possible a timely start of cART (≥350 cells/mm^3) in most patients. Both efficacy and tolerability of cART has improved over time, such that the majority of patients can remain on first-line cART for years. Starting cART within current guidelines and remaining on virologically successful therapy is important, because CD4-cell counts after only 8 years of continuous cART are comparable to those seen in HIV-1-uninfected individuals. As cART is now recommended relatively early in HIV disease, when CD4-cell counts have reached 350 cells/mm^3, monitoring adherence and, when necessary, measures to improve adherence are important. Because cART administration is currently lifelong, monitoring changes in viral load and CD4-cell count remains important in order to identify patients at risk for disease and to study the effect of the introduction of new assays and drugs on markers for disease.

cART in children and adolescents

The immunologic and virologic responses to combination antiretroviral therapy (cART) amongst HIV-infected children (aged 0-12 years at HIV diagnosis), adolescents (aged 13-17 years at HIV diagnosis) and young adults (aged 18-23) were compared. The proportion of cART use was highest amongst children. Although children showed a slower decrease in HIV RNA levels during the first 24 weeks on cART, the time between cART initiation and the first undetectable load did not differ amongst children, adolescents and young adults. The proportion of deaths was higher amongst the adolescents and young adults; the risk of death was lower in children compared to young adults.

cART in pregnant women

In this section, we report the response to combination antiretroviral therapy (cART) in 2382 women infected with the human immunodeficiency virus (HIV), 751 of whom were pregnant when monitored during follow-up. Of the pregnant women, 246 initiated cART, and 505 did so during their pregnancy. Median CD4-cell counts at the time of cART initiation were significantly higher amongst women who initiated cART during their pregnancy. These women initiated cART while pregnant not only because of low CD4-cell counts but also to prevent mother-to-child transmission (MTCT). No significant differences were found in the time to viral suppression for pregnant women compared to non-pregnant women. However, pregnant women had a significantly higher risk of virologic failure. The majority of women who initiated cART during pregnancy experienced virologic failure after delivery. Lower adherence rates postpartum might have caused this increased risk of virologic failure. Amongst the women who initiated cART before the start of their pregnancy, 16% had a detectable HIV RNA plasma level during pregnancy. The majority of the women who started cART before pregnancy and experienced treatment failure during the pregnancy had a treatment change while pregnant. An intervention to improve adherence during the postpartum period in HIV-infected pregnant women is needed to prevent virologic failure after pregnancy, whereas active preconception counselling in women with a known HIV infection and treatment changes amongst those who are trying to conceive are likely to prevent detectable HIV RNA plasma levels at delivery.

cART in volwassenen

In 2010 zijn 1157 HIV-1-geïnfecteerde patiënten gestart met combinatie antiretrovirale therapie (cART). Van hen had 70% een CD4-celaantal van 350 cellen/mm³ of minder, de grens die in de huidige richtlijn wordt aanbevolen als moment om therapie te starten. Het percentage Nederlandse patiënten dat onder deze grens van 350 CD4-cellen/mm³ startte (68%), was lager dan het percentage patiënten afkomstig uit Zuid-Amerika of de Cariben (77%) of uit sub-Sahara Afrika (81%). HIV-diagnose in een laat stadium was de voornaamste reden voor een late start.

Bij 72% van patiënten die sinds 2008 zijn gestart daalt de HIV-RNA-concentratie in plasma binnen 9 maanden tot onder de 50 kopieën/ml. Dit percentage is lager bij mannen, jongere patiënten en patiënten die therapie starten met 350 CD4-cellen/mm³ of meer – in deze laatste groep mogelijk door een mindere therapietrouw. Hoewel initiële virologische suppressie tot onder 50 kopieën/ml langer duurt bij patiënten die therapie starten met 350 CD4-cellen/mm³ of meer, hebben zij een kleinere kans op virologisch falen op elk van de 3 drugsklassen die momenteel worden voorgeschreven als eerste regime (nucleoside reverse transcriptase remmers, proteaseremmers en non-nucleoside reverse transcriptase remmers). De kans op virologisch falen op al deze 3 klassen was klein (3,4% van de patiënten, 5 jaar na starten van cART), maar groter bij patiënten afkomstig uit andere landen dan Nederland en patiënten die een lager CD4-celaantal hadden bij start van de behandeling. Dit kan het gevolg zijn van een verschil in zorgvraag tussen deze patiëntgroepen.

Na acht jaar therapie en virologische suppressie tot onder 50 HIV-1 RNA kopieën/ml stegen de gemiddelde CD4-celaantallen tot 800 cellen/mm³ wanneer cART werd gestart tussen 350 en 500 cellen/mm³. Deze aantallen zijn vergelijkbaar met normale waarden in ongeïnfecteerde personen. De stijging was kleiner wanneer met lagere CD4-celaantallen werd gestart, en wanneer HIV-1-RNA niet altijd tot onder 50 kopieën werd onderdrukt. De toename was ook kleiner bij mannen, oudere patiënten, een lagere HIV-RNA-concentratie in plasma bij de start van cART, en bij patiënten afkomstig uit sub-Sahara Afrika in vergelijking met patiënten uit West-Europa/Noord-Amerika.

De helft van de patiënten die sinds 2007 met cART zijn gestart, blijft tenminste 3 jaar dezelfde eerstelijnscombinatie gebruiken waarmee ze zijn gestart. Toxiciteit blijft de voornaamste reden om te stoppen; de incidentie van therapieveranderingen door toxiciteit is echter meer dan gehalveerd sinds de introductie van cART in 1996. Achttien procent van de patiënten die in 2007 en 2008 waren gestart, veranderde het eerste regime vanwege toxiciteit binnen 2 jaar. Patiënten met hoge CD4-celaantallen bij het starten met cART, vrouwen en oudere patiënten hadden een grotere kans op therapieverandering vanwege toxiciteit.

Uit deze resultaten van het monitoringsprogramma over het effect van cART in de volwassen populatie kan worden geconcludeerd dat het aantal HIV-testen nog steeds moet worden verhoogd om een tijdige start (bij ≥350 cellen/mm³) van therapie in de meerderheid van de patiënten mogelijk te maken. Effectiviteit en verdraagbaarheid van cART is in de loop van de tijd zodanig verbeterd dat de meerderheid van de patiënten jarenlang hetzelfde eerstelijnsregime

kan blijven gebruiken. Langdurige virologische suppressie en tijdig starten met cART zijn belangrijk omdat de CD4-celaantallen pas na 8 jaar continu succesvolle therapie vergelijkbaar zijn met die in de ongeïnfecteerde bevolking. Omdat volgens de huidige richtlijn wordt aanbevolen antiretrovirale behandeling relatief vroeg te starten, bij 350 CD4-cellen/mm^3, zijn monitoring van therapietrouw, en indien nodig therapietrouwbevorderende maatregelen belangrijk. Therapietrouw kan minder dan optimaal zijn bij patiënten die starten met een hoog CD4-celaantal vanwege een daling in kwaliteit van leven door bijwerkingen van de antiretrovirale therapie. Omdat cART momenteel gedurende de rest van het leven gebruikt dient te worden, blijft het belangrijk om veranderingen in de concentratie van het virus en de CD4-celaantallen te monitoren om problemen in de HIV-behandeling vroegtijdig te identificeren en het effect van nieuwe middelen en assays op ziektebeloop en epidemie te kunnen beoordelen.

cART in kinderen en adolescenten

De immunologische en virologische respons op behandeling met cART bij HIV-geïnfecteerde kinderen (0-12 jaar bij HIV-diagnose), adolescenten (13-17 jaar bij HIV-diagnose) en jongvolwassenen (18-23 jaar bij HIV-diagnose) wordt in deze paragraaf vergeleken. Het percentage kinderen dat wordt behandeld is hoger dan bij adolescenten of jongvolwassenen. Hoewel de daling in HIV-RNA in de eerste 24 weken bij kinderen het minst snel is, is er binnen deze drie groepen geen verschil in de tijd tussen start van cART en eerste ondetecteerbare HIV–RNA-concentratie. Het percentage sterfgevallen is hoger bij adolescenten en jongvolwassenen; kinderen hebben een kleinere kans op sterfte vergeleken met jongvolwassenen.

cART in zwangere vrouwen

In deze paragraaf onderzoeken we de respons op HIV-behandeling bij 2382 HIV-geïnfecteerde vrouwen, waarvan er 751 werden gemonitord tijdens de zwangerschap. In 246 vrouwen werd behandeling gestart vóór de zwangerschap en in 505 vrouwen tijdens de zwangerschap. Vrouwen die tijdens de zwangerschap met cART waren gestart hadden hogere CD4 aantallen bij de start. Deze vrouwen starten niet alleen vanwege lage CD4 aantallen maar ook om verticale transmissie van HIV te voorkomen. We vonden geen significant verschil in de tijd tussen start van behandeling en suppressie van de HIV-RNA-concentratie in plasma tussen zwangeren en niet-zwangeren. Zwangere vrouwen hadden wel een grotere kans op therapiefalen. De meeste vrouwen die tijdens de zwangerschap met cART begonnen, faalden op behandeling na de bevalling. Een mogelijke verklaring hiervoor is een lagere therapietrouw na de zwangerschap. Een detecteerbare HIV-RNA-concentratie in plasma werd gevonden in 16% van de vrouwen die vóór de zwangerschap met cART begonnen. De meeste vrouwen die vóór de zwangerschap met therapie begonnen en vervolgens faalden op hun therapie hadden hun therapie gewijzigd tijdens de zwangerschap. Interventies die therapietrouw na de zwangerschap verhogen en preconceptie-counseling met wijziging van het cART-regime bij vrouwen met een kinderwens kan de kans op therapiefalen tijdens of na de zwangerschap verkleinen.

cART in adults

Lower pill burden and once- or twice-daily dosing schemes, together with declining toxicity, have improved management of HIV treatment over time, although continuous and lifelong combination antiretroviral therapy (cART) is still needed to prevent HIV disease progression to AIDS and death [80]. During the first six months after the start 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 seen in uninfected subjects [81], and plasma HIV RNA can be maintained <50 copies/ml for long periods of time, provided adherence to therapy is high. Two new drug classes (integrase strand transfer inhibitors (INSTI) and chemokine co-receptor entry inhibitors) are now available, and together with new drugs in existing classes, they provide more therapy options not only for therapy-experienced patients but also for therapy-naïve patients. Still, questions about the effectiveness of cART remain. Patients starting cART with the INSTI raltegravir have shown a strong virologic and immunologic response [82], and raltegravir is now recommended as a first-line regimen in the United States. However, raltegravir is not recommended as part of initial cART in the Netherlands because of its unknown long-tem side effects and twice-daily dosing schedule; in the Netherlands once-daily regimens are preferred. Furthermore, in patients with a high viral load, the optimal combination of antiretroviral (ART) drugs is unclear [83]. Although there has been a shift towards starting HIV treatment at an earlier stage, debate is ongoing regarding at which stage of infection cART should be initiated [84-86]. Starting cART in a late stage puts patients at a higher risk of death, AIDS and serious adverse events [29, 87]. Disadvantages of starting cART early are that adherence may be poor due to the perceived loss of quality of life because of the toxic effect of antiretroviral drugs on cells and cell metabolism. This may cause suboptimal drug levels and possibly treatment failure [88, 89] and resistance [90]. Furthermore, long-term exposure to ART drugs and high-level viraemia increase the risk of clinical events [55, 57, 73, 91, 92].

Serious complications as a result of inadequate therapy may not emerge for years. 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

Of the 18,735 patients with an HIV-1 infection and a known date of diagnosis registered by Stichting HIV Monitoring (SHM), 14,874 started cART between January 1995 and December 2010 and had follow-up available after therapy initiation. Of these, 2520 were mono- or dual ART-experienced at the start of cART, and 12,354 were ART-naïve. To study changes over time in demographic and clinical characteristics at the start of cART possibly associated with efficacy and tolerability of cART, ART-naïve patients were further classified according to the

period of starting. In total, 6984 started cART prior to 2006 (early cART), 4213 between 2006 and 2009 (recent cART), and 1157 in 2010 (*Table 3.1*). Patients starting in 2011 are not included as follow-up for these patients was too short to report a response to cART.

Table 3.1: *Baseline characteristics of 14,874 patients starting combination antiretroviral therapy (cART) between 1 January 1995 and 31 December 2010.*

	Year of starting cART							
	1995–1999		2000–2005		2006–2009		2010	
	N	%	N	%	N	%	N	%
Total	4470		4935		4297		1172	
Gender								
Male	3739	83.6	3512	71.2	3475	80.9	991	84.6
Transmission risk group								
MSM	2767	61.9	2187	44.3	2587	60.2	778	66.4
IDU	1014	22.7	2032	41.2	1301	30.3	306	26.1
Heterosexual contact	345	7.7	303	6.1	129	3.0	32	2.7
Blood or blood products	99	2.2	69	1.4	35	0.8	4	0.3
Unknown	245	5.5	344	7.0	245	5.7	52	4.5
Region of origin								
Netherlands	2910	65.1	2309	46.8	2525	58.8	729	62.2
W-Europe/N-America/Australia	520	11.6	358	7.3	286	6.7	88	7.5
Caribbean/S-America	386	8.6	602	12.2	490	11.4	115	9.8
Sub-Saharan Africa	403	9.0	1274	25.8	641	14.9	134	11.4
Other	251	5.6	392	7.9	355	8.3	106	9.0
Clinical stage CDC-C	1516	33.9	1397	28.3	819	19.1	210	17.9
HCV								
Negative	3314	74.1	3990	80.9	3680	85.6	1018	86.9
Positive	411	9.2	399	8.1	342	8.0	77	6.6
Unknown	745	16.7	546	11.1	275	6.4	77	6.6
HBV								
Negative	3761	84.1	4300	87.1	3849	89.6	1053	89.8
Positive	330	7.4	335	6.8	277	6.4	58	4.9
Unknown	379	8.5	300	6.1	171	4.0	61	5.2
Other drug class next to NRTI in initial regimen								
NNRT	464	10.4	2445	49.5	2941	68.4	829	70.7
PI	3942	88.2	2006	40.6	1106	25.7	273	23.3
NNRT+INSTI					9	0.2	15	1.3
PI+INSTI					19	0.4	10	0.9
INSTI					32	0.7	15	1.3
Other*	64	1.4	484	9.8	190	4.4	30	2.6

	Year of starting cART							
	1995–1999		2000–2005		2006–2009		2010	
	N	%	N	%	N	%	N	%
Daily frequency of initial regimen								
1	20	0.4	1029	20.9	3064	71.3	979	83.5
2	1936	43.3	3768	76.4	1198	27.9	179	15.3
3	2431	54.4	67	1.4	4	0.1		
≥4	26	0.6	16	0.3	1	0.0	2	0.2
Unknown	57	1.3	55	1.1	30	0.7	12	1.0
ART-experienced at start cART	2059	46.1	362	7.3	84	2.0	15	1.3
cART started during pregnancy	47	1.1	398	8.1	206	4.8	33	2.8
cART started during primary infection	89	2.0	258	5.2	335	7.8	111	9.5
	Med	IQR	Med	IQR	Med	IQR	Med	IQR
Age at starting cART	37.6	32.5–44.8	37.6	31.2–44.5	40.5	33.6–47.5	40.9	33.5–48.6
CD4-cell count at start cART (cells/mm^3)	200	80–340	190	80–300	240	140–310	300	180–360
HIV RNA at start cART (log_{10} cps/ml)	4.75	4.04–5.28	5.00	4.43–5.34	4.95	4.40–5.34	4.93	4.39–5.35

** Other includes regimens including only NRTIs, regimens including both PIs and NNRTIs and other combinations.*
***Legend:** cART= combination antiretroviral therapy; MSM=men having sex with men; IDU=injecting drug use; W-Europe=Western Europe; N-America=North America; S-America=South America; CDC-C=Centers for Disease Control category C; HCV=hepatitis C virus; HBV=hepatitis B virus; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; INSTI=integrase strand transfer inhibitor; med=median; IQR=interquartile range*

A higher proportion of men having sex with men (MSM) (p=0.0001) and of patients originating from the Netherlands (p<0.0001) were found in the group of patients starting in 2010 compared to all patients starting between 2000 and 2009.

According to current guidelines [28, 93, 94], the recommendation is to start cART before CD4 counts reach a threshold of 350 cells/mm^3; this has been reflected since 2008 in the higher median CD4 count found at the start of cART. The median CD4-cell count increased from 240 cells/mm^3 in 2008 to 280 cells/mm^3 in 2009 and 300 cells/mm^3 in 2010 (test for trend p<0.0001). Median CD4-cell counts were 190 cells/mm^3 between 2000 and 2005 (p<0.0001 compared to 2010) and 200 cells/mm^3 between 1995 and 1999 (p<0.0001). Of patients starting cART in 2010 with a known CD4-cell count, 26% had a count of less than 200 cells/mm^3, which was similar to 2009 (also 26%) but lower than the 35% in 2008 (p<0.0001). When we took the current threshold of 350 CD4-cells/mm^3 into account, 30% of the patients started cART in time in 2010, which was an improvement from 25% in 2009 (p=0.002). In 2009 and 2010, the percentage of MSM (31%) and patients from the Netherlands (29%) who started at CD4-cell counts of 350 cells/mm^3 or more was higher than amongst heterosexually infected

patients (20%, p<0.0001 compared to MSM), patients from sub-Saharan Africa (18%, p<0.0001 compared to patients from the Netherlands) and amongst those from South America and the Caribbean (21%, p=0.01). A timely diagnosis of HIV is an obvious prerequisite for a timely start of cART. In 2009 and 2010, the median CD4-cell counts at HIV diagnosis amongst those starting with 350 or more CD4-cells/mm^3 were 520 cells/mm^3 (interquartile range [IQR], 430-670); amongst those starting with less than 350 CD4-cells/mm^3, the median was 326 cells/mm^3 (150-480). These figures show that a timely diagnosis does not guarantee a timely start of cART; in 2009 and 2010 combined, 25% of patients starting cART with less than 350 CD4-cells/mm^3 had more than 480 CD4-cells/mm^3 at HIV diagnosis. It has been shown that repeated testing for HIV may lead to a diagnosis at a less advanced stage, making a timely start of cART more likely [19]. Apart from late presentation, late cART initiation has been associated with missed visits [95]. Reasons associated with patients' refusal to start cART have been fear of adverse events, no perceived necessity for starting, too much of an extra psychological burden of living with HIV and fear for stigmatization when taking pills [96, 97]. However, now that first-line regimens have become less toxic and administration is mostly once daily, it is unknown whether these remain the reasons for non-initiation, as the reason for starting cART late is not recorded in the data collection.

Because CD4-cell counts at the start of cART have increased over time, the percentage of patients with an AIDS diagnosis at the start of cART has decreased over time (from 33.9% before 2000 to 18% in 2010, p<0.0001). The median plasma HIV RNA concentration at the start of cART in 2010 was similar to that between 2006 and 2009 (Wilcoxon test, p=0.61). Over time, daily dosing of the initial regimen has shifted from three times daily (54% amongst patients starting cART between 1995 and 1999) to once daily (84% amongst those starting in 2010). Of patients starting in 2010, 71% used an NNRTI-based initial regimen. All recommended first-line regimens (efavirenz/tenofovir/emtricitabine [NNRTI-based], ritonavir-boosted atazanavir/ tenofovir/emtricitabine or ritonavir-boosted darunavir/ tenofovir/emtricitabine [both PI-based]) are once-daily regimens [28]. Once-daily regimens have been associated with a modestly better adherence compared to twice-daily regimens [98].

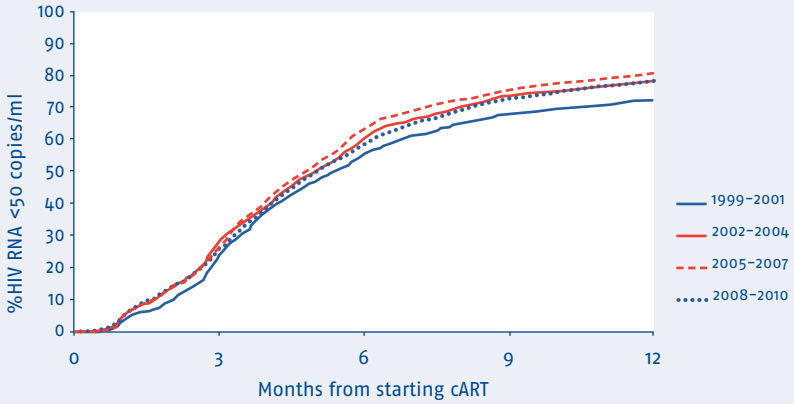
The percentage of patients in 2010 with hepatitis B virus (HBV) or hepatitis C virus (HCV) co-infection at the start of cART was non-significantly lower than the percentage between 2006 and 2009 (p=0.06 and p=0.17, respectively).

In summary, our monitoring results show that patients start cART currently at higher CD4-cell counts than ever before. Still, 70% of the patients commence cART too late according to current guidelines, and the percentage of late starters is even higher amongst heterosexually infected patients and those from sub-Saharan Africa or South America and the Caribbean. Repeated testing for HIV in individuals at risk for infection may lead to an earlier diagnosis, making a timely start of cART more likely. To ensure a timely start of cART, it is equally important to keep diagnosed patients in regular follow-up. To improve the percentage of patients who begin cART in a timely manner, it is important to gain more insight into the reasons for a late start.

Virological response

The short-term virological response to cART is an important marker for longer-term clinical outcome. HIV RNA in plasma after 36 weeks of cART still had additional prognostic value for predicting AIDS, even after adjustment for viral load levels at three years after the start of cART [99]. We therefore monitor the time to virological suppression to below 50 copies/ml during the first year after the start of cART. Overall, the percentage of patients with initial virological suppression to below 50 copies/ml increased from 58.3% (95% CI, 56.5-60.1%) at 6 months to 72.3% (70.6-74.0%) at 9 months and 80.0% (78.4-81.6%) at 12 months. The percentage of patients with a plasma viral load less than 50 copies/ml nine months after starting cART increased from 67.8% (95% CI, 64.9-70.7%) between 1999 and 2001, to 73.5% (71.3-75.6%) between 2002 and 2004 and to 75.2% (73.3-77.0%) between 2005 and 2007 (*Figure 3.1*). Between 2008 and 2010, it was 72.3% (95% CI, 70.5-73.9%). Time to initial suppression across the four periods for the start of cART significantly differed between each group (overall log rank test p<0.0001).

Figure 3.1: *Kaplan–Meier estimates of the percentage of patients with initial suppression <50 copies/ml during the first year after starting combination antiretroviral therapy (cART) by starting year.*

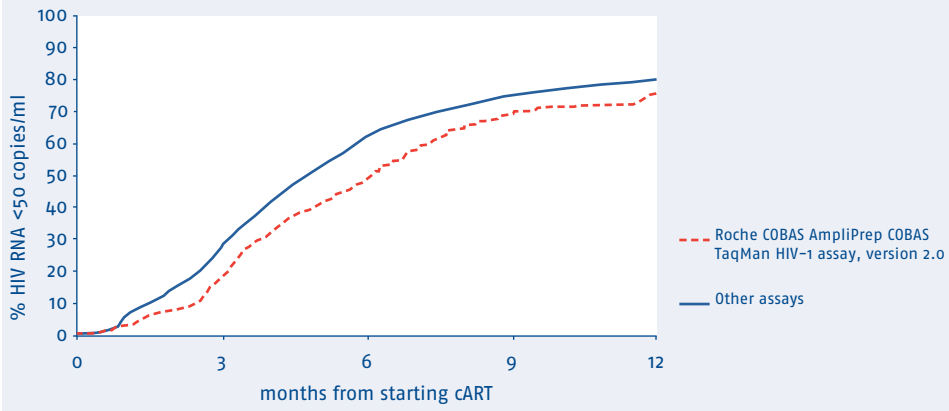


Since 2008, some laboratories have begun using the new Roche COBAS AmpliPrep COBAS TaqMan HIV-1 assay, version 2.0 (CAP/CTM v2.0) in routine practice. HIV RNA concentrations <50 copies/ml measured with earlier assays were frequently found to be >50 copies (mostly between 50-1000 copies/ml) when measured with the new CAP/CTM v2.0 assay [100]. The clinical meaning of low-level viraemia detected with the CAP/CTM v2.0 assay remains unclear, but it has been associated with a shorter duration of viral load <50 copies/ml, as measured with other assays before the use of the CAP/CTM v2.0 assay [101]. Implications for the monitoring of patients with low-level viraemia as measured by the CAP/CTM v2.0 assay include additional viral-load testing and clinical visits, both of which put an additional stress on patients and care providers [102].

We determined if and when laboratories had started to use the CAP/CTM v2.0 assay as the standard test to measure the level of HIV RNA in plasma. The level of RNA was determined by the CAP/CTM 2.0 assay in 24% of all plasma samples taken during 2009. This increased to 42% in 2010 and then 63% in 2011. The CAP/CTM 2.0 assay was used as the standard test to determine the viral load in 31% of patients starting cART in 2009, with an increase to 45% in 2010.

The Kaplan–Meier estimates of the percentage of patients with initial suppression to <50 copies/ml by type of assay is shown in *Figure 3.2* for 2822 patients starting cART in 2008, 2009 or 2010. Results of one laboratory were excluded from further analyses because of internal problems in viral load quantification. Time to initial suppression was significantly shorter when measured with an assay other than CAP/CTM v2.0 (log rank p<0.0001). Median time to observing HIV RNA <50 copies/ml was 6.1 months after starting cART when CAP/CTM v2.0 was used and 4.8 months when other assays were used. When plasma viral load was measured with the CAP/CTM v2.0 assay, the viral load of 75.1% (95% CI, 70.0-79.9%) of the patients was suppressed to ≤50 copies/ml within one year from the start of cART compared to 83.3% (95% CI, 81.7-84.9) when other assays were used.

Figure 3.2: *Kaplan–Meier estimates of the percentage of patients with initial suppression <50 copies/ml during the first year after starting cART according to type of assay used for viral load quantification.*



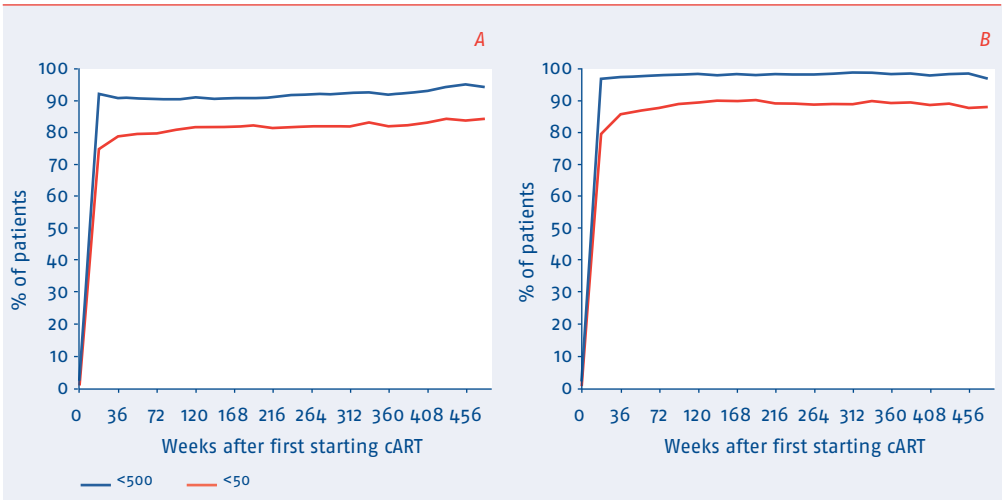
To study factors associated with a shorter time to initial suppression to HIV RNA <50 copies, we performed Cox regression analyses using data from 7864 patients who had started cART from 1999 onwards and were subsequently tested with an assay with a lower quantification limit of ≤50 copies/ml. *Web Appendix Table 3.1* shows that the probability of reaching viral-load levels <50 copies/ml by the calendar year of starting cART, unadjusted for other confounders, increased from 1999 to 2004, was stable between 2004 and 2008 and decreased in 2009 and 2010. In analyses adjusted for demographic and clinical confounders, as well as the type of initial regimen, laboratory testing and type of standard assay used to measure viral load, the trend of a longer time to initial suppression to ≤50 copies in patients starting in 2009 or 2010 was no longer apparent. In other words, when the trend over time was adjusted, it could be explained by changes of other confounders, such as increased use of the CAP/CTM v2.0 assay (amongst others). The hazard ratio (HR) of reaching <50 copies/ml when comparing the CAP/CTTM v2.0 assay with other assays was 0.72 (95% CI, 0.62-0.83). Starting a regimen that included an integrase inhibitor was significantly associated with a shorter time to suppression. Starting a twice-daily PI-based regimen was not significantly associated with a shorter time to initial suppression compared to starting a once-daily PI-based regimen (HR, 1.10 [95% CI, 0.97-1.24)]). Once-daily lopinavir-containing regimens have been associated with improved adherence but not with improved initial virological response [103, 104]. NNRT-based once-daily regimens were associated with a shorter time to initial suppression (HR compared to twice-daily regimens, mostly prescribed until 2005, 0.88 [95% CI, 0.80-0.97; p=0.15]). In agreement with other studies [105, 106], time to suppression was significantly longer in patients aged <30 years (HR compared to 30-39 years, 0.89 [95% CI, 0.82-0.96; p=0.003]), in male patients (HR, 0.84, [95% CI, 0.77-0.92; p<0.0001]), patients infected through intravenous drug use (HR compared with MSM, 0.76, [95% CI, 0.65-0.89; p=0.0005]), patients with higher CD4-cell counts at the start of cART (HR 350-500 compared to 200-350 cells/mm^3, 0.89 [95% CI, 0.82-0.97; p=0.01]) 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 lower perceived necessity for therapy, and lowered perception is associated with higher CD4-cell counts at the start of cART [107]. Data collection in this last study was between 2002 and 2004; it is unknown what the effect of a lower pill burden and more tolerable regimens in more recent years is on these associations.

After initial virological success, more than 30% of patients on cART experienced episodes of viraemia [108]. High-level viraemia has been associated with a poorer clinical outcome and smaller increases in CD4-cell count [108-110], but low-level viraemia seems to be of limited clinical significance. Short-term low-level viraemia was not associated with AIDS, death or CD4-cell count response [108, 111-113]. However, frequent or persistent periods of low-level viraemia have been reported to be associated with treatment failure and emergence of drug resistance [114, 115]. Also, detectable plasma viral load <50 copies/ml measured with more sensitive viral load assays was associated with a lower probability of sustained virological suppression [116]. We therefore monitored long-term virological response.

Figure 3.3 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 88% to 90% for those continuously on cART and remained stable up to 480 weeks from the start of cART. The percentage of patients on cART with a plasma viral load >500 copies/ml after 48 weeks fluctuated between 1% and 2%. A higher percentage of the patients on cART (8% to 10%) had low-level viraemia, which was between 50 and 500 copies/ml. Younger age and sub-Saharan African origin have been associated with a smaller probability of virological suppression to <50 copies/ml during long-term follow-up [1].

Introduction of new viral-load assays, drug classes and drugs in existing drug classes all impact HIV care. Monitoring changes in short-term and long-term virological responses therefore remains important

Figure 3.3: *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 of ≤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. In total, 8720 patients starting cART were included, but this number diminished over time due to differences in length of follow-up.*



Triple-class virological failure

Current regimens contain drugs from five different classes: nucleotide reverse-transcriptase inhibitors (NRTIs), non-NRTIs (NNRTIs), protease inhibitors (PIs), integrase inhibitors (INSTI) and entry inhibitors. As the latter two drug classes have been available for only a few years and recommended first-line combinations contain two NRTIs and either an NNRTI or a boosted PI, virological failure of all of the three original drug classes represent a key stage in a patient's history of drug failure. Triple-class virological failure has been studied by the Pursuing Later Treatment Options II (PLATO II) study, a European collaboration of several HIV observational cohorts including data reported in this chapter [117]. We followed the PLATO II study definitions and analyses to gain greater insight into the number of patients with triple-class virological failure and risk factors for triple-class virological failure in the Netherlands.

The median (IQR) follow-up of the 9211 patients was 3.7 years (IQR, 1.7-6.9 years). Patient selection and definitions are described in *Table 3.2*. In total, 110 patients experienced a triple-class virological failure (1.2%). The incidence of triple-class virological failure increased during the first two years after starting cART and fluctuated between 2.3 and 4.8 per 1000 person-years of follow-up between 2 and 10 years after starting cART. The cumulative percentage of patients with triple-class virological failure at 5 years and 10 years after starting cART was 1.5% and 3.7%, respectively. A significantly higher risk of triple-class virological failure was observed in younger patients (HR for every 10 years older, 0.55 [95% CI, 0.44-068; p<0.0001]), in accord with the earlier reports of poorer short-term virological response compared to that in older patients. Patients originating from South America and the Caribbean and sub-Saharan Africa had a higher risk of triple-class virological failure than patients from the Netherlands. Also, patients with lower CD4-cell counts and higher plasma viral load at the start of cART had a borderline significantly higher risk of triple-class virological failure (overall p-value=0.06 for differences across CD4-cell count categories and p=0.15 for differences across viral load categories). Patients who start cART in a timely manner and are thus diagnosed in an early disease stage are likely to have a different pattern of health-seeking behaviour than those diagnosed at a later stage, and region of origin may be associated with these differences. Patients with HBV co-infection at the start of cART were also at significantly higher risk of triple-class virological failure. The risk of triple-class virological failure did not differ significantly according to the calendar year of starting cART (1998-2003 vs. 2004-2010, p=0.36).

Table 3.2: Unadjusted and adjusted risk estimates for the hazard of triple-class virological failure. Time from the start of cART to triple-class virological failure was analysed by Cox regression. The 9211 patients who are represented comprise a subgroup of the 14,875 patients shown in Table 3.1. Patients who were ART-naïve at the start of cART or who started in or after 1998 with a regimen containing either two NRTIs and one NNRTI or two NRTIs and one PI/r were included. Virological failure was defined as one viral-load measurement above 500 copies/ml following at least four months of continuous antiretroviral therapy. Triple-class virological failure was defined as virological failure whilst receiving two NRTIs, one NNRTI and one PI/r, provided the last failure was at least four months after a switch to a new drug class. The number of person-years at risk was calculated as the number of years from four months after starting cART to the date of triple-class virological failure, the last clinical visit, CD4-cell count or viral-load measurement, whichever came first.

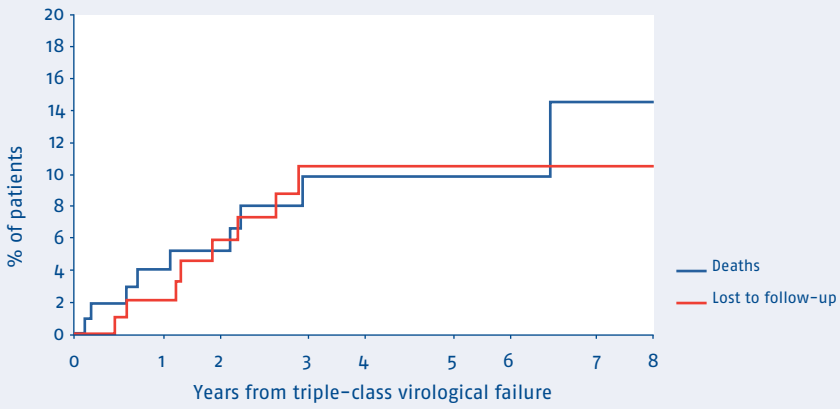
	Unadjusted		Adjusted	
	HR (95% CI)	P value	HR (95% CI)	P value
Female gender	1.83 (1.23-2.72)	0.003		
Transmission risk group				0.06
MSM	1.00			
Heterosexual contact	2.30 (1.50-3.53)	0.0001	1.14 (0.66-1.95)	0.65
IDU	2.54 (1.13-5.71)	0.02	1.59 (0.67-3.77)	0.29
Other	3.54 (1.96-6.40)	<.0001	2.25 (1.16-4.35)	0.0161
Region of origin				0.002
Netherlands	1.00		1.00	
W-Europe/N-America	0.87 (0.31-2.44)	0.79	0.78 (0.27-2.23)	0.65
Caribbean/South America	2.79 (1.61-4.82)	0.0002	2.23 (1.26-3.96)	0.006
Sub-Saharan Africa	4.32 (2.78-6.72)	<.0001	2.47 (1.38-4.41)	0.002
Other	0.43 (0.10-1.78)	0.24	0.28 (0.07-1.18)	0.08
Age at the start of cART (per 10 year older)	0.55 (0.44-0.68)	<0.0001	0.61 (0.49-0.77)	<0.0001
CD4-cell count at the start of cART (cells/mm^3)				0.06
<50	2.52 (1.46-4.33)	0.0009	2.03 (1.15-3.58)	0.01
50-200	1.60 (0.96-2.67)	0.07	1.40 (0.83-2.36)	0.21
200-350	1.00		1.00	
350-500	0.29 (0.07-1.21)	0.09	0.33 (0.08-1.41)	0.14
≥500	1.24 (0.47	0.66	1.26 (0.47-3.34)	0.65
Year of starting cART				
1998-2003	1.34 (0.86-2.08)	0.20		
2004-2010	1.00			
HIV RNA at the start of cART (copies/ml)				0.15
<10,000	0.67 (0.26-2.08)	0.41	0.53 (0.20-1.39)	0.20
10,000-100,000	1.00			
≥100,000	1.50 (0.96-2.35)	0.07	1.40 (0.89-2.23)	0.15
AIDS at the start of cART	1.43 (0.97-2.12)	0.07		
HCV Positive	0.49 (0.18-1.34)	0.17		

		Unadjusted		Adjusted
	HR (95% CI)	P value	HR (95% CI)	P value
HBV Positive	1.95 (1.09–3.49)	0.02	1.89 (1.05–3.39)	0.03
Initial regimen				
2 NRTIs + 1 NNRTI	1.00			
2 NRTI + 1 PI/r	1.20 (0.82–1.75)	0.36		
cART started during pregnancy	1.97 (0.86–4.48)	0.11		
cART started during primary infection	0.54 (0.17–1.69)	0.28		

Legend: cART=combination antiretroviral therapy; HR=hazard ratio; CI=confidence interval; MSM=men having sex with men; IDU=injecting drug use; W-Europe=Western Europe; N-America=North America; HCV=hepatitis C virus; HBV=hepatitis B virus; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI/r=ritonavir-boosted protease inhibitor

We further selected the 110 patients with triple-class virological failure to study its clinical significance. The Kaplan–Meier estimate of the percentage of patients who died after triple-class failure was 14.5% at eight years (*Figure 3.4*). However, there was also a high percentage of patients who were lost to follow-up (10.5% at eight years), which suggests the true rate of death might be higher.

Figure 3.4: Kaplan–Meier estimates of the percentage of patients who died and who became lost to follow-up after triple-class virological failure.



Development of triple-class virological failure does not mean that all three classes have been exhausted. Newer PIs and NNRTIs such as darunavir and etravirine have been shown to be effective in treatment-experienced patients [118, 119]. Also, we did not look for the presence of resistance-associated mutations, but this is currently being investigated in the PLATO II study. Virological failure could have occurred without the emergence of resistance mutations, especially when adherence was very poor, but viral suppression might be achieved without having to change the regimen.

The rate of triple-class virological failure in the Netherlands is lower than the rate reported by the PLATO II multi-cohort study, which included data reported in this chapter (1.5% vs. 3.4% at five years). An, at least partial, explanation for the lower rate in the Netherlands is the low proportion of heterosexually infected patients in our cohort. Heterosexually infected patients in the PLATO study had a higher risk of triple-class virological failure.

Although there was a trend toward an increased risk of triple-class virological failure with lower CD4-cell counts at the start of cART, patients starting cART with lower counts (<350 cells/mm^3) had a shorter time to initial suppression to ≤50 copies/ml than patients with higher viral loads. These contrasting results need more study. Patients with high CD4-cell counts may be less adherent initially because of the side effects of the drugs; however, they may seek a comfortable combination that they can tolerate for a longer time more actively than patients with low CD4-cell counts, who may have a less active health-seeking behaviour.

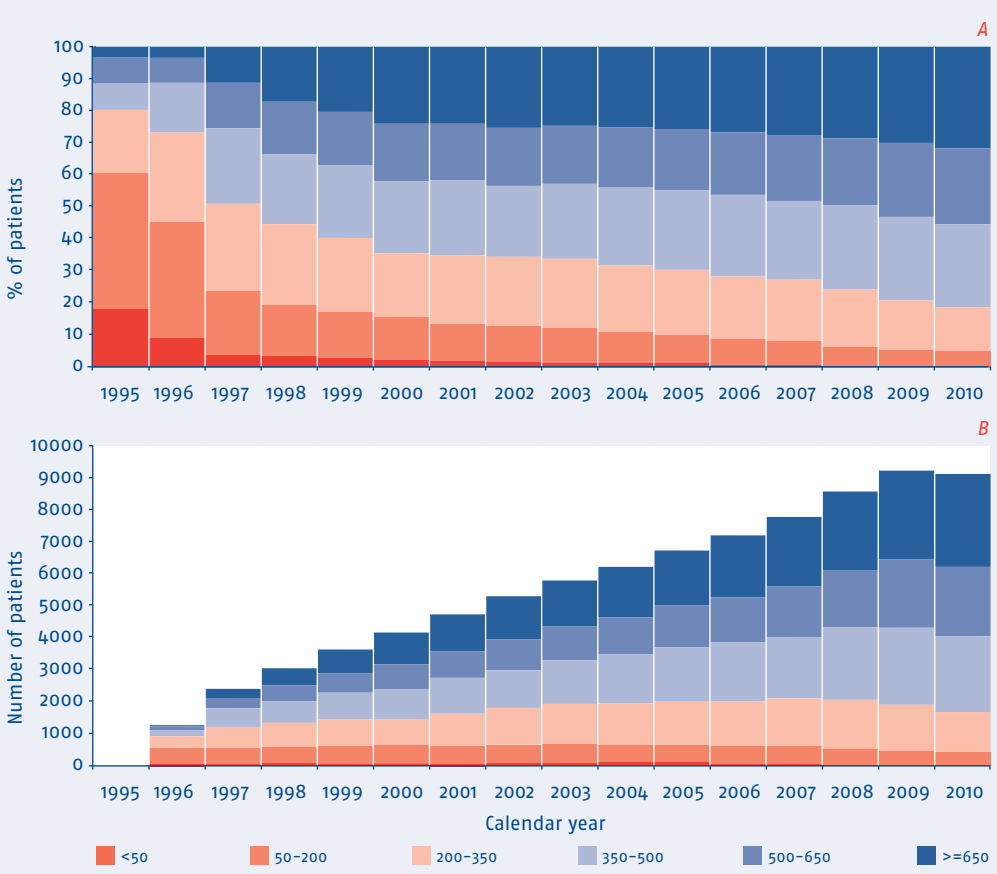
Immunologic response

The clinical benefit of cART is strongly related to the level of recovery of CD4-cell count (Chapter 2) [17, 87, 120]. Furthermore, longitudinal modelling the long-term effect of cART on the immune status of patients can assist in deciding when to start cART. Therefore, in this section, we report on the immune status in the treated population in the cART era and long-term CD4-cell count responses after the start of cART.

Immune status in the treated population by calendar year

Figure 3.5 shows the immune status of patients in each calendar year after the start of cART. After starting cART, the percentage of patients with counts <200 cells/mm^3 that put them at higher risk for AIDS dropped from 45% in 1996 to 5% in 2010. This decrease was not only relative but also absolute. The number of patients with low CD4-cell counts (<200 cells/mm^3) at the end of each calendar year decreased from 710 in 2003 to 504 in 2009. Figures for 2010 should be interpreted with caution as they are not yet complete. The trend of starting cART with higher CD4-cell counts that was begun in 2007 partly explains the drop in absolute number of patients with low CD4-cell counts at the end of each calendar year.

Figure 3.5: Last available CD4-cell count in each calendar year after the start of cART. The percentage (A) and the number (B) of patients with CD4-cell counts is shown as 0-50, 50-200, 200-350, 350-500, 500-650 and ≥650 cells/mm³. For each patient the last available CD4-cell count between July and December of each year and after starting cART was selected.

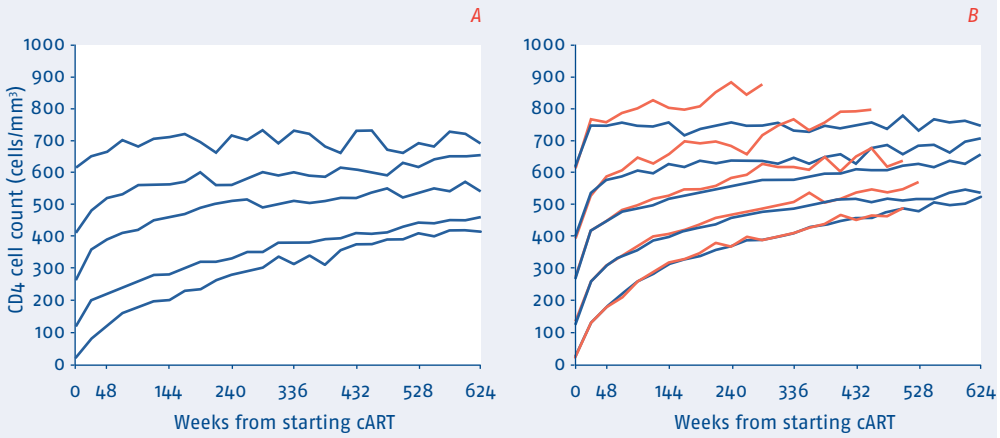


Longitudinal CD4-cell count changes after starting cART

Out of the 14,874 patients who started cART, a CD4-cell count at the start of therapy was unavailable for 1375 (9%), and they were excluded from further analyses. We then studied CD4-cell count changes in the entire population of 13,499 patients who had started cART, including those on cART and those experiencing a therapy interruption. ART-experienced patients started cART at median CD4 counts of 197 cells/mm³ (IQR, 80-340; the median increased to 310 CD4-cells/mm³ (IQR, 175-490) at 48 weeks, 440 (IQR, 270-640) at 240 weeks, 498 (IQR, 320-700) at 480 weeks and 529 (IQR, 370-730) at 624 weeks. 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 220 cells/mm³ (IQR, 100-320) at the start of cART, but showed greater increases to 391 (IQR, 260-540) at 48 weeks, 500 (IQR, 360-670) at 240 weeks, 580 (IQR, 410-770) at 480 weeks, and 610 (IQR, 440-840) at 624 weeks. *Figure 3.6* shows the median CD4-cell count after the start of cART stratified by the CD4-cell count at the start of cART. Median CD4-cell counts for patients starting cART with <50 and 50-200 cells/mm³ and for those with 200-350 and 350-500 cells/mm³ seemed to converge after ten years, which could be because of the "healthy survivor effect", which means that patients with low CD4-cell counts are more likely to die and patients who do well remain in follow-up. Another explanation is that there are different levels of adherence in these patient groups, although adherence in all patients was high enough to maintain virological suppression.

Figure 3.6: *Median CD4 count according to the count at the start of combination antiretroviral therapy (cART) in (A) ART-experienced patients and (B) ART-naïve patients, determined by CD4-cell count at the start of cART (<50, 50-200, 200-350, 350-500 and ≥500 cells/mm³). Blue lines show the median CD4-cell counts in all patients after starting cART, including patients on cART and those experiencing a therapy interruption. Red lines in the right plot show the median CD4-cell counts for patients with an initial suppression to <50 copies/ml within nine months after starting cART and with plasma HIV RNA concentration levels <50 copies/ml thereafter. In this 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.*



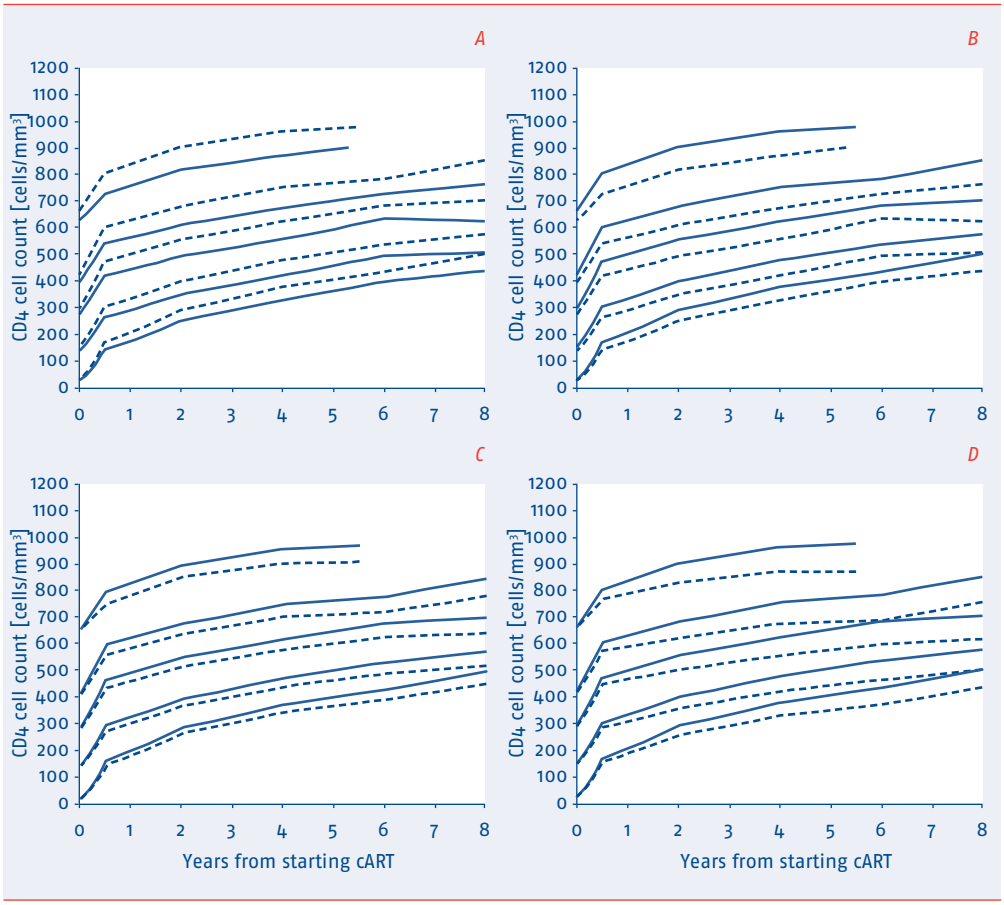
Increases in long-term CD4-cell count are known to depend on the level of virological suppression during cART [81,121-123]. To study the maximum capacity of cART to restore CD4-cell counts, we restricted analyses to therapy-naive patients with continuous viral suppression (<50 copies/ml). Only patients were included who had reached HIV RNA levels of <50

copiers/ml within nine months after the start of cART. CD4-cell counts after virological failure (defined as two consecutive viral-load measurements >50 copies/ml) were excluded. Median CD4 counts at week 432 were 453 cells/mm^3 for patients starting with <50 cells/mm^3, 540 cells/mm^3 for those starting between 50 and 200 cells/mm^3, 653 cells/mm^3 for those starting between 200 and 350 cells/mm^3 and 795 cells/mm^3 for patients starting between 350-500 cells/mm^3 (*Figure 3.6 B*, blue lines). Fewer than 50 patients who had started cART with a CD4 count of 500 cells/mm^3 or higher had a suppressed viral load at 432 weeks. Although median CD4-cell counts fluctuated over time and did occasionally decrease, the trend over time was an increase in median CD4-cell counts in patients succeeding on cART. For patients starting cART with <50 CD4-cells/mm^3, the median CD4-cell counts did not differ greatly from the median CD4-cell counts for those with suppressed viral load. The difference in median CD4-cell counts over time between all patients and those with a suppressed viral load increased with higher CD4-cell counts at the start of cART. This is because a substantial proportion of patients starting cART with high CD4-cell counts either interrupt therapy or do not maintain a viral load <50 copies/ml whilst on therapy.

To minimize the effect of random fluctuations in CD4-cell count and to be able to study other factors influencing CD4-cell count during successful cART, we performed a mixed-effects regression analysis, including all available CD4-cell counts after the start of cART up to the first date of either the moment virological suppression <50 copies/ml was lost or eight years after the start of cART. Besides CD4-cell count at the start of cART, gender, HIV RNA at the start of cART, injecting drug use as the most likely mode of HIV transmission, age (<50 and ≥50 years) and region of origin were also included in the model. The slopes of the CD4-cell count were allowed to change at 6 months, 2, 4 and 6 years.

Model estimates show that the mean CD4-cell counts continue to increase with virologically successful cART. For those starting cART with <350 cells the mean CD4-cell counts significantly increased up to six years. Changes between six and eight years were still positive, but due to the smaller number of patients with longer-term follow-up, they were significant only for patients with <200 CD4-cells/mm^3 at the start of cART. The mean CD4-cell counts eight years after starting cART for patients starting with 50, 50-200, 200-350 and 350-500 CD4-cells/mm^3 were 485 (95% CI, 457-516), 551 (95% CI, 530-574), 665 (95% CI, 637-694) and 800 cells/mm^3 (95% CI, 746-856), respectively. *Figures 3.7 A-D* show changes in CD4-cell count for subgroups. Mean annual changes were significantly higher up to four years after first starting cART for women compared to men and up to two years for individuals less than 50 years of age compared to those 50 years or more. Reduced thymic function with older age probably explains the smaller increases in older patients [70, 124]. The mean change was significantly higher during the first six months after starting cART for those with a plasma viral load of 100,000 copies/ml or more compared to those with less than 100,000 copies/ml and for patients from Western Europe and North America compared to patients from sub-Saharan Africa. After six months the rate of change did not differ significantly among these patient groups. Once the mean CD4-cell count began to differ between subgroups, the difference remained during further follow-up.

Figure 3.7 A-D: Estimated CD4-cell count trajectories during virologically successful combination antiretroviral therapy (cART) by CD4-cell count at the start of cART. The solid lines in every graph shows the CD4-cell count response for a male patient from Western Europe or North America infected through sexual contact less than 50 years of age with ≥100,000 HIV RNA copies/ml at the start of cART. In the dashed lines in each of graphs A-D one of the 1 variables is changed. A) shows differences in CD4-cell count response according to gender (solid line: male, dashed line: female), B) CD4 count response according to region of origin (solid line: Western Europe or North America, dashed line: sub-Saharan Africa), C) CD4-cell count response according to HIV RNA at the start of cART (solid line: ≥100,000, dashed line: 10,000-100,000 copies/ml), and D) CD4-cell count response according to age at the start of cART (solid line <50, dashed line ≥50 years). CD4-cell counts were back-transformed from the modelled $\sqrt[3]{cells/mm^3}$ to the original scale. All lines show the response for a typical patient (with a median change in CD4-cell count during every period).



Several studies have reported the existence of a "plateau effect" in the response to CD4-cell count [81,125-127], whereas others have not [128,129]. It is true that individual patients on virologically successful cART experience periods of decreasing CD4 count, but the fact that CD4-cell counts show a decreasing pattern on a population level in certain cohorts and not in others could reflect different levels of ongoing viraemia, immune activation or different age distributions amongst studies. Also, there might be differences in the definition of decreasing CD4-cell counts, CD4 "plateaus" or CD4 set point across studies. Longer time on virologically successful cART has been associated with a higher risk of decreasing CD4-cell counts, even though the counts had not reached normal levels [130].

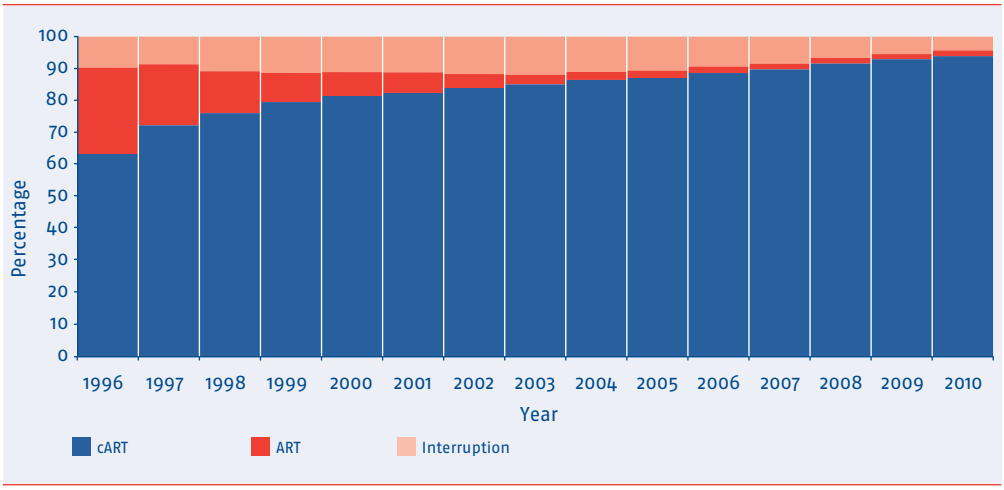
Our results presented in this section show that the mean CD4-cell count of patients starting cART with a count between 350 and 500 cells/mm^3 after eight years of virologically successful cART is near normal. Normal CD4 levels in uninfected subjects have been reported to be 1050, 840, and 800 cells/mm^3 for women, heterosexual men, and MSM, respectively [131], with a likely geographic variation in normal ranges [132]. 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 they drop to <500 cells/mm^3.

Therapy switches and incidence of toxicity-driven regimen change during the first three years after start of cART

Antiretroviral therapy is associated with adverse clinical events and laboratory toxicities. This may lead to poor adherence and treatment discontinuation, which are major reasons for treatment failure and development of resistant strains [88-90]. As switching to sequential regimens leads to less effective virological suppression than the first-line regimens and a higher number of treatment switches has been associated with smaller gains in CD4-cell count, the avoidance of toxicity is important [133, 134]. In this section we report on trends over time in treatment switches and especially treatment-limiting toxicities during the first three years after starting cART.

Over time the percentage of patients who remained on cART after the initial start increased (*Figure 3.8*) from 63% in 1996 to 94% in 2010. The increasing proportion over time may be due to more tolerable drugs and easier dosing schedules. Staying on cART is important, as therapy interruptions have been linked to adverse outcomes such as death, opportunistic infection, cardiovascular and liver disease [135].

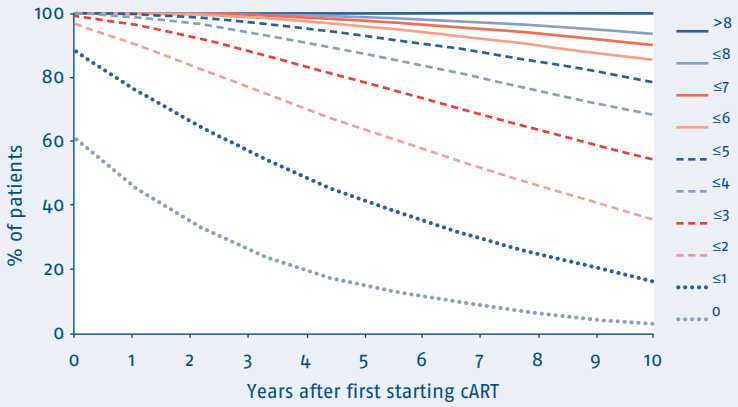
Figure 3.8: Percentage of patients on cART, ART (but not cART) or not on therapy on 31 December of each year after starting cART.



Legend: cART=combination antiretroviral therapy; ART=antiretroviral therapy

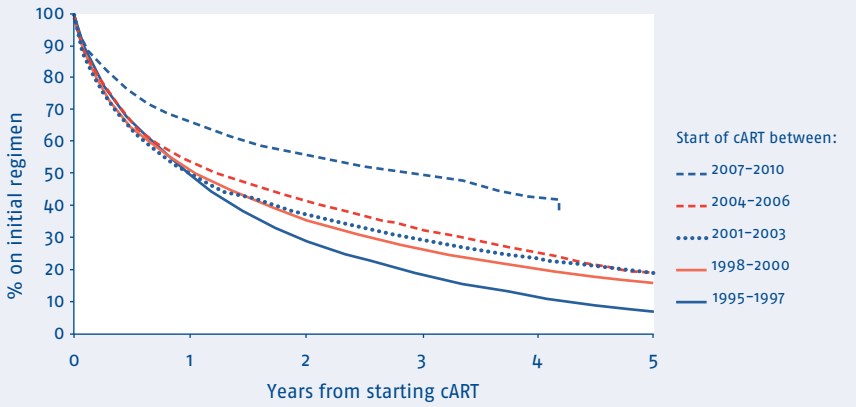
The number of sequential regimens after starting cART is shown in *Figure 3.9*. One year after starting cART 61% of patients were still on the initial regimen, and 89% were either on the first or second regimen. However, only 12% of patients still in follow-up after ten years after the first start had had less than two different regimens. The Multicenter AIDS Cohort Study (MACS) found a similar distribution of the number of regimen changes after five years of cART [133]. Furthermore, they found that more than two regimen changes after five years of cART was associated with lower increases in CD4-cell count between 5 and 12 years, but the association became less strong when the analysis was restricted to patients who were ART-naïve at the start.

Figure 3.9: Number of patients with combination antiretroviral therapy (cART) regimen changes by year after starting cART. Restarting a cART regimen after a therapy interruption of less than two weeks was not regarded as a change.



There is a clear trend over time towards a longer interval before discontinuation of the initial cART regimen, as *Figure 3.10* shows. Of the 14,874 patients who had started cART, 10,465 discontinued the initial regimen. The percentage of patients still on the initial cART regimen two years after starting was 29% (95% CI, 17-31%) for those starting during 1995-1997, 36% (95% CI, 34-38%) during 1998-2000, 37% (95% CI, 35-39%) during 2001-2003, 41% (95% CI, 39-43%) during 2004-2006, and 56% (95% CI, 54-58%) for those starting in or after 2007. The most common reasons for discontinuing were: toxicity (39%), patient decision (12%), simplification (12%), and treatment failure (11%), similar to results reported by others [136]. Over time, the percentage of patients who switched the initial cART regimen because of toxicity within two years decreased from 28% of all patients starting cART between 1998 and 2000 to 18% of patients starting in 2007 and 2008 (test for trend, $p<0.0001$). However, amongst those starting in 2007 and 2008, toxicity was also the most common reason for initial discontinuation of the cART regimen.

Figure 3.10: Kaplan–Meier estimates of the percentage of patients still on initial combination antiretroviral therapy (cART) regimen by period of initiation. Planned switches according to protocol and changes to fixed co-formulation dosages were not counted as a regimen change.



As toxicity is the most common reason for discontinuing not only the first regimen but also subsequent regimens, we now focus on trends over time in changes related to toxicity of regimen during the first three years of cART.

During the first three years after the start of cART, patients were followed for a total of 34,185 person-years (PY); of that number, 33,226 person-years (97.2%) included cART (PYcART). The overall incidence of toxicity-driven regimen changes was 213 (95% CI, 208-218) per 1000 PYcART. Patients could change the regimen more than once. During follow-up, 10,150 of the 14,874 patients (68.2%) did not change the regimen because of toxicity. The maximum number of changes because of toxicity in a single patient was 15.

The incidence was highest (538 per 1000 PYcART) during the first three months after the start of cART; it declined to 239 per 1000 PYcART between three and six months, 184 per 1000 PYcART between 6 and 12 months, and 139 per 1000 PYcART between 24 and 36 months ($p<0.0001$). The incidence of toxicity-driven therapy changes during the first three years following cART initiation was highest in 2000 and declined with later calendar year of initiation (*Table 3.3*). The increase in incidence in 2009 and 2010 can be largely attributed to patients not yet having three years of follow-up after starting cART. A relatively large part of the total person-years on cART were those during the first three months after the start of cART, when the number of toxicity-driven therapy changes is high. However, when models were further adjusted for the period after cART initiation and other risk factors, the relative risk for starting in 2009 and 2010 was still slightly higher compared to starting in 2008 ($p=0.38$ and $p=0.17$, respectively).

Table 3.3: Toxicity-driven changes in therapy during the first three years after the start of cART. Ninety-five percent confidence intervals (95% CI) for the incidence per 1000 PYcART were obtained by the Poisson distribution. Adjusted estimates of relative risk were obtained with logistic regression models including: age, gender, region of origin, transmission risk group, time after starting cART (0-6, 6-12, 12-24 and 24-36 months)

Year of starting cART	PYcART	N	Incidence per 1000 PYcART (95% CI)	Adjusted relative risk (95% CI)
1995	193	63	327 (251-418)	2.14 (1.56-2.93)
1996	3908	1259	322 (305-340)	1.87 (1.64-2.14)
1997	3104	825	266 (248-285)	1.58 (1.39-1.80)
1998	2069	523	253 (232-275)	1.49 (1.30-1.70)
1999	2025	473	234 (213-256)	1.42 (1.23-1.64)
2000	1872	527	281 (258-307)	1.61 (1.40-1.84)
2001	2060	418	203 (184-223)	1.23 (1.07-1.42)
2002	1997	390	195 (176-216)	1.20 (1.02-1.40)
2003	2024	384	190 (171-210)	1.14 (0.98-1.32)
2004	2137	396	185 (168-205)	1.11 (0.97-1.28)
2005	2205	363	165 (148-182)	1.00
2006	2105	346	164 (147-183)	1.02 (0.88-1.18)
2007	2541	357	140 (126-156)	0.88 (0.75-1.02)
2008	2777	358	129 (116-143)	0.78 (0.67-0.91)
2009	1748	298	171 (152-191)	0.84 (0.72-0.99)
2010	461	109	236 (194-285)	0.91 (0.74-1.12)

***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*

A previous toxicity-driven therapy change was associated with a 93% increased risk of a new toxicity-driven therapy change (95% CI, 81-106%; p<0.0001) compared to no previous change. This was also found in another study and may be because some patients are more prone to toxicity due to underlying conditions not accounted for in the analysis [137]. Patients with higher CD4-cell counts at the start of cART also had a higher risk of a toxicity-related therapy change (≥500 vs. 200-350 cells/mm^3). Patients in an early stage of HIV infection in our experience are more likely to stop than are patients in a more advanced stage when they experience therapy-induced loss of quality of life [138, 139]. However, other observers have not found an increased risk for discontinuation of antiretroviral drugs because of toxicity at higher CD4-cell counts [140, 141]. Patients starting cART during the primary infection phase had a 43% (95% CI, 28-59%; p<0.0001) increased risk for a toxicity-driven therapy change, independent of the CD4-cell count at the start of cART. The risk increased when patients were older than 40 years at the start of cART. Compared to patients aged 30-40 years, the risk was increased by 12, 14 and 29% for patients aged between 40-50, 50-60 and 60 years or more, respectively. Older age has been associated with an increased risk for a toxicity-driven therapy change in other reports [142], and this may partly be because the pharmacokinetic

profile of drugs in the plasma of older patients is different from that of younger patients. In accordance with results from other studies [138, 141, 143], women had a 35% higher risk of toxicity-driven therapy change compared to men (95% CI, 25-47%; p<0.0001). This has been attributed to a lower body mass index [144] and a higher drug concentration in plasma in women [145], but in our analysis differences in men and women remained after adjusting for weight. The risk was similar amongst women who were pregnant and non-pregnant when cART was started (p=0.42). Finally, patients with an HCV co-infection when cART was started had a 26% increased risk (95% CI, 14-38%, p<0.0001) and men who have sex with men (MSM) compared to heterosexually infected patients with a 21% increased risk (95% CI, 5-39%; p=0.006).

Dyslipidemia in the cART-treated population

Dyslipidemia is common in treated patients infected with HIV-1 and has been defined as having a total cholesterol level of ≥6.2 mmol/l, a high-density lipoprotein (HDL) cholesterol level of ≤0.9 mmol/l or a triglyceride level of ≥2.3 mmol/l or having received lipid-lowering drugs [56]. Dyslipidemia may increase the risk of cardiovascular disease [146]. The prevalence of hypercholesterolemia (total cholesterol level above 6.2 mmol/l) was 27% in patients on cART that included PIs and 23% of those on cART that included NNRTIs, as compared to 8% in untreated patients. Prevalence for hypertriglyceridemia (triglyceride level above 2.3 mmol/l) was 40% in patients on cART that included PIs, 32% when NNRTIs were included and 15% in untreated patients [147]. Exposure to certain drugs or drug classes has been associated with an increased risk of dyslipidemia [148, 149], but hypertriglyceridema was also commonly observed before the cART era [150]. Here we report on changes in total cholesterol, HDL cholesterol and triglyceride level in the cART-treated population over time.

Figure 3.11: Last available total cholesterol value in each calendar year after the start of cART. (A) shows the percentage and (B) the number of patients with total cholesterol levels according to level of total cholesterol. For each patient the last available total cholesterol measurement between July and December of each year and after starting cART was selected.

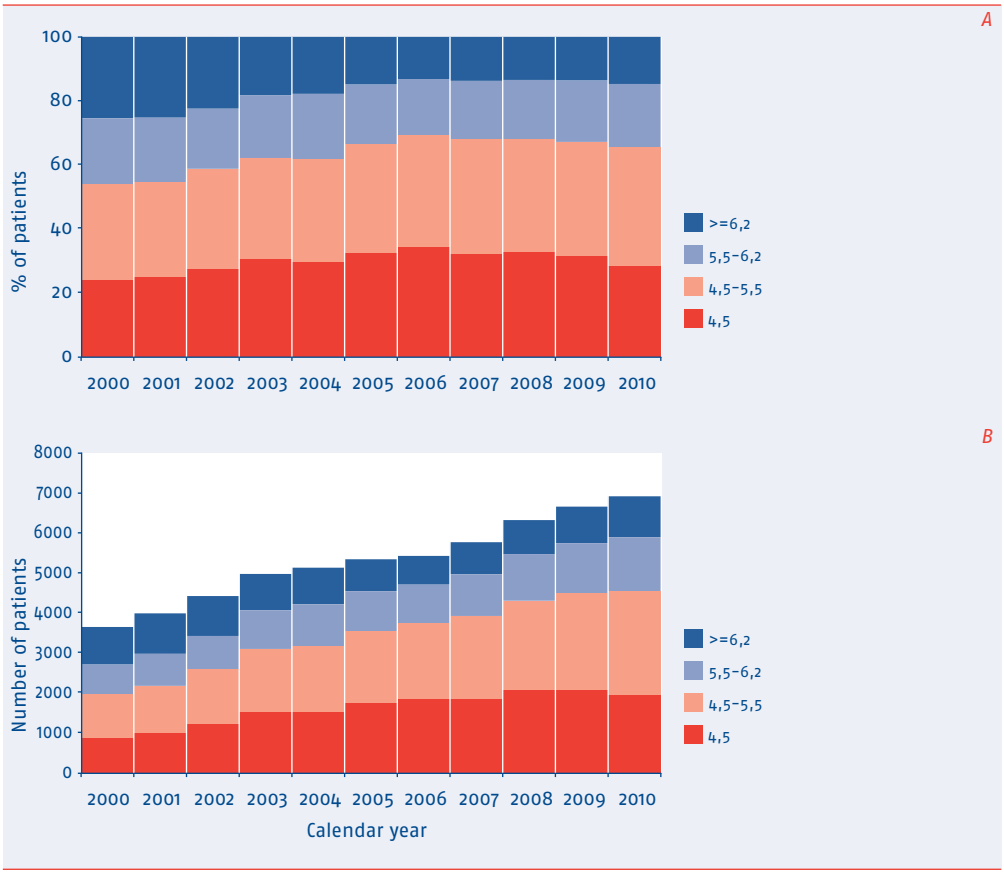


Figure 3.12: Last available total high density lipoprotein (HDL) cholesterol in each calendar year after the start of cART. (A) shows the percentage and (B) the number of patients according to HDL cholesterol levels. For each patient the last available HDL cholesterol measurement between July and December of each year and after starting cART was selected.

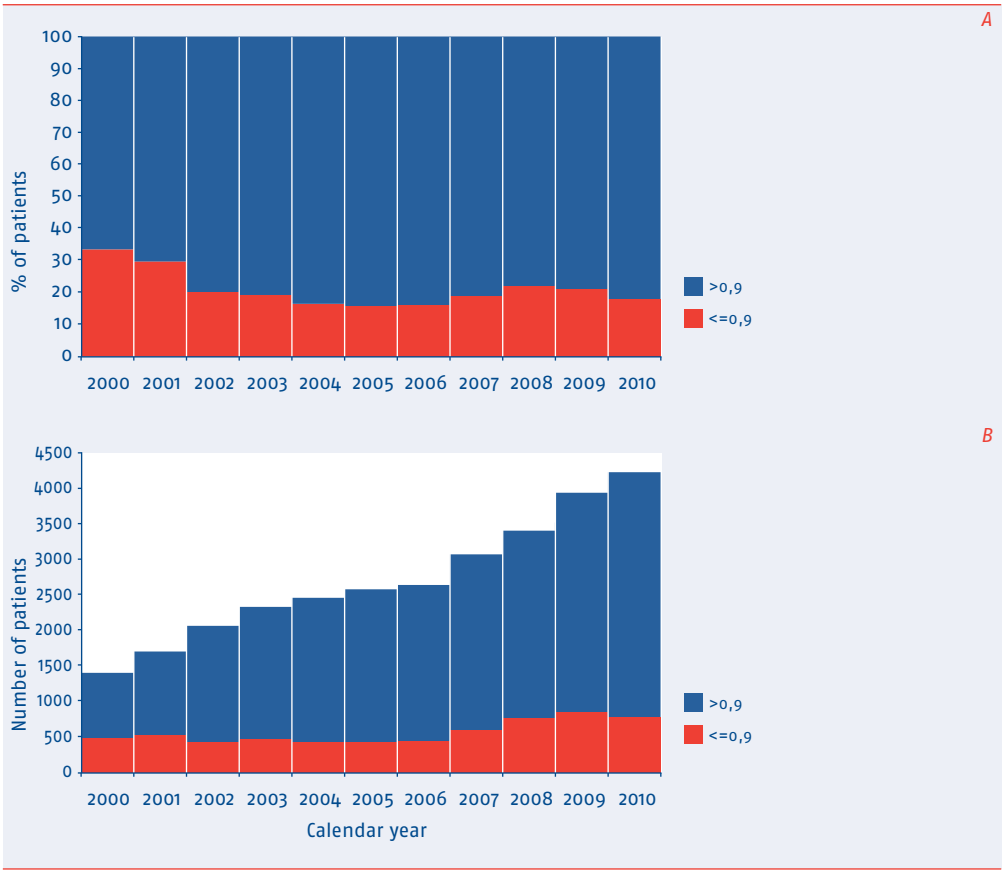
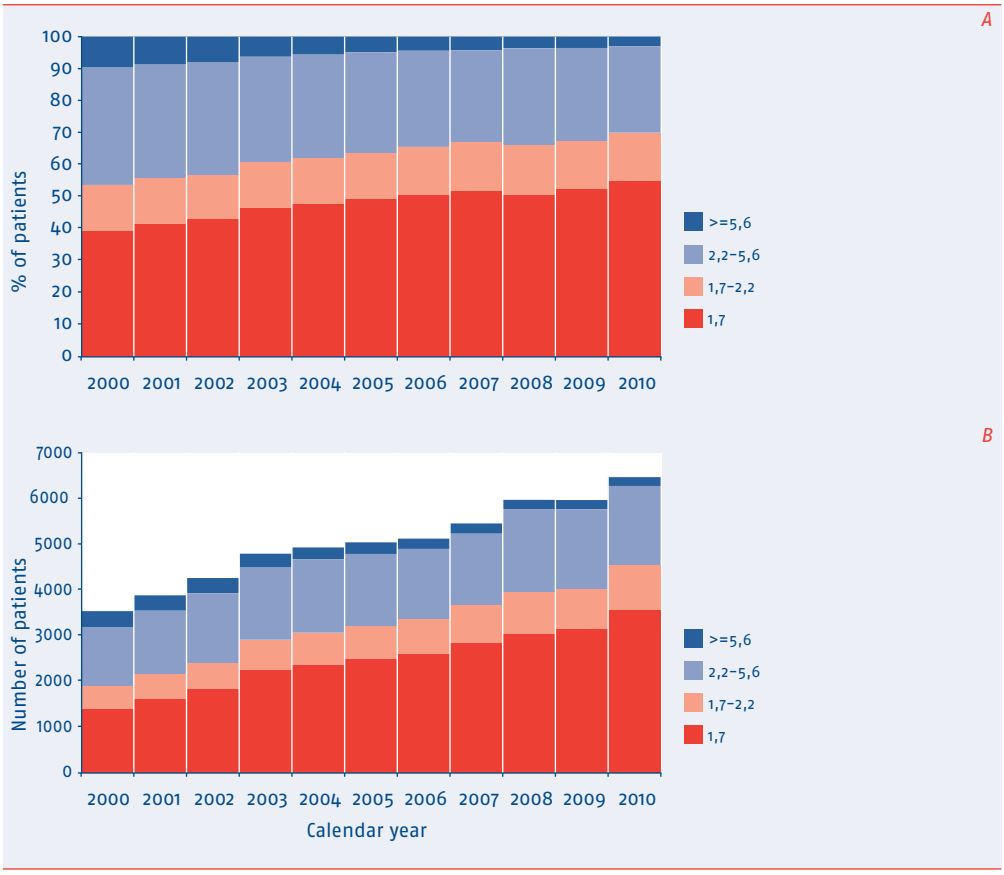


Figure 3.13: *Last available triglyceride level in each calendar year after the start of cART. (A) shows the percentage and (B) the number of patients according to triglyceride levels. For each patient the last available total triglyceride measurement between July and December of each year and after the start of cART was selected. No information on fasting was recorded.*



Figures 3.11-3.13 show that the proportion of patients with high total cholesterol and triglyceride levels continued to decline with later calendar years. The proportion of patients with hypercholesterolemia between 2005 and 2010 showed a stable level of 13% to 15%. The number of patients with an available HDL-cholesterol measurement is nearly half that of patients with cholesterol or triglyceride levels. The number of patients with low levels of HDL cholesterol increased from 410 in 2004 to 837 in 2009. Over time, the proportion of patients with low-level HDL cholesterol was lowest with 16% of patients in 2005 and 2006, and then it increased to 21% in 2009. Between 2001 and 2010 the absolute number of patients with hypertriglyceridemia fluctuated between 1800 and 2000. Because the number

of patients with low triglyceride levels increased at a higher rate over time, the proportion with hypertriglyceridemia decreased from 44% in 2001 to 30% in 2010. Better management of patients at risk for dyslipidemia, 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 clearer understanding of pathways, may explain the decreasing proportion of patients with dyslipidemia over time.

Lifelong use of ART requires tolerable and durable regimens, so it is important to study such durability. Approximately 50% of patients currently starting cART can remain on the first-line regimen for more than three years. Toxicity remains the main reason for therapy discontinuation, although the incidence of therapy changes driven by toxicity has dramatically declined since the introduction of cART. Patients with high CD4-cell counts starting cART, women and older patients had a higher risk for a toxicity-driven therapy change.

Although in later calendar years we observed a smaller proportion of treated patients with hypercholesterolemia or hypertriglyceridemia, an increase in the proportion of patients with dyslipidemia is to be expected in the future as the HIV population ages. Close monitoring of lipid levels in HIV-infected patients will remain an important issue for the future management of these patients.

In summary, although CD4-cell counts at the time of cART initiation have increased in the last few years, HIV testing rates will need to improve in order to make a timely start ($\geq$350 cells/mm^3) possible in most patients. A study exploring the reasons for a late start of cART is therefore important. If the goal of antiretroviral therapy is to restore CD4-cell counts to levels seen in uninfected patients, it is important to start cART with $\geq$350 CD4-cells/mm^3 or more as normal cell counts with virologically successful cART are approached only after eight years of continuous therapy. A timely start of cART is especially important in older patients as increases in CD4-cell counts on successful cART are smaller in this patient group. It is unknown if restoration to normal levels is feasible when cART is started at lower CD4-cell counts and, if so, how long this will take. Ensuring a quick suppression of plasma viral load with a maintenance level of <50 copies/ml is important as high-level viraemia or longer periods of low-level viraemia are associated with smaller CD4-cell count increases, higher probability of treatment failure and development of resistance. In younger patients and patients from sub-Saharan Africa, South America and the Caribbean, measures to improve adherence might improve virological response to cART. The incidence of toxicity-driven therapy switches has nearly halved since the introduction of cART in 1996. Regimens that are easily used and tolerated are especially important when cART is initiated at higher CD4-cell counts, when the patient's perceived necessity for treatment is lower. Monitoring of lipid levels in an aging HIV-1 infected population will remain important in identifying patients at higher risk of cardiovascular disease and other serious non-AIDS-defining diseases.

Response to cART in pregnant women

Without intervention, the risk of mother-to-child transmission (MTCT) in HIV-infected pregnant women is 15% to 20% [151]. HIV-infected women with a detectable viral load at the time of delivery have a high risk of vertical transmission of HIV. From 1998 onwards, pregnant HIV-infected women in the Netherlands have been treated with cART, which has reduced MTCT substantially [13].

Not all HIV-infected women are identified and treated with cART before becoming pregnant; 48% are diagnosed with HIV in the first trimester of their pregnancy following the screening for HIV as part of the national screening programme. Subsequently, these women initiate cART aiming to prevent transmission during pregnancy and delivery, irrespective of their own stage of infection. A short time to an undetectable viral load after cART initiation in pregnancy is an important predictor of an undetectable viral load level by the time of delivery.

The physiological changes during pregnancy affect the pharmacologic kinetics of cART. During pregnancy, gastrointestinal transit time is prolonged, and the amount of total body water and fat decreases. In addition, hepatic metabolism changes. As a result of these physiological changes, plasma drug levels are lower during pregnancy [152], but it is unclear if lower plasma drug levels in pregnancy are associated with virologic failure.

In our monitoring programme, we compared the immunologic and virologic responses to cART between HIV-infected pregnant and non-pregnant women aged between 16 and 45 years who initiated cART after 1 January 1998. The HIV-infected pregnant women were categorized into two groups according to the time of cART initiation in relation to when they became pregnant, i.e., before becoming pregnant or during pregnancy. A total of 751 pregnant women and 1631 non-pregnant women on cART were selected for these analyses. In 246 women cART was initiated before they became pregnant, and in 505 women it was initiated during their pregnancy (*Table 3.4*). Pregnant women were 5 years younger than non-pregnant women at the time of cART initiation ($p<0.0001$).

Table 3.4: Characteristics of HIV-infected pregnant and non-pregnant women aged between 16 and 45 years initiating combination antiretroviral therapy (cART) 1 January 1998 to 1 June 2011.

	Nonpregnant women	Pregnant women	
		cART initiation before pregnancy	cART initiation during pregnancy
Total	1631	246	505
Median age at cART (years, IQR)	34 (29-39)	29 (24-33)	28 (24-32)
Calendar year of HIV diagnosis			
1998-2002	548 (34%)	145 (59%)	178 (35%)
2003-2007	652 (40%)	92 (37%)	271 (54%)
2008-2011	431 (27%)	9 (4%)	56 (11%)
At cART initiation			
CD4-cell counts (cells/mm^3) (median, IQR)	200 (89-300)	191 (102-290)	360 (220-526)
HIV RNA levels (log_{10} copies/ml) (median, IQR)	4.8 (4.2-5.2)	4.7 (3.9-5.3)	3.9 (3.3-4.5)
Undetectable HIV RNA plasma levels at cART initiation	38 (2%)	12 (5%)	19 (8%)
At 24 weeks after cART initiation			
CD4-cell counts at week 24 (cells/mm^3, median, IQR)	320 (200-460)	300 (210-465)	538 (390-710)
HIV RNA levels week 24 (log_{10} copies/ml)	1.7 (1.7-2.0)	1.7 (1.7-2.6)	1.7 (1.7-3.3))
Undetectable HIV RNA levels at week 24	993 (61%)	164 (67%)	232 (46%)

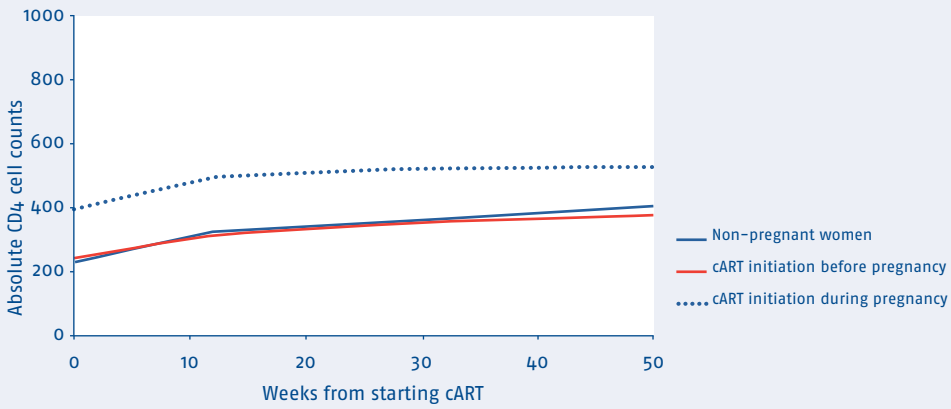
Legend: IQR=interquartile range

Immunologic trajectory

The median CD4-cell count at the start of cART and at week 24 after cART initiation are shown in *Table 3.4*.

Median CD4-cell counts varied between 191 cells/mm^3 (interquartile range [IQR]: 102-290) for the pregnant women who started cART before becoming pregnant and 360 cells/mm^3 (IQR; 220-526) for women who started the treatment during their pregnancy, ($p<0.0001$). The immunologic trajectories after cART initiation were analyzed using a random effects model. Its design allowed for a random intercept for CD4-cell counts per individual. Time was expressed as weeks since cART initiation. Since changes in the slope of CD4-cell counts during treatment might have occurred, slopes were allowed to change at week 12 and 28 after treatment initiation. *Figure 3.14* shows the piecewise modelled immunologic changes after treatment initiation for non-pregnant women, pregnant women who initiated cART before becoming pregnant and women who started cART during pregnancy. In the first 12 weeks after treatment initiation, CD4-cell counts increased significantly in the three groups. The slope of the increase in CD4-cell counts was significantly steeper in the non-pregnant women compared to both groups of pregnant women. Between week 12 and 28 after treatment initiation, the increase in CD4-cell counts slowed in all three groups. After 28 weeks of treatment, CD4-cell counts continued to increase very slowly in all three groups, and slopes did not differ significantly.

Figure 3.14: CD4-cell counts since the start of combination antiretroviral therapy (cART) amongst HIV-infected non-pregnant women (blue line), pregnant women who initiated cART before becoming pregnant (red line) and women who initiated cART during pregnancy (blue dotted line).

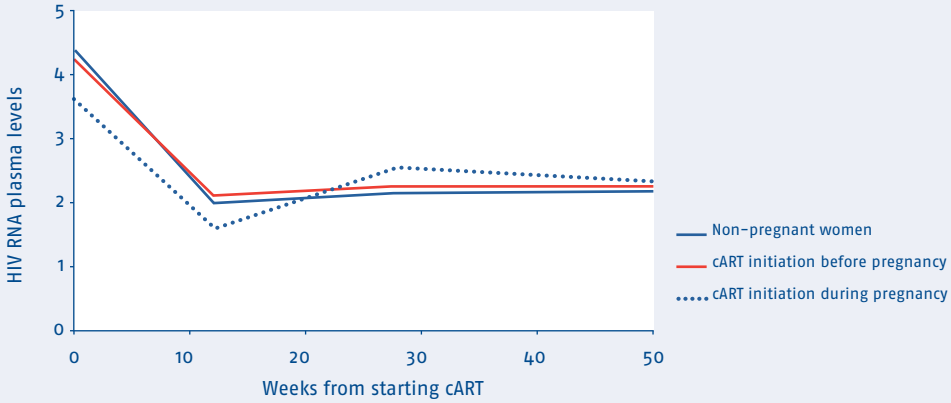


HIV-1 RNA trajectories after cART initiation

At the start of cART, women who initiated the therapy during their pregnancy had significantly lower HIV RNA plasma levels (*Table 3.4*) and at 24 weeks of cART the proportion of women who started cART before pregnancy with a detectable HIV RNA plasma level was significantly higher compared to non-pregnant women and women who initiated cART before becoming pregnant ($p<0.0001$).

During the first 12 weeks of cART a significant decline was seen in non-pregnant and pregnant women, irrespective of when the latter started cART relative to when they became pregnant (*Figure 3.15*), although the decline was significantly stronger in the non-pregnant women. As expected, HIV RNA plasma levels increased significantly between 12 and 28 weeks of cART amongst women who initiated treatment during their pregnancy, and the level started to decrease again from week 28 onwards.

Figure 3.15: Log HIV-RNA levels since the start of combination antiretroviral therapy (cART) in non-pregnant women (blue line), pregnant women who initiated cART before becoming pregnant (red line) and women who initiated cART during pregnancy (blue dotted line).

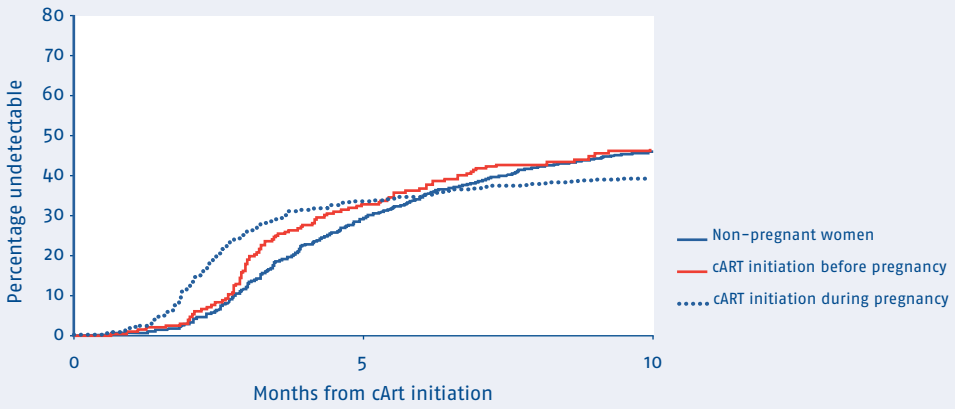


Time to initial virologic success

We analysed Kaplan–Meier estimates of the time from cART initiation to the first of 2 consecutive plasma HIV RNA concentrations of <50 copies/ml in pregnant and non-pregnant women who started cART between 1 January 1998 and 1 January 2011.

Estimates of the proportion of women with viral suppression (<50 copies/ml) within 6 months after the start of cART was 44% (95% confidence interval [CI]: 41-46) for the non-pregnant women, 47% (95% CI: 40-54) for women who initiated cART before becoming pregnant and 44% (95% CI: 38-48) for women who initiated cART during the pregnancy (*Figure 3.16*). Hazard ratios for the time to initial viral suppression did not significantly differ between the pregnant and non-pregnant women.

Figure 3.16: Time to initial viral suppression of HIV RNA to <50 copies/ml after combination antiretroviral therapy (cART) initiation amongst HIV-infected non-pregnant women, women who initiated cART before becoming pregnant and women who initiated cART during pregnancy.



Time to virologic failure after initial virologic success

The Kaplan–Meier estimates for time to virologic failure (>500 copies/ml) after initial viral suppression were 2.8% (95% CI: 1.9-4.3) within 6 months in non-pregnant women, 6.9% (95%CI: 3.5-13.3) in pregnant women who initiated cART before becoming pregnant and 23.1% (95% CI: 17.5-30.2) in women who started cART whilst being pregnant (P<0.001, log rank) (*Figure 3.17*). Pregnant women had a significantly higher risk of virologic failure (*Table 3.5*). This risk was highest amongst women who initiated cART when pregnant (HR: 3.79, 95% CI: 2.86-5.03). Although women who initiated cART during pregnancy were at higher risk of virologic failure, the majority who experienced virologic failure did so after delivery (230/232, 99%), whilst 16% of the women who initiated cART before becoming pregnant had a detectable HIV RNA plasma level during pregnancy. Most of these women changed their regimen during their pregnancy. Treatment changes to a safer regimen for maternal health during pregnancy have been associated with less optimal viral suppression at the end of the pregnancy [153].

Figure 3.17: Time to failure after initial viral suppression (HIV RNA >500 copies/ml) amongst HIV-infected non-pregnant women, women who initiated cART before becoming pregnant and women who initiated cART during pregnancy.

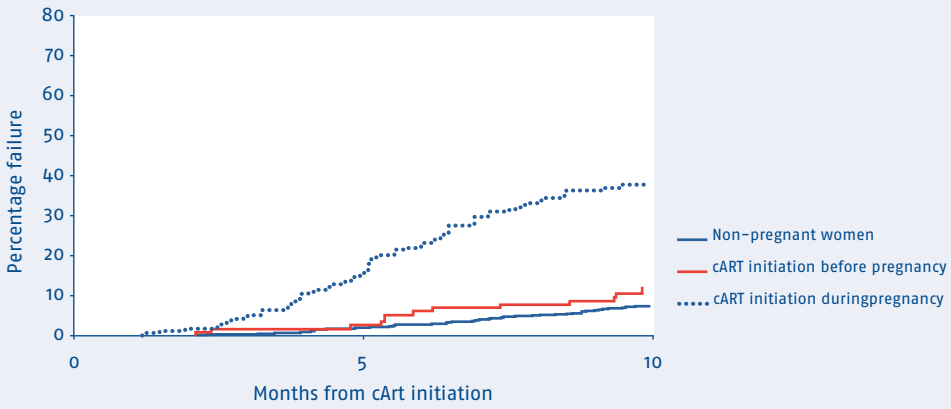


Table 3.5: Results from an adjusted Cox proportional hazard model of the time from first HIV RNA concentrations of <50 copies/ml to failure whilst on combination antiretroviral therapy (cART) in pregnant and non-pregnant women who started cART between 1 January 1998 and 1 January 2011.

	Hazard ratio*	95% Confidence interval	p-value
Non-pregnant women	1		
cART initiation before becoming pregnant	1.58	1.10-2.27	0.01
cART initiation during pregnancy	3.79	2.86-5.03	<0.0001

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

It is known that a longer duration of cART treatment during pregnancy and a sustained undetectable HIV RNA plasma level are associated with a decreased risk of MTCT [154]. Factors associated with detectable viral load at delivery are lower CD4-cell counts and higher HIV RNA plasma levels at the start of the pregnancy [155]. In our population we did not find a difference in the time from cART initiation until initial virologic suppression between pregnant and non-pregnant women. However, we did find an increased risk of virologic failure amongst pregnant women irrespective of when they started cART. In women who initiated cART during pregnancy, these virologic failures occurred only after delivery, although drug concentrations were low [156] due to physiological changes during pregnancy [157]. Lower adherence rates postpartum might cause this increased risk of virologic failure after delivery. We do not have data on treatment adherence. However, lower adherence rates postpartum compared to adherence rates during pregnancy have been reported [158].

Prevention of vertical HIV transmission is likely to be the major motivation in pregnant women to adhere to treatment. Adherence intervention during the postpartum period in HIV-infected pregnant women is needed to prevent virologic failure after the pregnancy.

In contrast, virologic failures were observed during pregnancy among women who initiated cART before they became pregnant. These failures occurred in women who changed treatment regimen. Most of these changes were switches to a maternally safer regimen [153]. In women with a known HIV infection, active preconception counselling and treatment changes amongst those who are trying to conceive are likely to prevent detectable HIV RNA plasma levels at delivery.

Response to cART in HIV-infected children, adolescents and young adults

Successful treatment and prevention of mother-to-child transmission of HIV has changed the epidemic amongst children and adolescents in Western countries [159]. The majority of HIV-infected children and adolescents in the Netherlands are now receiving cART. Children and adolescents with HIV are surviving their childhood and teenage years to reach adulthood. The immunologic and virologic responses to cART have been studied extensively in adults [160], but only a few studies have been conducted amongst HIV-infected children and adolescents. Results from studies amongst adult patients might not be applicable to children and adolescents as the progression of HIV in children and adolescents might differ from that in adults [161]. We compared the immunologic and virologic outcomes of HIV-infected children (aged 0-12 years at time of HIV diagnosis) and adolescents (aged 13-17 years at HIV diagnosis) on cART with HIV-infected young adults (aged 18-23 years at HIV diagnosis) initiating cART.

cART initiation

In the Stichting HIV Monitoring (SHM) database, 218 out of 236 (92%) children initiated cART between 1997 and 2011. The proportion of adolescents and adults on cART was somewhat lower; 148 out of 180 (82%) adolescents and 1176 out of 1481 (79%) young adults initiated cART. A protease inhibitor (PI)-based regimen was initiated in most of the children, whereas amongst adolescents and young adults there was an equal distribution of PI-based and non-nucleoside reverse transcriptase inhibitor-based regimens (*Table 3.6*).

cART initiation is recommended as early as possible in HIV-infected children aged less than one year [162]. This recommendation is based on the recent finding that the risk of HIV progression and mortality is lower when cART is initiated when the children are less than three months of age compared to cART initiation at a later age [163]. In the Netherlands, the time between HIV diagnosis and cART initiation is very short amongst children, with a median of 0.3 year (interquartile range [IQR]: 0.1-2.5).

Table 3.6: Demographic and clinical characteristics of HIV-infected children (aged 0-12 years at time of HIV diagnosis), HIV-infected adolescents (aged 13-17 years at HIV diagnosis) and young adults (aged 18-23 years at HIV diagnosis).

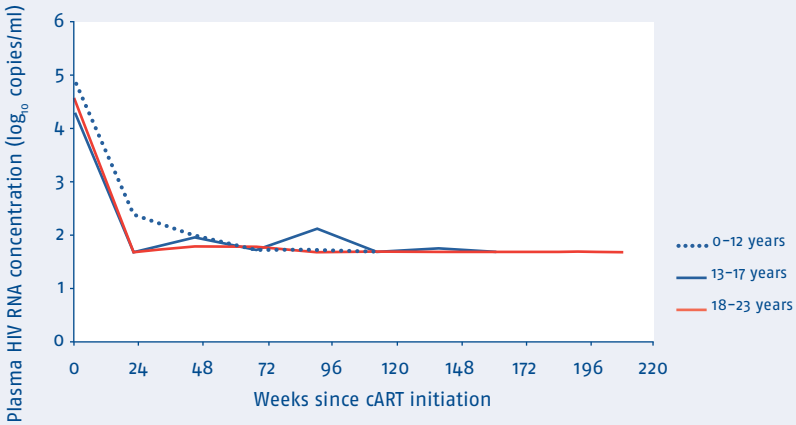
	Children	Adolescents	Young adults
Total	236	180	1481
Median age at diagnosis (years, IQR)	3 (0.6-7)	17 (16-18)	22 (20-23)
Median follow-up time (years, IQR)	7 (3-8)	6 (2-8)	5 (2-8)
Men	132 (56)	63 (35)	904 (61)
Transmission route			
Homosexual contact	1 (0.4)	23 (13)	621 (42)
Heterosexual contact	1 (0.4)	120 (67)	673 (45)
Other	234 (99)	37 (21)	187 (13)
Region of origin			
Netherlands	116 (49)	43 (24)	553 (37)
Sub-Saharan Africa	88 (37)	107 (59)	429 (29)
Other	32 (14)	30 (17)	499 (34)
Calendar year of HIV diagnosis			
<1998	74 (31)	37 (21)	482 (33)
1999-2000	23 (10)	14 (8)	78 (5)
2001-2003	50 (21)	75 (42)	241 (16)
2004-2011	89 (38)	52 (29)	666 (46)
ART use	218 (92)	148 (82)	1176 (79)
NNRTI	52 (24)	61 (41)	457 (39)
PI	113 (52)	59 (40)	480 (41)
PI+NNRTI	5 (2)	4 (3)	30 (3)
NRTI	48 (22)	24 (16)	214 (18)
Median time between diagnosis and cART initiation (years, IQR)	0.3 (0.1-2.5)	0.8 (0.2-4.2)	1.8 (0.2-6)
CD4-cell counts at cART initiation (cells/mm^3, median, IQR)	400 (170-866)	263 (160-390)	260 (120-340)
HIV RNA levels at cART initiation (log_{10} copies/ml)	5.0 (4.5-5.8)	4.4 (3.6-5.1)	4.6 (4.0-5.1)
Lost to follow-up	25 (11)	47 (26)	316 (21)
Deaths	3 (1)	9 (5)	86 (6)

***Legend:** IQR=interquartile range; ART=antiretroviral therapy; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; cART=combination antiretroviral therapy.*

Virologic response

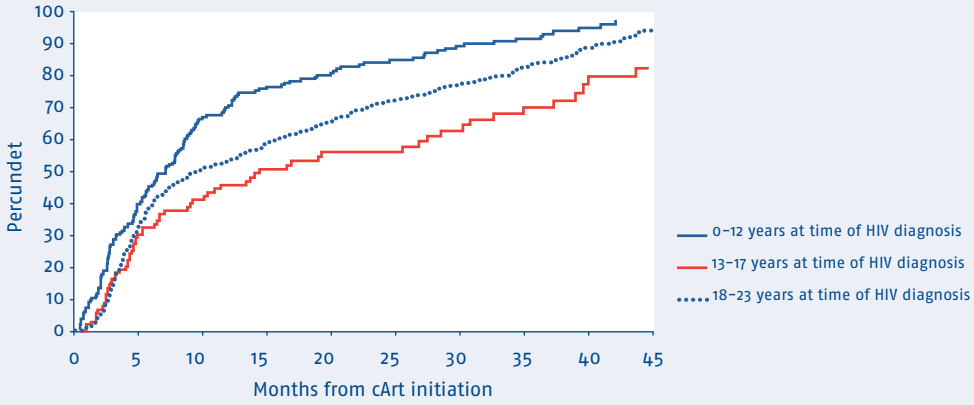
At time of cART initiation, 85% of the children, 88% of the adolescents and 91% of the young adults had a detectable viral load (*Table 3.6*). HIV RNA plasma levels at cART initiation were significantly higher in children compared to in adolescents and young adults. In the first 24 weeks of cART HIV RNA levels significantly decreased amongst all groups (p<0.0001). However, in HIV-infected children a slower decline in HIV RNA levels in the first 24 weeks on cART was observed (P<0.0001) (*Figure 3.18*).

Figure 3.18: *HIV RNA plasma concentrations from the start of cART amongst children aged 0–12 years at time of HIV diagnosis, adolescents aged 13–17 years at HIV diagnosis and young adults aged 18–23 years at HIV diagnosis.*



The Kaplan–Meier method was used to calculate the percentage of patients reaching initial treatment success within six months after starting cART. Initial treatment success was defined as the first of two consecutive plasma HIV RNA concentrations <50 copies/ml. Time included in the Kaplan–Meier analysis was the time from the date of cART initiation to the date of the first of two consecutive plasma HIV RNA concentrations <50 copies/ml. The Kaplan–Meier estimates for the time to initial treatment success within six months after cART initiation were 45% (95% confidence interval [CI]: 38-53) for children aged 0-12 years at time of HIV diagnosis, 32% (95% CI: 24-42%) for adolescents aged 13-17 years at time of HIV diagnosis and 39% (95% CI: 35-43) (p-value logrank<0.0001), *Figure 3.19*.

Figure 3.19: Cumulative incidence of initial treatment success, defined as the first of two consecutive plasma HIV RNA concentrations <50 copies/ml, in children aged 0–12 years at time of HIV diagnosis, adolescents aged 13–17 years at time of HIV diagnosis and young adults aged 18–23 years at time of HIV diagnosis.



Hazard ratios for time to the first of two consecutive plasma HIV RNA concentrations <50 copies/ml showed that compared to adults aged between 18-23 years at the time of HIV diagnosis, time to an undetectable HIV RNA plasma level was not significantly different in children and adolescents (*Table 3.7*).

***Table 3.7:** Results from an adjusted Cox proportional hazard model of the time from the start of cART to the first of two consecutive plasma HIV RNA concentrations <50 copies/ml in children, adolescents and young adults who started cART between 1 January 1997 and 1 January 2011.*

	Hazard ratio*	95% Confidence interval	p-value
Children 0–12 years of age	1.67	0.98–2.83	0.06
Adolescents 13–17 years of age	1.00	0.77–1.29	0.98
Adults 18–23 years of age	1		

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

Kaplan–Meier estimates for the time to virologic failure (defined as the first date of two consecutive HIV RNA plasma levels >500 after initial suppression) within six months after initial treatment success is 6% (95% CI: 3-11) for children aged 0-12 years at time of HIV diagnosis, 4% (95% CI: 1-12%) for adolescents aged 13-17 years at time of HIV diagnosis and 4% (95% CI: 3-6) for young adults aged 18-23 years at time of HIV diagnosis. The proportion of patients with treatment failure did not significantly differ between children, adolescents and young adults. Time to virologic failure (adjusted for gender, calendar year of HIV

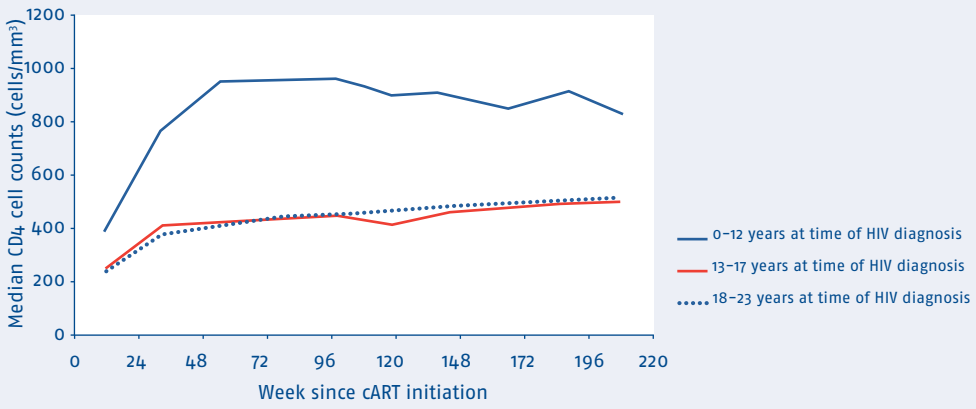
diagnosis, transmission risk group, region of origin, time between HIV diagnosis and cART initiation, log RNA levels and CD4-cell counts at time of cART initiation) estimated in a Cox proportional hazard model again did not differ significantly in children (HR: 0.87, 95% CI: 0.29-2.66) and adolescents (HR: 1.23, 95% CI: 0.71-2.12) compared to young adults.

Immunologic response

CD4-cell counts were higher amongst all HIV-negative and HIV-positive young children compared to adolescents and adults, and the counts decreased with increasing age [164]. After the initiation of cART, CD4-cell counts increased in children, adolescents and young adults. Although children had higher age-specific CD4-cell counts at treatment initiation, the increase in CD4-cell counts did not significantly differ with the slope of CD4-cell change in adolescents and young adults (*Figure 3.20*).

The increase in CD4-cell counts was steepest in the first 24 weeks on cART and then leveled off. A small increase in CD4-cells counts was observed from week 24 onwards amongst adolescents and young adults, whilst CD4-cell counts started to decrease amongst children. This decrease in CD4-cell counts is a reflection of the age-related decrease in CD4-cell counts amongst children [164].

Figure 3.20: *CD4-cell counts from the start of cART amongst children aged 0-12 years at time of HIV diagnosis, adolescents aged 13-17 years at HIV diagnosis and young adults aged 18-23 years at time of HIV diagnosis.*



Mortality

The use of cART has been shown to be very effective in reducing mortality amongst HIV-infected children and adolescents [165]. The three deaths that occurred amongst children were caused by AIDS (n=2) and renal failure (n=1). The proportion of deaths was higher amongst the adolescents (5%) and young adults (6%). Amongst the adolescents, six patients died of an AIDS-defining event. For young adults aged 18-23 years at HIV diagnosis, the most frequent causes of death were AIDS (n=28), non-natural causes (n=10), liver-related disease (n=7), cancer (n=6) and infections (n=6). *Table 3.8* shows the risk of death amongst children and adolescents compared to young adults. The risk of death was significantly lower amongst children.

Table 3.8: *Results from an adjusted Cox proportional hazard model of the time from cART initiation to death in children, adolescents and young adults who started cART between 1 January 1997 and 1 January 2011.*

	Hazard ratio*	95% Confidence interval	p-value
Children 0–12 years of age	0.18	0.03–0.98	0.045
Adolescents 13–17 years of age	0.83	0.29–2.39	0.72
Adults 18–23 years of age	1		

Adjusted for gender, calendar year of HIV diagnosis, transmission risk group, region of origin, time between HIV diagnosis and cART initiation, log RNA levels and CD4-cell counts at time of cART initiation.

The results of this analysis indicate that there were no substantial differences in long-term virologic and immunologic responses amongst HIV-infected children, adolescents and young adults. However, a higher proportion of children receive cART, than do adolescents or young adults, where the proportions are similar. The proportion of cART-treated adolescents in the Netherlands is higher compared to that of HIV-infected adolescents in the USA, where only 69% of those who meet the criteria for cART initiation actually receive cART [166]. The decrease in HIV RNA plasma levels in the first 24 weeks after cART initiation was slower amongst the children. This is probably explained by the differences in the natural history of HIV infection between children and adults [161]. HIV RNA levels are higher amongst HIV-infected young children compared to those in untreated infected adults [167]. At the time of cART initiation, HIV-infected children registered in the SHM database had higher HIV RNA levels compared to those in adolescents and young adults. Although children showed a slower decrease in HIV RNA levels during the first weeks of cART treatment, the time to the first undetectable HIV RNA level did not differ amongst children, adolescents and young adults. The proportion of deaths was higher amongst adolescents and young adults compared to children, and the risk of death was lower in children. Amongst the young adults, deaths were more often related to causes other than AIDS, such as non-natural causes, liver disease or cancer, compared to causes in children and adolescents.

Cost of treatment

More patients on treatment

Since the introduction of combination antiretroviral therapy (cART) approximately 15 years ago, HIV has gradually become a chronic disease requiring lifelong antiretroviral treatment. The life expectancy of HIV-infected patients has dramatically improved, and, as a result, the number of people living with HIV is increasing. Furthermore, every year more than 1200 patients start cART. The increase in the number of treated patients is likely to result in increased population cost for HIV treatment, as in the United Kingdom [168].

Total cost of treatment

Indeed, we found that the total monthly cost of antiretroviral treatment increased from EUR 5.0 million in January 2004 to EUR 10.4 million in January 2010 (*Figure 3.21*). During the same time, the monthly follow-up time increased from 6489 to 11,057 person-months, such that, on average, the monthly cost of treatment per patient increased 21%, from EUR 777 to EUR 938. Hence, the increase in total expenditure on antiretroviral medication is mainly the result of a growing number of treated patients.

Cost of specific combinations

The increase in population cost could be attributed almost entirely to an increase in the use of treatment combinations containing tenofovir/emtricitabine and efavirenz, nevirapine, or a ritonavir-boosted protease inhibitor, which are primarily the regimens recommended as first-line treatment (*Figure 3.22*) [28]. In January 2010, these combinations were used by 52% of the treated patients and accounted for 50% of the total cost of antiretroviral treatment in that month (*Figure 3.22*). Since the beginning of 2007, total monthly costs associated with other combinations have decreased from EUR 6.0 to EUR 5.2 million.

In general, the cost of treatment regimens containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) in addition to tenofovir/emtricitabine was approximately EUR 800 per month, whilst the monthly costs of regimens based on boosted protease inhibitors were EUR 1200. Combinations with the same NNRTI or protease inhibitor, but with a different backbone of nucleoside reverse transcriptase inhibitors were cheaper at EUR 675 and EUR 1000, respectively. These backbones included zidovudine/lamivudine and abacavir/lamivudine, which are no longer preferred because of less favourable toxicity profiles. The average monthly cost of other combinations was approximately EUR 1200.

Changes in cost of treatment

The observed changes in cost of antiretroviral treatment over calendar time in *Figure 3.21* and *3.22* need to be interpreted with care. Since costs were calculated using the price in February 2011, changes over time reflect only changes in the number of treated patients and in prescribed medication. In general, however, costs of individual antiretroviral drugs have declined since they were first registered for use in the Netherlands. For instance, using the price listed in September 2008, the total population cost of antiretroviral treatment for January 2010 would equal EUR 11.6 million, which is 12% more than that based on the price in February 2011. With use of the respective prices, the average monthly per-patient treatment cost was EUR 1000 in September 2008, with almost no change by February 2011 (EUR 990).

Figure 3.21: *Total costs of antiretroviral treatment (ART) and follow-up time on treatment for all HIV-infected patients treated with combination antiretroviral therapy in each month. Costs increased from EUR 5.0 million in January 2004 to EUR 10.4 million in January 2010, whilst during the same time, the follow-up time on treatment rose from 6489 to 11,057 person-months.*

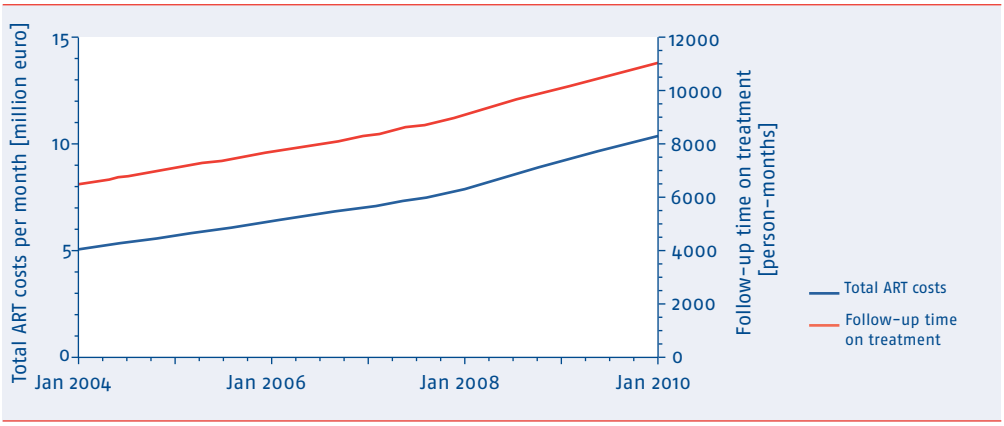
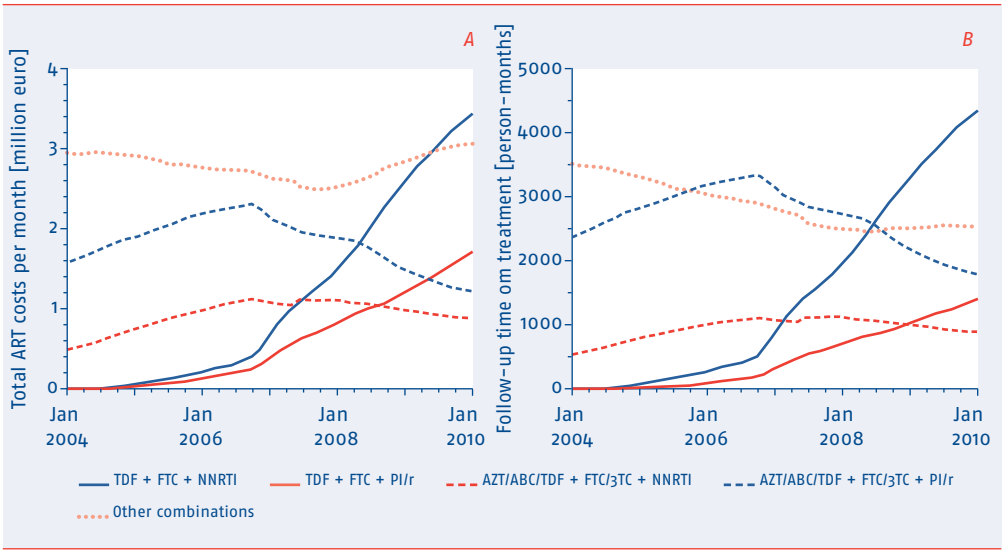


Figure 3.22: Total costs of antiretroviral treatment (ART) per type of combination (A) and follow-up time on treatment (B) for all HIV-infected patients treated with combination antiretroviral therapy in each month.



Legend: NNRTI=non-nucleoside reverse transcriptase inhibitor, including efavirenz and nevirapine; PI/r=ritonavir-boosted protease inhibitor, including darunavir, atazanavir, lopinavir, and fosamprenavir; TDF=tenofovir; FTC=emtricitabine; AZT=zidovudine; ABC=abacavir; 3TC=lamivudine.

4. Virologic failure and drug resistance

Ard van Sighem

Generally, HIV-infected patients on combination antiretroviral treatment (cART) nowadays achieve sustained suppression of HIV viral load, such that replication of the virus is virtually blocked. For a small group of patients, however, suppression is incomplete, which may be a marker of inadequate adherence to therapy and herald the presence of drug resistance. In the Netherlands, incomplete suppression, or virologic failure, is observed in 5% of the treated patients annually. In approximately 50% to 80% of patients experiencing virologic failure, resistance to non-nucleoside reverse transcriptase (RT) inhibitors and to the nucleoside RT inhibitors lamivudine and emtricitabine has been found. Resistance to other nucleoside RT inhibitors and protease inhibitors has been found only amongst a substantial proportion of patients previously treated with non-cART regimens. Altogether, 10% of patients currently in follow-up are resistant to at least one antiretroviral drug, although this proportion is probably an underestimation since a genotypic 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 patients, indicating that infections from the reservoir of treated patients with resistance are relatively rare and that new infections occur mainly via untreated HIV-infected individuals who may not yet be aware of their infection.

Het gros van de HIV-geïnfecteerden die met combinatietherapie (cART) worden behandeld, kan tegenwoordig zodanig langdurig de HIV-RNA-concentratie in plasma onder de detectielimiet van assays onderdrukken dat de HIV-replicatie praktisch gestopt wordt. In een kleine groep patiënten is onderdrukking echter onvolledig. Dit kan een teken zijn van onvoldoende therapietrouw en duiden op de aanwezigheid van resistentie. Onvolledige onderdrukking, oftewel virologisch falen, komt jaarlijks voor bij 5% van de in Nederland behandelde patiënten. Ongeveer 50% tot 80% van de patiënten met virologisch falen blijkt zowel resistent te zijn tegen non-nucleoside reverse transcriptase (RT) remmers als tegen de nucleoside RT-remmers lamivudine en emtricitabine. Alleen bij een groot aantal patiënten die eerder zijn behandeld met non-cART-regimes is ook resistentie tegen andere nucleoside RT-remmers en tegen proteaseremmers aangetroffen. Van de patiënten die momenteel nog in zorg zijn, is 10% resistent tegen minstens één antiretroviraal middel. Waarschijnlijk is dit een onderschatting van het werkelijke aantal, omdat bij minder dan een derde van de patiënten met virologisch falen een resistentieprofiel bepaald is. Minder dan 5% van de HIV-patiënten is geïnfecteerd met een resistente virusvariant. Dit duidt erop dat het aantal infecties door behandelde, resistente patiënten beperkt is en dat nieuwe infecties derhalve hoofdzakelijk plaatsvinden via onbehandelde HIV-geïnfecteerden die zelf misschien nog niet op de hoogte zijn van hun status.

Treatment with combination antiretroviral therapy (cART) generally results in sustained suppression of HIV viral load to levels below the threshold of quantification. It is believed that in a majority of patients, cART virtually inhibits viral replication completely [169]. However, patients may have difficulty maintaining optimal adherence to the treatment regimen because of, for instance, drug-related toxicities. As a result, drug concentrations may be too low to completely halt the replication of HIV, and mutations in the viral genome may be selected that confer resistance to one or more drugs in the regimen. Here we report on the development of resistance in the treated HIV-infected population followed by Stichting HIV Monitoring and the extent to which resistant virus strains are transmitted to uninfected individuals.

Resistance during treatment

Incomplete suppression

In clinical practice, incomplete suppression of HIV usually betrays itself by quantifiable viral load levels, typically above 50 copies/ml. Many patients, however, who have viral load levels consistently below 50 copies/ml may occasionally have a single measurement above 50 copies/ml [170, 171]. The clinical relevance of these so-called blips appears to be limited, and their occurrence may be related partially to random assay variations or to release of virus from the latent reservoir, neither of which herald the presence of resistance-associated mutations [108, 113].

Less virologic failure

To minimise the effect of blips, we used a viral load of 500 copies/ml as a marker of incomplete suppression, or virologic failure. To be more precise, virologic failure was defined as a viral load of at least 500 copies/ml whilst the patient was being treated, that was measured at least four months after the start of cART or four months after resumption of treatment following a treatment interruption. Amongst patients who started cART whilst being therapy-naive, virologic failure was found in 15% in 2000 and 5% in 2010. In patients who had been treated with mono- or dual therapy before starting cART, virologic failure was more common in 2000 (37%), but it also decreased to 5% in 2010 *(Web Appendix Figure 4.1)*. In part, this decline was due to a healthy survivor effect, in which those who experienced treatment failure died prematurely. In addition, in recent years new antiretroviral drugs have become available that are able to suppress viral load, even in patients who have had multiple episodes of virologic failure and who are resistant to many of the older drugs.

Scanning for drug resistance

In patients who experienced virologic failure, resistance to antiretroviral drugs was ascertained by scanning genotypic sequences of the reverse transcriptase (RT) and protease genes obtained at the time of virologic failure for specific mutations known to be associated with resistance to the three original classes of drugs: nucleoside RT inhibitors (NRTIs), non-nucleoside RT inhibitors (NNRTIs), and protease inhibitors (PIs) [172]. Although in recent years new drug classes have been introduced, including integrase inhibitors and entry inhibitors, genotypic sequences of the relevant genes are not yet routinely obtained. A genotypic resistance interpretation algorithm developed by Stanford University was used to infer a drug susceptibility score for each sequence according to a five-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance [173].

Sequences

In total, 3754 sequences were obtained from 2370 patients after they started cART. Pre-treated patients were disproportionally represented with 1541 sequences, or 41%. In recent years, however, only 17% of the sequences were from pre-treated patients, whereas approximately 16% of all patients in follow-up were pre-treated. Altogether, 3076 sequences, or 82%, were obtained whilst patients were on treatment. In 2315 of the 3076 sequences, or 75%, high-level resistance to at least one antiretroviral drug was found, including in 90% of the sequences obtained from pre-treated patients and 64% of those from previously therapy-naive patients *(Figure 4.1; Web Appendix Figures 4.2 and 4.3)*. Of note, 7% of the sequences from pre-treated patients and 29% of those from previously therapy-naive patients were susceptible to all antiretroviral drugs, indicating that the patients probably did not take their prescribed medication.

Figure 4.1: Annual proportion of sequences showing high-level resistance, according to the Stanford interpretation algorithm, in patients pre-treated with regimens considered not combination antiretroviral treatment (cART) and in previously therapy-naïve patients who started cART as their first treatment [173]. (A) resistance to lamivudine (3TC) and emtricitabine (FTC), (B) resistance to other nucleoside/nucleotide reverse transcriptase inhibitors, (C) resistance to non-nucleoside reverse transcriptase inhibitors, (D) resistance to protease inhibitors (PI).

Resistance to NRTIs

In 50% to 80% of the pre-treated patients with a genotypic sequence, high-level resistance to lamivudine and emtricitabine was observed *(Figure 4.1A)*. In previously therapy-naive patients, resistance levels have decreased in recent years and were approximately 30% in 2010. Resistance to these two drugs is expected to be common, because they are used by the majority of patients on cART and only one mutation is necessary to render the virus essentially insensitive to the drugs.

High-level resistance to other NRTIs was below 20% in therapy-naive patients *(Figure 4.1B)*. Amongst pre-treated patients, resistance to zidovudine and stavudine were less common; nevertheless, resistance to any NRTI, excluding lamivudine and emtricitabine, was still found in approximately 60% of the sequences. In the past few years, however, resistance to NRTIs has decreased to levels of approximately 30%.

Resistance to NNRTIs

In recent years, resistance to NNRTIs has been found in 30% to 40% of previously therapy-naive patients and in 50% to 60% of pre-treated patients *(Figure 4.1C)*. Despite a considerable amount of cross-resistance, the prevalence of high-level resistance to efavirenz appeared to be somewhat lower than to nevirapine. Since both drugs are used in approximately 60% of treatment regimens, resistance to them may be expected to be common in patients with virologic failure. Less than 10% of patients had high-level resistance to etravirine, a new NNRTI with little cross-resistance to the other two drugs in its class.

Resistance to PIs

After the introduction of protease inhibitors in the mid-1990s, resistance to this drug class rapidly increased to levels around 40% in therapy-naive patients and 60% in pre-treated-patients *(Figure 4.1D)*. In recent years, resistance was found in less than 10% of the therapy-naive patients, whilst resistance levels were decreasing in pre-treated patients, most likely as a result of the availability of better treatment options. In pre-treated patients, the prevalence of resistance was highest for the older generation of PIs, including nelfinavir, indinavir, and saquinavir, but resistance levels for lopinavir and atazanavir were similar. High-level resistance to darunavir, on the other hand, was almost never observed.

Prevalence of resistance

Altogether, as of June 2011, resistance-associated mutations had been found in 1773 patients, or 12%, of the 14,610 HIV-infected patients who were still in active follow-up. For 1400 patients, or 10%, including 592 patients who had been treated with non-cART regimens, these mutations resulted in high-level resistance to at least one antiretroviral drug. Since resistance tests were performed in only 30% of patients with virologic failure in or after 2000, probably the true prevalence of resistance is higher. A crude estimate would put the true prevalence at approximately 30%, which would be more in line with findings in other European countries. For instance, in Switzerland, approximately 40% of the antiretroviral therapy-exposed population have been found to harbour resistance-associated mutations [174].

Of the 1400 patients with evidence of high-level resistance, 74% had resistance to lamivudine and emtricitabine, whilst 38% had resistance to at least one other NRTI. Resistance to at least one protease inhibitor was found in 33% and to at least one NNRTI in 60%. High-level resistance to drugs from one class was observed in 40% of patients, resistance to two classes in 44%, and resistance to all three original drug classes in 16%. *Web Appendix Table 4.1* shows the inferred resistance level for each antiretroviral drug.

Transmission of drug-resistant virus

Limited treatment options

Treatment options may be limited when patients are infected with an HIV virus strain that is already resistant to one or more of the currently available antiretroviral drugs. In such patients, standard treatment combinations may not be the most efficacious ones, and as a result, patients may experience delayed viral suppression, with a resulting increased risk of virologic failure. It is, therefore, important that patients be screened for the possible presence of resistance-associated mutations to optimise the initial treatment regimen [175, 176].

Back-mutation

Since a resistant virus strain may change to a drug-susceptible virus by back-mutation, the presence of resistant virus needs to be established as close to the moment of infection as possible [177-179]. In particular, the M184V mutation in RT, which is associated with high-level resistance to lamivudine and emtricitabine, can revert back relatively early after transmission. Other mutations will reverse at a much slower pace or not reverse at all, depending on the extent to which the virus becomes capable of replicating.

Screening for resistance

In 2003, screening for resistance at the time of entry into clinical care became part of the treatment guidelines. Since that time, 3781 patients have been screened for resistance, which comprises 42% of all 9101 patients diagnosed with HIV during that same period. In order to reduce a possible effect of back-mutation on observed levels of resistance, only patients who had a genotypic sequence within one year of diagnosis and who had not started antiretroviral treatment were considered. In addition, the patients were divided into two groups, one with recent infection and one with long-standing infection. Altogether, 1188, or 31%, of the 3781 infections were recent, whereas the remaining 2593 infections were classified as long-standing. These two groups were quite different regarding patient characteristics. Dutch homosexual men represented 70% of the recently infected group, but only 42% of the long-standing infections. In contrast, sub-Saharan Africans accounted for 18% of the long-standing infections, but only 3% of the recent infections.

Transmitted drug resistance

Altogether, 63 patients had high-level resistance to drugs from one class, 13 patients to two classes, and 3 patients to all three classes. It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. All three classes include drugs with little cross-resistance between them. Moreover, other classes of drugs have recently become available. As a result, even for patients with resistance to all three classes, there may be efficacious cART combinations. High-level resistance to at least one antiretroviral drug was found in 79 patients, whilst 116 patients had intermediate levels of resistance *(Table 4.1)*. Whereas the proportion of patients with high-level resistance to any drug was not significantly different, a higher proportion of patients with recent infections compared to those with long-standing infections appeared to have intermediate levels of resistance. This difference was caused mainly by predicted resistance levels to protease inhibitors, which were higher for recent infections. In contrast, the proportion of patients with resistance to NNRTIs appeared to be somewhat higher amongst those with long-standing infection.

Table 4.1: *Number of patients with intermediate or high-level resistance to any drug, protease inhibitors (PI), nucleoside reverse transcriptase inhibitors (NRTI), or non-nucleoside RT inhibitors (NNRTI), according to the Stanford genotypic interpretation algorithm [173]. Only patients diagnosed in 2003 or later were considered. The numbers between brackets apply to the 3735 patients who did not have M46L or M46I as only major mutation in protease.*

	Recent infection, N=1188		Long-standing infection, N=2593		All infections, N=3781	
	N	%	N	%	N	%
Any drug						
Intermediate	48 (21)	4.0 (1.8)	68 (49)	2.6 (1.9)	116 (70)	3.1 (1.9)
High-level	20	1.7	59	2.3	79	2.1
PI						
Intermediate	30 (3)	2.5 (0.3)	23 (4)	0.9 (0.2)	53 (7)	1.4 (0.2)
High-level	7	0.6	13	0.5	20	0.5
NRTI						
Intermediate	21	1.8	42	1.6	63	1.7
High-level	4	0.3	11	0.4	15	0.4
NNRTI						
Intermediate	0	0.0	9	0.3	9	0.2
High-level	13	1.1	50	1.9	63	1.7

Subepidemics

A closer look revealed that intermediate resistance to protease inhibitors involved mainly patients who had an M46L or M46I mutation as the only major mutation in protease, which predicts intermediate resistance to only nelfinavir [172]. Excluding these patients reduced the number of those with intermediate resistance to protease inhibitors from 53 to 7. As previously noted, virus strains harbouring an M46L mutation, as well as strains with revertant mutations in RT such as 215S or 215D, have established themselves as subepidemics [1, 180].

Conclusion

In terms of percentage, virologic failure and resistance to antiretroviral drugs are less common than they were 10 years ago, thanks to an improved availability of treatment options, even for patients pre-treated with mono- or dual therapy. However, due to a growing volume of treated HIV-infected patients, approximately 500 patients per year still experience virologic failure. Resistance patterns seem to indicate that in one third of previously therapy-naive patients in whom treatment fails, the failure is the result of the patients not taking the prescribed medication. Meanwhile, less than 5% of patients are infected with HIV virus that is already resistant to antiretroviral drugs, indicating that transmission from the pool of resistant patients is limited or, conversely, that HIV infections are primarily caused by HIV-infected individuals who are not yet treated and who may not even be aware of their infection.

5. Hepatitis B and C co-infection

Colette Smit

Hepatitis B (HBV) and hepatitis C (HCV) infections are frequently occurring infections in HIV-patients. HBV- and HCV-infections are associated with progression to chronic liver disease. Amongst HIV patients in the Stichting HIV Monitoring (SHM) database who were screened for co-infection, 8% were infected with HBV and 12% with HCV. Most co-infected patients were males who were infected with HIV through homosexual contact. The number of new HCV diagnoses has significantly increased over time, making homosexual men the largest group of patients co-infected with HCV. Fifty-nine percent of the patients co-infected with HIV and HBV and 27% of the patients co-infected with HIV and HCV received treatment for their co-infection. The risk of death amongst co-infected patients was no higher than amongst patients who were infected with only HIV. Both HBV and HCV co-infections were strongly associated with progression to severe chronic liver disease, which stresses the need for improved antiviral treatment of HBV and HCV co-infections.

Hepatitis B (HBV) en hepatitis C (HCV) zijn vaak voorkomende infecties bij HIV-patiënten. HBV- en HCV-infecties worden geassocieerd met progressie naar chronische leveraandoeningen. Van de HIV-patiënten die in de Stichting HIV Monitoring (SHM) database zijn gescreend op de aanwezigheid van een HBV- of HCV-co-infectie, bleek 8% geïnfecteerd met HBV en 12% met HCV. HBV- en HCV-co-infecties komen voornamelijk voor bij mannen die met HIV zijn geïnfecteerd via homoseksueel contact. Het aantal nieuwe HCV-diagnoses is sinds 2000 sterk gestegen onder homoseksuele mannen en zij vormen [op dit moment] dan ook de grootste groep HIV-patiënten met een HCV-co-infectie. Van de patiënten met HIV en HBV wordt 59% behandeld voor hun co-infectie; bij HIV en HCV is dit 27%. Patiënten met een co-infectie hadden geen hogere sterftekans dan patiënten met alleen HIV. Zowel HBV als HCV bleek sterk geassocieerd met een snellere ontwikkeling van ernstige chronische leverziekten. Daarom is optimale behandeling van HBV- en HCV-co-infecties bij HIV-patiënten van groot belang.

Prevalence and Demographics

Infection with hepatitis B virus (HBV) and hepatitis C virus (HCV) is common amongst patients infected with HIV [181,182]. Irrespective of HIV co-infection, HBV and HCV infections are associated with serious liver-related disease such as fibrosis, cirrhosis and hepatocellular carcinoma [183, 184]. Progression to serious liver disease takes 20 to 25 years of chronic HBV and HCV infection. Hence, faster progression of untreated HIV infection masks the progression to serious liver disease in co-infected patients, although progression of liver disease may also be accelerated by HIV [185, 186]. Since progression of HIV infection and death dramatically declined after the introduction of combination antiretroviral therapy (cART), liver disease has become apparent as a frequent cause of death in HIV-infected populations [187].

Hepatitis B co-infection

Prevalence

We defined HBV co-infection by a positive test for hepatitis B surface antigen (HBsAg). In total, 17,745 patients were tested for the presence of HBsAg antibodies. Co-infection with HBV was found in 1372 (8%) of the HIV-infected patients. HBV co-infected patients were predominantly male; 57% were infected with HIV through homosexual contact and 30% through heterosexual contact. Half of the HBV co-infected patients were born in the Netherlands, and 91% of the HIV/HBV co-infected patients were receiving cART (*Table 5.1*).

HBV diagnoses

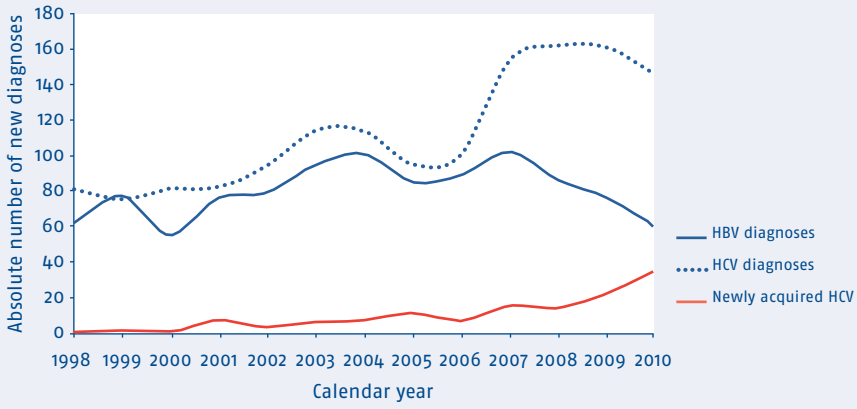
The number of HBV diagnoses per calendar year varied over time between 55 and 102 ($P<0.0001$) (*Figure 5.1*). Between 1999 and 2004, the number of new HBV diagnoses was approximately the same amongst homosexual men and heterosexuals. From 2004 onwards, there was a small decrease in the number of new diagnoses amongst heterosexuals. In 2007, we observed a small peak in the number of new HBV diagnoses amongst homosexual men. The number of new HBV diagnoses remained stable over time amongst patients infected with HIV through injecting drug use.

Table 5.1: Characteristics of HBV and HCV HIV co-infected patients

	HBV co-infection	HCV co-infection
N	1372	2004
Age at first HBV or HCV positive test date	37 (31-44)	39 (33-45)
Male gender	1160 (85)	1619 (81)
Year of first positive HBV or HCV test		
<1996	203 (15)	272 (14)
1996-1999	258 (19)	368 (18)
2000-2004	406 (30)	498 (25)
>=2005	505 (37)	866 (43)
HIV transmission		
MSM	776 (57)	831 (41)
Heterosexual	405 (30)	261 (13)
IDU	76 (6)	632 (32)
Other	115 (8)	280 (14)
Region of origin		
NL	682 (50)	1221(61)
Western	120 (9)	362 (18)
SSA	296 (22)	123 (6)
Other	274 (20)	298 (15)
Median CD4 count at first HBV or HCV test	310 (137-500)	380 (230-570)
Median log HIV RNA at first HBV/HCV positive test	4.5 (2.86-5.06)	3.7 (1.7-4.8)
cART	1245 (91)	502 (92)
HBV treatment	723 (89)	
HCV treatment		545 (27)
HCV genotype		
1	-	677 (64)
2		49 (5)
3		164 (16)
4		163 (15)
5		1((0.1)
6		2 (0.2)
Unknown		948
Total liver fibrosis	108 (8)	349 (17)
Severe chronic liver disease		
- confirmed	16 (1)	36 (2)
- probable	53 (4)	113 (6)
Hepatocelluliar carcinoma	16 (1)	10 (0.5)
Deaths	181 (13)	387(19)
Cause of death related to viral hepatitis	28 (2)	58 (3)

Legend: *HBV=hepatitis B virus; HCV=hepatitis C virus; MSM=men who have sex with men; IDU=injecting drug use; NL=Netherlands; SSA=sub-Saharan Africa; cART=combination antiretroviral therapy*

Figure 5.1: Number of HBV and HCV diagnoses between 1998 and 2010 among HIV-infected patients in the Netherlands.



Legend: HBV=hepatitis B virus; HCV=hepatitis C virus

Hepatitis C co-infection

Prevalence

In total, 17,082 HIV-positive patients in the Stichting HIV Monitoring (SHM) database were tested for the presence of HCV co-infection. HCV co-infection is defined as a positive test result on an HCV antibody test (EIA, Asym), a qualitative RNA test, and/or a quantitative RNA test.

In total, 2004 (12%) of the patients had a positive HCV-antibody or HCV-RNA test result; in 792 (40%) of the patients the HCV co-infection was confirmed by a positive HCV RNA test result. In 1212 (60%) HCV RNA test results were not available. Most of the HIV/HCV co-infected patients were male and originated from the Netherlands (*Table 5.1*). Forty-one percent of the co-infected patients were infected with HIV through homosexual contact and comprised the largest group of HIV/HCV co-infected patients. The second largest group of HIV/HCV co-infected patients consisted of patients infected with HIV by injecting drug use (31%). Almost all the patients (89%) were treated with cART, which translates to a high median CD4-cell count at the time of HCV diagnosis (median, interquartile range (IQR), 450 [282-646]). An HCV genotype was known for 53% of the HIV/HCV co-infected patients. Most patients were infected with HCV genotype 1 (n=677, 64% of the known genotypes).

HCV diagnoses

There was a significant increase in the number of HCV diagnoses from 2000 onwards (P<0.001). In 2000, the number of new HCV diagnoses amongst homosexual men was 6, and it rose to 127 in 2008. The number of new HCV diagnoses amongst the other HIV transmission risk groups has slowly decreased over time (p<0.0001). The number of new diagnoses amongst the other HIV transmission risk groups was 75 in 2000 and 35 in 2008 (*Figure 5.1*).

Newly acquired HCV infections

In the past few years, several studies have reported an increase in the number of newly acquired HCV infections amongst HIV-infected homosexual men [188,189]. In total, 153 patients with a known HCV-negative test date and a first HCV-positive test date within 24 months have been reported to the SHM. This number of newly acquired HCV infections has significantly increased since 2003 (*Figure 5.1*). Most of the patients (81%) that were infected with HIV through homosexual contact were born in the Netherlands. The median time between HIV diagnosis and newly acquired HCV infection was 2.5 (1-8) years. HCV genotype 1 was the most frequent genotype (59%). HCV genotype 4 was more common in newly acquired HCV infections (26%) in comparison to prevalent HCV infections (15%).

In Europe most HCV-infected patients are infected with HCV genotypes 1, 2 or 3 [190], but the prevalence of HVC genotype 4 has increased over time [191,192]. A recent study showed that the Netherlands has become endemic for HCV genotype 4 due to an influx from countries where HCV genotype 4 is endemic and to further local spread amongst injecting drug users and homosexual men infected with HIV [193].

Morbidity and mortality

Liver disease caused by HBV and HCV is currently an important cause of death amongst HIV-infected patients [29]. Progression of HBV- and HCV-associated liver disease is accelerated by the presence of HIV, with more rapid development of chronic liver disease, fibrosis and cirrhosis [194-196].

Liver morbidity

Amongst the patients co-infected with HBV, a total of 108 (8%) progressed to liver fibrosis, including all Metavir scores (*Table 5.1*) [197]. We divided severe chronic liver disease as "confirmed" or "probable". Confirmed severe chronic liver disease was defined as:

1. Clinical symptoms of end-stage liver failure based on the diagnosis documented in a clinical note including bleeding from gastric or oesophageal varices, hepatic encephalopathy or hepatorenal syndrome, confirmed with a pathology report or FibroScan® report documenting severe liver fibrosis or cirrhosis (Metavir f3-f4 or FibroScan stiffness>=8kPa).

2. Clinical evidence of chronic liver disease based on radiographic or endoscopic documentation of the presence of portal hypertension by oesophageal varices, ascites, splenomegaly and reversal of portal blood flow, confirmed with a pathology report or FibroScan report documenting severe liver fibrosis or cirrhosis. A probable diagnosis of severe chronic liver disease is defined on the basis of clinical symptoms, clinical evidence or a pathology report.

Severe chronic liver disease developed in 69 (5%) of HBV-co-infected patients; 16 (1%) had a confirmed diagnosis, and 53 (4%) had a probable diagnosis of severe chronic disease (*Table 5.1*). Hepatocellular carcinoma was diagnosed in 16 (1%) of the patients.

In the HCV-co-infected patients, a total of 349 (17%) progressed to liver fibrosis (*Table 5.1*). Confirmed severe chronic liver disease was diagnosed in 36 (2%), and a probable diagnosis was observed in 113 (6%) of the patients. Hepatocellular carcinoma was less frequent in HCV-co-infected patients compared to HBV-co-infected patients (0.5% and 1%, respectively).

Figure 5.2A shows the time to severe chronic liver disease stratified by co-infection amongst patients treated with cART. Ten years after cART initiation, progression to liver disease was higher amongst HIV/HCV co-infected patients (9%; 95% CI, 6-10%), compared to HBV-co-infected patients (5%; 95% CI, 4-8%) and was lowest amongst the HIV mono-infected patients (1%; 95% CI, 0-1%). HIV/HCV co-infected patients have been shown to have the most rapid progression to liver disease [198]. Hazard ratios for time to severe chronic liver disease in the SHM database are summarized in *Table 5.2*. After adjustment for differences in demographic and clinical characteristics, HCV co-infected patients had the highest risk for the development of severe chronic liver disease. HBV co-infection was associated with risk of severe chronic liver disease 10 times higher than that of patients mono-infected with HIV. For HCV-co-infected patients the hazard ratio of severe chronic liver disease was 20.1 (95% CI, 12.4-34.2).

Figure 5.2A: Probability of the development of chronic severe liver disease amongst patients infected with HIV only, patients co-infected with HIV/HBV, and patients co-infected with HIV/HCV. Kaplan–Meier method was used to estimate the time to severe chronic liver disease. The follow-up time was from the date of cART initiation to the date of last contact, date of most recent follow up visit, date of diagnosis of liver disease, date of death, or 1 June 2011.

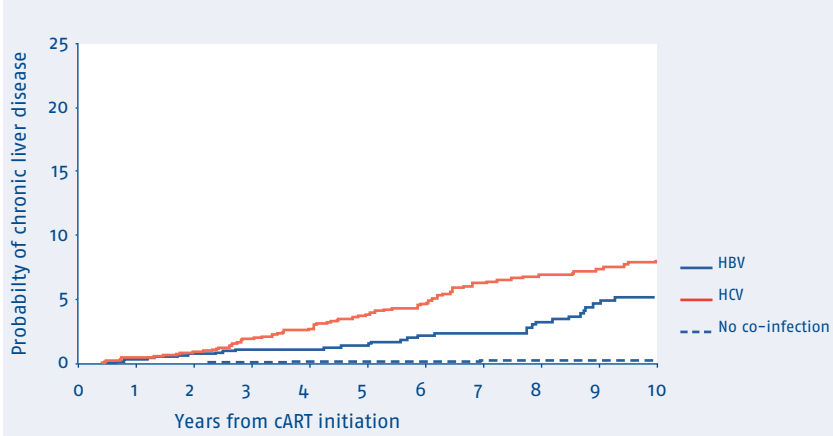
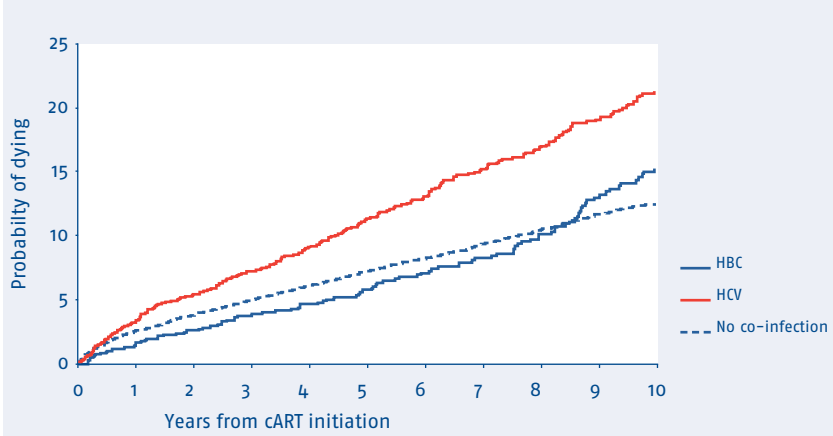


Figure 5.2B: Probability of death among patients infected with HIV only, patients co-infected with HIV/HBV, and patients co-infected with HIV/HCV. Kaplan–Meier method was used to estimate the time to death. The follow-up time was from the date of cART initiation to the date of last contact, date of most recent follow up visit, date of death, or 1 June 2011.



Mortality

In the SHM database, the proportion of deaths amongst HBV-co-infected patients is 13%. An active HBV infection is a strong predictor for liver-related death in HIV/HBV co-infected patients [199]. Of the deaths in patients co-infected with HIV/HBV, 15% were related to a complication of viral hepatitis. Ten years after cART initiation 16% (95% CI, 13-19%) of the HBV-co-infected patients had died (*Figure 5.2B*).

The proportion of deaths was 19% in the HCV-co-infected patients, and 58 out of 387 (15%) were related to complications of viral hepatitis (*Table 5.1*). The same proportion of deaths related to liver disease amongst HIV/HCV co-infected patients has been found in other populations [200]. Ten years after the initiation of cART, 21% (95% CI, 19-24%) of the HCV-co-infected patients on cART had died (*Figure 5.2B*).

Table 5.2 shows the hazard ratios for the time to death. After adjustment for differences in demographic and clinical characteristics, patients with HIV who are co-infected with HBV or HCV do not have a higher risk of death than do HIV mono-infected patients. Several studies reported an increased risk of death in the HIV/HCV co-infected population, which was mainly found amongst injecting drug users [187, 201]. The impact of co-infection on the risk of death remains controversial, as others did not find such an increase [202]. In the SHM database the risk of death was not increased amongst the population co-infected with HBV and HCV after adjustment for differences in demographic and clinical differences, including HIV transmission route. Most of the HVC infections were in homosexual men. We observed an increase in the number of HCV diagnoses over calendar time, and a large proportion of these diagnoses were confirmed to be newly acquired HCV infections (confirmation was based on an earlier HCV negative test result). These recently acquired HCV infections had probably not yet progressed to the advanced liver disease that results in death. Most of the newly acquired HCV infections were in homosexual men who were well treated for their HIV infection. Clearance of HCV is associated with high CD4-cell counts [203]. Thus, successful treatment of HIV might have impacted the clearance of HCV and the risk of death.

Table 5.2: Risk of progression to severe chronic liver disease and death amongst HIV-infected patients with hepatitis co-infection treated with combination antiretroviral therapy (cART) compared to patients infected with only HIV treated with cART. To evaluate the impact of HBV and HCV co-infection on risk of liver disease and death, time to liver disease or death was estimated by a Cox proportional hazard model. Follow-up time was from the date of cART initiation until date of last contact, date of most recent follow up visit, date of diagnosis of liver event or death, or 1 June 2011.

	Severe chronic liver disease Hazard ratio (95% CI)	p-value	Risk of dying Hazard ratio (95% CI)	p-value
HIV	1	<0.0001	1	0.82
HIV/HBV	10.0 (5.40-18.6)		0.92 (0.72-1.19)	
HIV/HCV	20.6 (12.4-34.2)		0.99 (0.80-1.23)	

Legend: CI=confidence interval; HBV=hepatitis B virus; HCV=hepatitis C virus

** adjusted for age, gender, region of origin, transmission risk group, calendar year of cART initiation, baseline CD4 and HIV RNA levels, alcohol use and smoking*

Treatment and treatment effects

HBV treatment

At present, anti-HBV treatment is aimed at suppression of HBV production, thereby delaying progression towards liver fibrosis and cirrhosis [204]. Several antiretroviral drugs, such as lamivudine, emtricitabine and tenofovir used for the treatment of HIV, also suppress HBV [205].

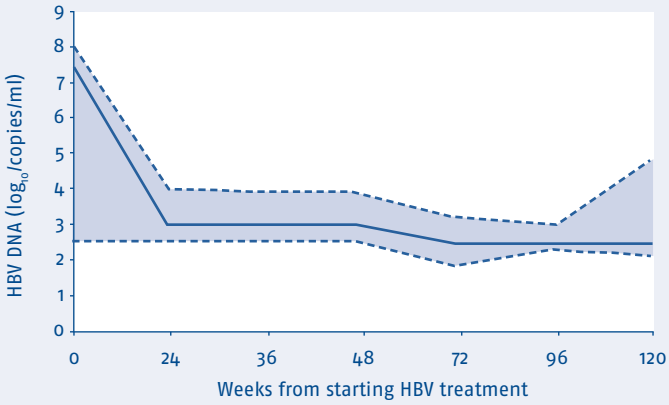
In the SHM database a total of 816 (59%) HIV/HBV co-infected patients were receiving a cART regimen that included an agent that was also active against HBV. The median time between HBV diagnosis and the start of treatment was 13.3 months (IQR, 2.4-41.0). In most treated HIV/HBV co-infected patients, lamivudine was the initial anti-HBV agent (n=723, 89%); 10% of the patients started their HBV treatment with tenofovir.

HBV treatment outcome

Complete data on HBV DNA measurements were available from patients in follow-up in eight HIV treatment centres. For 287 patients in follow-up in these treatment centres, two or more HBV DNA measurements after treatment initiation were available. Data on treatment responses presented in this paragraph are based on the selection of patients in follow-up in these eight treatment centres. *Figure 5.3* shows the time course of HBV DNA plasma levels after the initiation of HBV treatment. At the start of HBV treatment initiation, the median HBV DNA level was 7.4 (IQR, 2.5-8.0) $\log_{10}$ copies/ml.

Median HBV DNA decreased to 3.0 (IQR, 2.5-4.0) $\log_{10}$ copies/ml in the first 24 weeks after HBV treatment initiation ($p<0.0001$) and further decreased to 2.5 (IQR, 2.3-3) $\log_{10}$ copies/ml when patients were treated for more than 72 weeks.

Figure 5.3: Changes in HBV DNA plasma levels (log copies/ml) since the start of hepatitis B virus (HBV) treatment in patients co-infected with HIV and HBV, median with interquartile range (IQR).



Anti-HCV treatment

Chronic infection with HCV is treated with a combination of pegylated interferon (PEG-IFN) and ribavirine (RBV) [206]. Anti-HCV treatment was registered during follow-up for 545 patients co-infected with HCV, equivalent to 27% of the total HCV co-infected patients. The number of HCV-co-infected patients treated with (PEG)-IFN and RBV in the course of their HIV infection is relatively low, but this is consistent with published treatment rates [207-209]. However, numbers have increased over time (P<0.0001) (*Web Appendix Figure 5.1*), and especially for those starting treatment within one year after HCV diagnosis. Before 2005 the median time between HCV diagnosis and the start of anti-HCV treatment was two years (IQR, 0.6-6.3); this has decreased to 0.7 years (IQR, 0.2-4) from 2005 onwards. In 2009 more than half of the patients started anti-HCV treatment within six months after HCV diagnosis.

HCV treatment outcome

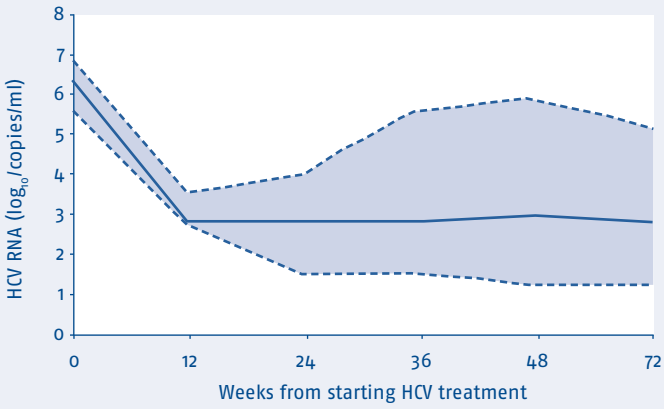
We obtained HCV RNA results for 294 (54%) of the 545 HIV/HCV co-infected patients who initiated anti-HCV treatment; this selection included patients from the eight HIV treatment centres in which all data on HCV treatment is collected and linked to the SHM. HCV RNA levels after initiation of HCV treatment are presented in *Figure 5.4*. At the start of HCV treatment, the median HCV RNA level was 6.4 (IQR, 5.6-6.9) $\log_{10}$ copies/ml. Median HCV RNA levels significantly decreased to 2.8 (IQR, 2.7-3.5) $\log_{10}$ copies/ml in the first 12 weeks after treatment initiation (p<0.0001). An early virologic response (defined as HCV RNA plasma levels below the detection border of the quantitative HCV RNA assay 12 weeks after the start of treatment for HCV) was found in 42% of the patients. The median HCV RNA levels 72 weeks after HCV treatment initiation were 2.8 (IQRL: 1.2-5.2) $\log_{10}$ copies/ml, and 46% of the patients had a detectable HCV RNA measurement at week 72. The sustained

virologic response (SVR) (defined as HCV RNA levels below the detection border of the quantitative HCV RNA assay 6 months after treatment discontinuation) was recorded for 106 patients, and an overall SVR was reached for 48 (45%) of the patients.

Amongst the 48 patients who achieved an SVR, HCV RNA was still undetectable in 43 of them at the last available HCV RNA measurement, which was obtained at a median of 15 weeks later (IQR, 4-24 weeks). In the remaining 5 patients, HCV RNA became detectable again after a median of 24 weeks (IQR, 11-44 weeks) after achieving an SVR. No data on HCV genotypes were available after relapse; hence, re-infection with HCV could not be excluded.

In randomized clinical trials that mainly have included a small selection of patients the SVR has varied between 7 and 67% [210-213]. SVR might be different in clinical practice. We found an SVR between 34% and 61% amongst the patients co-infected with HIV/HCV who were receiving HIV treatment, and in an earlier report on the HCV treatment response in the Swiss HIV Cohort Study, the SVR varied between 28-52% [209]. The results from both observational cohorts show that an SVR comparable to those in randomised clinical trials can be achieved.

Figure 5.4: Changes in HCV RNA plasma levels (log copies/ml) since the start of hepatitis C virus (HCV) treatment in HIV/HCV co-infected patients, median with interquartile range (IQR).



Conclusion

Since 2000, the number of HCV diagnoses in the Dutch HIV-infected population has increased. Most of these diagnoses are amongst homosexual men. The increase in HCV diagnoses coincides in this population with an increase in acute HCV infections, both of which probably have been caused by sexual transmission [189]. The number of HBV diagnoses, however, remained stable over time until 2007, when it started to decrease.

Our data shows that patients co-infected with HBV and HCV are at increased risk of developing severe chronic liver disease. Optimal management of HBV and HCV co-infection in HIV-infected individuals is needed to limit the impact of co-infection on the progression to severe chronic liver disease. Fifty-nine percent of the HIV/HBV co-infected patients and 27% of the HIV/HCV co-infected patients received treatment for their co-infection. We had difficulty obtaining a complete picture of treatment responses, because all the data on HBV DNA and HCV RNA plasma levels were available for only 8 of the 25 centres. Improvement of data collection and linking is a future priority of SHM.

We reported HBV and HCV treatment responses in the selected group of patients with complete data on treatment response. In both HBV- and HCV-treated patients, substantial decreases in HBV DNA and HCV RNA levels after the start of treatment were observed. Although the absolute number of patients with complete data regarding response to treatment is small, the successful responses for HBV and HCV shown in our data are comparable to those found in other studies [209, 214].

Treatment of HBV replication for long-term control will slow the progression of chronic liver disease, but this treatment should be combined with the control of HIV because earlier studies showed that patients with low CD4-cell counts remain at increased risk of progression to chronic liver disease [215]. Patients with HIV/HBV co-infection and untreated HBV might benefit from cART to reduce the risk of chronic liver disease. In our population, 99% of the patients co-infected with HBV who were receiving HBV treatment were also treated for their HIV infection.

The number of patients co-infected with HIV and HCV who are able to clear their HCV infection by receiving PEG-IFN and RBV is small, as revealed not only in our data but also in randomized clinical trials [211-213, 216]. New anti-HCV drugs are urgently needed and are now being developed [217], in particular, because of the increasing number of HCV diagnoses. These new therapeutic strategies, such as the direct acting agents of the protease inhibitor class, may provide more treatment options for patients co-infected with HIV and HCV and may contribute to reducing severe chronic liver disease in such patients.

Special reports

6. The Amsterdam Cohort Studies on HIV infection – Annual Report 2010

Ineke Stolte, Maria Prins for the ACS

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS were started shortly after the first cases of AIDS were diagnosed in the Netherlands in the early eighties. 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 2010, the cohorts reached 26 years of follow-up. The initial aim of the ACS was to investigate the prevalence of, 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 26 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 (STI) amongst 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 in Nederland werden gediagnosticeerd. Sinds oktober 1984 worden mannen die seks hebben met mannen (MSM) gevolgd in een prospectieve cohortstudie. Een tweede cohort onder drugsgebruikers startte in 1985. In 2010 bestonden de cohorten 26 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 de HIV-1-infectie en het evalueren van de effecten van interventies. De afgelopen 26 jaar zijn deze doelen min of meer gelijk gebleven maar is de nadruk van de studies wel verschoven. In het begin lag de focus vooral op het verkrijgen van inzicht in de epidemiologie van HIV-1. Later zijn meer verdiepende studies uitgevoerd naar met name de pathogenese van HIV-1. In de afgelopen jaren werden eveneens de epidemiologie en het natuurlijk beloop van andere bloedoverdraagbare en seksueel overdraagbare aandoeningen (SOA's) onder deelnemers aan de ACS 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 in belangrijke mate inzicht gegeven in de verschillende aspecten van HIV-1. Deze expertise heeft direct bijgedragen aan de vooruitgang en verbetering van de preventie, diagnose en behandeling van de HIV-infectie.

As of 31 December 2010, 2447 MSM and 1657 (injecting) DU were included in the ACS. Every three to six months, participants 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 underwent a medical examination (HIV-positive participants and, in the past, HIV-negative drug users as well), and blood was drawn for diagnostic tests and storage. The ACS has 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 2447 MSM, 596 were HIV-positive at study entry, and 216 seroconverted during follow-up. For the 1657 DU, 322 were HIV-positive at study entry, and 98 seroconverted during follow-up. By 31 December 2010, 342 MSM and 452 DU had died, and several other participants were asked to leave the study or left at their own request. Almost 95% 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 49,647 times by MSM and 26,164 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, the 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, the ACS collaborates with many other research groups both within and outside of the Netherlands.

The ACS is a collaboration between the Public Health Service of Amsterdam, the Academic Medical Center of the University of Amsterdam, the Sanquin Blood Supply Foundation, the University Medical Center Utrecht, and the Jan van Goyen Medical Center. The ACS is

part of Stichting HIV Monitoring (SHM) 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 2010

The cohort of men having sex with men

In 2010, 542 MSM were followed at the PHSA of Amsterdam. Thirty-six of them had been newly recruited since January 2010, and one participant died. From 2005, recruitment has been open to MSM of all ages with at least one sexual partner in the preceding six months. Of the MSM followed in 2010 at the PHSA, 473 men were HIV-negative, and 69 men were HIV-positive. The HIV-positive men, of whom 46 were HIV seroconverters, were followed according to the 'HIV Onderzoek onder Positieven' (HOP) protocol. This protocol 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 been routinely screened for sexually transmitted infections (STI), and as of July 2010, additional screening for human papillomavirus (HPV) was started among all MSM to investigate the prevalence, incidence, and clearance of anal, penile and oral HPV infections among HIV-negative and HIV-positive MSM (H2M study).

In 2010, 17 HIV-positive men were included in the HOP, of whom 7 were exclusively followed in an HIV treatment centre outside the PHSA. By the end of 2010, a total of 100 HIV-positive men were still in active follow-up according to the HOP protocol at the PHSA or in an HIV treatment centre outside the PHSA. From June 2006 onwards, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants have also been invited to participate in the ACS. Thirteen 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 2010.

Plasma and cells from 58 of the 135 HIV-positive MSM in active follow-up at the Jan van Goyen clinic since 1999 were stored in 2010. Of these, 36 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 ten years and had a CD4 count greater than 400 cells/µl after ten years of follow-up after an HIV-positive result without effective therapy.

The cohort of drug users

In 2010, 351 drug users were followed at the PHSA. Of the 351 DU followed in 2010, 29 were HIV-positive at entry, 16 seroconverted for HIV during follow-up in the ACS, and 5 had their first study visit in 2010. Since December 2010, all DU followed at the PHSA have also been screened for STI as part of a pilot study to assess whether regular STI screening is indicated for this group.,

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 2010, as part of this project, 8 DU who were mono-infected with HCV and 1 with an HCV/HIV co-infection initiated HCV therapy, resulting in a total group of 73 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.

Sub-studies

Primo-SHM study results

This randomized study compared no treatment during primary HIV infection (PHI) with 24 weeks or 60 weeks of antiretroviral treatment.

The optimal clinical management of PHI is controversial. Treatment during PHI may result in a more effective immune response to the virus, resulting in lowering of the viral set point and delaying the loss of CD4 T cells. Several ongoing randomized controlled trials in the combination antiretroviral therapy (cART) era have addressed the question whether such temporary treatment also has clinical benefits for the patient, but none have been published so far. The aim of the Primo-SHM study was to assess the clinical benefit of temporary cART during PHI.

The study was a multicenter, open-label, randomized controlled trial in which patients with laboratory evidence of PHI were randomly assigned to receive no treatment or 24 weeks or 60 weeks of cART. If therapy was clinically indicated, subjects were randomized over the 2 treatment arms. Patients were recruited in 13 Dutch HIV treatment centres. Recruitment started in May 2003 and continued until March 2010. Primary endpoints were the viral set point (defined as the plasma viral load [pVL] 36 weeks after randomization in the no-treatment arm and 36 weeks after treatment interruption in the treatment arms) and the total time that patients were off therapy (defined as the time between randomization and start of cART in the no-treatment arm and the time between treatment interruption and restart of cART in the treatment arms). cART was (re)started in the event of a confirmed CD4 count <350 cells/mm^3 or symptomatic HIV disease. Time off therapy was compared across study arms using Kaplan–Meier plots and multivariate Cox survival analyses adjusted for confounding factors.

The modified intention-to-treat-analysis comprised 168 patients: 115 were randomized over the three study arms and 53 were randomized over the two treatment arms only. The vast majority of patients randomized over the three study arms was MSM, had a negative or indeterminate Western blot and was symptomatic during PHI. Treatment in the treatment arms was well tolerated. The mean viral set point was significantly lower in the 24-week and 60-week treatment arms as compared to the no-treatment arm. The median total time off therapy was significantly longer in the 24-week and 60-week treatment arms as compared to the no-treatment arm; restart of cART during chronic HIV infection was

deferred by approximately 2 years. When all treated patients, including the patients randomized over the two treatment arms, were combined, the median total time off therapy did not differ between the 24-week and 60-week treatment arms. In the adjusted Cox analyses, temporary cART was independently associated with time to (re)start of cART.

The present randomized trial provides the first evidence of a clinical benefit of temporary cART during PHI. Temporary cART lowered the viral set point and deferred the need for initiation of cART during chronic HIV infection. These results were presented as an oral presentation at the 18th Conference on Retroviruses and Opportunistic Infections, February 2011 in Boston.

AgeHIV Cohort Study

In October 2010 the AgeHIV Cohort Study was started, a collaboration between the AMC Department of Infectious Diseases and the Department of Global Health and Amsterdam Institute of Global Health and Development, the PHSA and the SHM. This ongoing prospective cohort study aims to recruit 800 HIV-1-infected patients amongst AMC HIV outpatient clinic attendees and a control group of 400-600 HIV-uninfected individuals belonging to the same HIV exposure groups at the STI clinic of the PHSA and among participants of the Amsterdam Cohort Studies. Both groups will be aged ≥45 years and comparable as closely as possible in age, gender, ethnicity and risk behaviour. The aim of the study is to assess the prevalence and incidence of a broad range of co-morbidities and known risk factors for these co-morbidities in HIV-infected patients aged 45 years or more and to determine the extent to which co-morbidities, as well as risk factors for co-morbidities and their relation to quality of life, differ between HIV-infected and uninfected individuals.

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. 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 seroconverted for HIV in 2010. HIV incidence in 2010 was almost 2 per 100 person-years among MSM. The incidence has slowly increased since 1996, the year that cART became generally available in developed countries including the Netherlands.

The current trend in HIV incidence seen in the MSM cohort differs from that observed in the DU cohort. HIV incidence in drug users has continued to decline and is now less than 1.0/100 person-years. *Figures 6.1* and *6.2* show the yearly observed HIV incidence rates for MSM and drug users from the start of the ACS through 2010.

Figure 6.1: *HIV incidence per calendar year in the ACS among men having sex with men, 1984–2010*

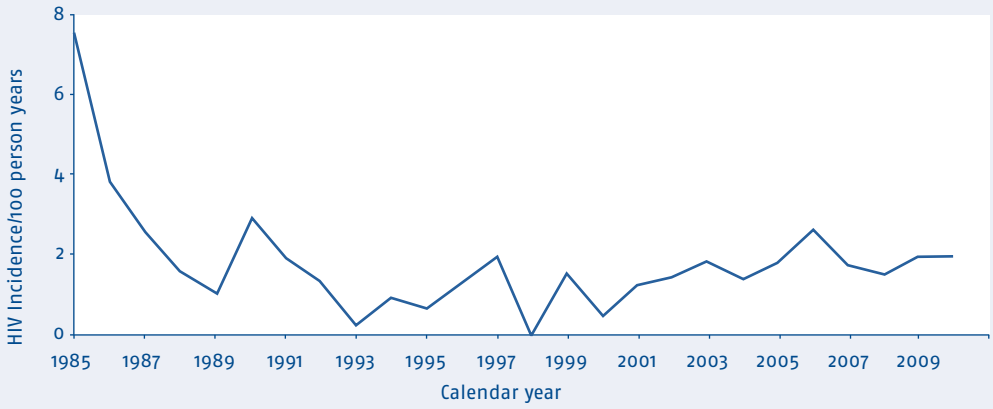
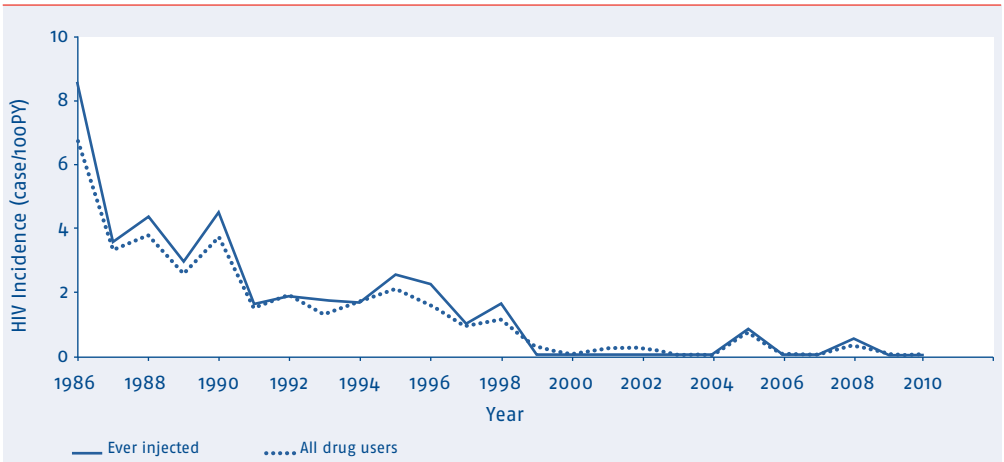


Figure 6.2: *HIV incidence per calendar year in the ACS among drug users, 1986–2010*



Transmission of therapy-resistant HIV strains

Surveillance of transmission of drug-resistant HIV-1 strains was performed for six MSM seroconverters and for four MSM seropositive at study entry in 2010. Two individuals were infected with virus harbouring resistance-associated mutations; a 41L, 210W and a so-called 215-revertant (215D) mutation were found in one of the seroconverters, and a 41L and 215D mutation were found in one of the seroprevalent participants. In the other eight individuals only a naturally occurring sequence variation was found. Phylogenetic analysis showed that nine individuals harboured subtype B HIV-1 strains, and one individual was infected with subtype CRF06-cpx.

In the cohort of drug users, one DU with a previous HIV-negative test result in the ACS was newly diagnosed with HIV. However, the seroconversion interval of this participant was 42 months; the last seronegative test was performed in 2006. In the first seropositive sample no HIV-1 RNA could be detected; therefore, baseline resistance testing could not be performed.

Combination antiretroviral therapy (cART) uptake

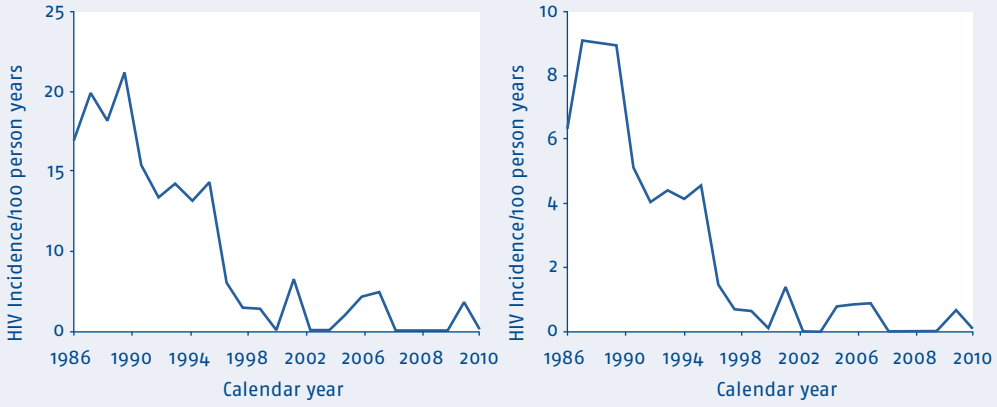
Of all 203 HIV-positive MSM visiting the Jan van Goyen Clinic or one of the other HIV treatment centers in the Netherlands according to the ACS protocols in 2010 and for whom treatment data were available in 2010, 190 (94%) received some form of antiretroviral therapy. Of 200 MSM for whom viral load results were available in 2010, 187 (94%) had a viral load of less than 50 copies/ml (assays: M²000rt).

Of the 45 HIV-positive DU who visited the PHSA in 2010, 31 (69%) received some combination of antiretroviral therapy. Of these 31, 29 (94%) had an undetectable viral load (≤150 copies/ml [assay: m²000rt]) at their latest visit. Of 14 HIV-positive DU not receiving HAART, 13 (93%) had an undetectable viral load.

Hepatitis C virus (HCV) incidence in drug users

In 2010 the HCV incidence was updated for the DU cohort. The HCV incidence strongly declined over a period of years amongst injectors only and in the total group; it was 0/100 person-years in 2010 (see *Figure 6.3*).

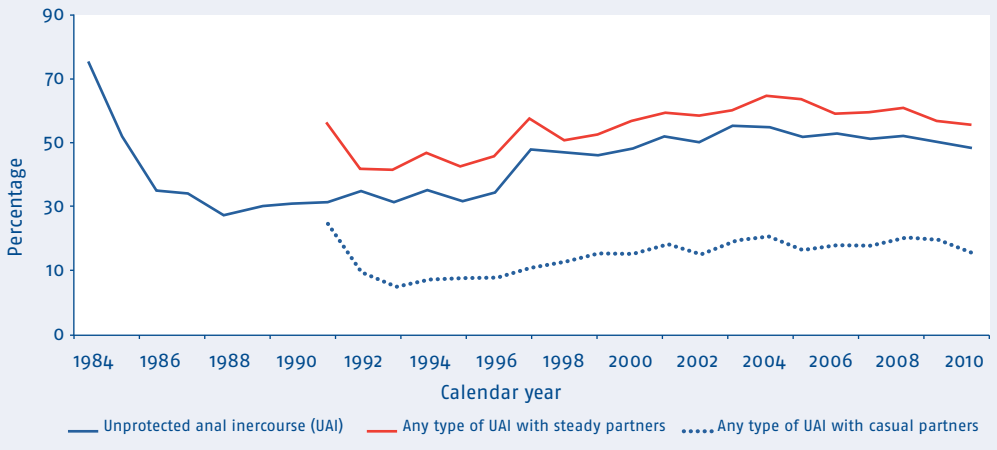
Figure 6.3: Hepatitis C virus incidence per calendar year in the ACS among all (left) and ever injecting (right) drug users, 1986–2010.



Risk behaviour of MSM

Information from the 867 questionnaires filled in by 473 HIV-negative MSM during cohort visits in 2010 resulted in 458 (53%) reports of unprotected anal intercourse (UAI) in the preceding six months. Highest rates of UAI were reported with steady partners (59%). Trends in UAI among HIV-negative MSM participating in the ACS have slowly increased since 1996, but have remained relatively stable in recent years.

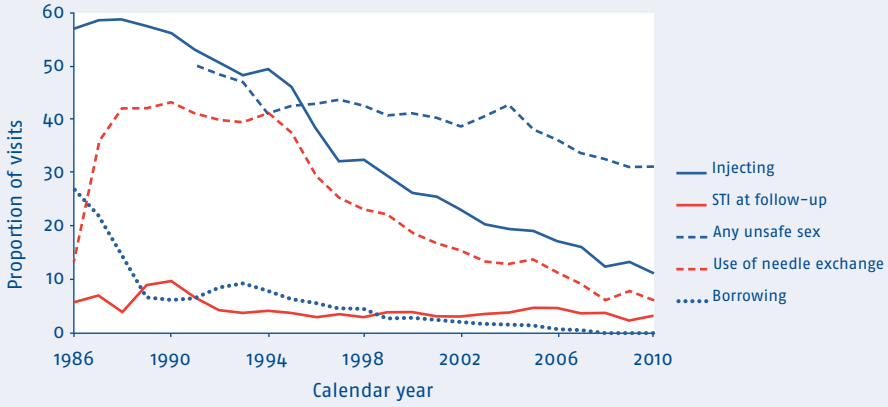
Figure 6.4: Trends in unprotected anal intercourse in the past six months amongst HIV-negative men having sex with men from the Amsterdam Cohort Study 1984–2010.



Risk behaviour of DU

In HIV-negative DU, reports of both injection and borrowing of needles significantly declined over the period 1985-2010. Reports of high-risk sexual behaviour at follow-up visits decreased before 1996, remained relatively stable until 2005 and further decreased to approximately 35% in 2010. Reports of STI have remained relatively stable around 5% in recent years (see *Figure 6.5*).

Figure 6.5: *Proportion of visits per calendar year at which injecting and high risk sexual behaviour was reported amongst 1315 drug users who were HIV-negative on ACS entry, 1986-2010.*



Legend: *STI=sexually transmitted infection*

STI screening among MSM in ACS

Since October 2008 all MSM in the ACS have been routinely screened for chlamydia and gonorrhoea using PCR techniques on samples from pharyngeal and rectal swabs and urine. Cases of syphilis are detected by *Treponema pallidum* haemagglutination assay (TPHA). In 2010 a total of 505 MSM from the ACS were screened for STI; 88 MSM once, 387 MSM twice and 30 MSM more than twice. The majority was HIV-negative (449 MSM, 835 visit), 40 MSM were HIV-positive (92 visits) and 16 had an unknown HIV status (31 visits). The prevalence of any STI at the first visit in 2010 was 9.5% (48/505), and the prevalence of any STI at the subsequent visit in 2010 was 8.6% (39/453). The prevalence of STI was significantly higher among HIV-infected MSM (24%) compared to HIV-uninfected MSM (7.5%).

ACS research highlights 2010

A key 2007 publication on the impact of participation in comprehensive harm reduction programmes of needle exchange, opiate substitution therapy, and social care on HIV and HCV transmission among DU was republished by invitation in 2010 [218]. Although we did not find evidence of any independent intervention effects, this was the first worldwide study demonstrating that the combination of interventions was effective not only in reducing HIV but also HCV. A recent meta-analysis and a systematic review have confirmed the ACS finding.

Recently, evidence has been provided that HIV-1 adapts over time to host cellular immune responses by losing epitopes restricted by the most abundant human leukocyte antigen types in a population. The hypothesis that, over the course of the epidemic, HIV-1 has also become more resistant to antibody neutralization was tested in participants from the ACS. HIV-1 variants obtained from participants who became infected at the beginning of the epidemic and from participants who recently contracted the virus were analyzed for their sensitivity to cross-reactive neutralizing antibodies. Over calendar time, HIV-1 developed an enhanced resistance to antibody neutralization, which was accompanied by an increase in the length of the variable loops and in the number of potential N-linked glycosylation sites on the HIV-1 envelope gp120 subunit [219].

A study was carried out examining the incidence of HIV-1 superinfection during the first year after infection amongst homosexual participants in the Amsterdam Cohort Studies on HIV infection and AIDS who seroconverted between 1985 and 1997. Sequence analysis of the viral env gene did not reveal evidence for superinfection, indicating that the incidence of HIV-1 superinfection soon after seroconversion in this cohort is low [220]. Risk reduction shortly after HIV-1 diagnosis early during the HIV-1 epidemic in the Netherlands may have contributed to the absence of HIV-1 superinfection observed in this study.

The ACS has participated in a genome-wide association study in a multiethnic cohort of HIV-1 controllers and progressors [221]. This study revealed >300 genome-wide significant single-nucleotide polymorphisms (SNPs) within the MHC and none elsewhere. Specific amino acids in the HLA-B peptide binding groove, as well as an independent HLA-C effect, explain the SNP associations and reconcile both protective and risk HLA alleles.

A longitudinal study was performed to assess the potential contribution of HIV-specific T-cell immunity in viral load containment after discontinuation of HAART [222]. Individuals who could maintain a low plasma viral load (<15,000 copies/mL) after treatment interruption (TI) were compared to those who could not do so (>50,000 copies/mL). Individuals maintaining a low viral load showed a more pronounced increase in HIV-specific CD8(+) T-cell numbers, leading to a significantly higher magnitude of the total HIV-1-specific CD8(+) T-cell response (IFN-γ(+) and/or IL-2(+) and/or CD107a(+)) 4 weeks after TI. Whether increased T-cell functionality is a cause or consequence of low viral load remains to be elucidated.

Xenotropic murine leukaemia virus-related virus (XMRV) is a recently discovered human gammaretrovirus with yet unknown prevalence and transmission route(s). Its presence in prostate stromal fibroblasts and prostatic secretions suggests that XMRV might be sexually transmitted. We searched for XMRV in seminal plasma, a compartment closely connected to the prostate, which is the only location where XMRV was unambiguously detected in independent studies. Seminal plasma from 54 HIV-1-infected men was analyzed. Although HIV-1 was amplified from 25% of the seminal plasma samples, no XMRV was detected, suggesting that either the prevalence of XMRV is very low in the Netherlands or XMRV is not naturally present in the seminal plasma [223].

Steering committee: The politburo

In 2010, the "politburo" met four times. Twenty-one proposals for use of data and/or samples (serum/PBMC) were submitted to the politburo: eight from AMC-Experimental Immunology, six from the AMC-Medical Microbiology, four from the UMCU, one from the GGD, one from AMC-internal medicine and one from researchers not affiliated with the ACS. Twenty requests were approved, some after revision, one request was resubmitted in 2011 after extensive revisions and one request was denied.

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Andrea Rachinger, April 16th 2010, "HIV-1 superinfection in homosexual men". Promotor is Prof. H. Schuitemaker; co-promotor is Dr A. B. van 't Wout.

Martijn Stax, October 1st 2010, "Characterization of DC-SIGN binding glycoproteins and the role in HIV-1 infection". Promotor is Prof. dr. B. Berkhout; co-promotor is Dr W.A. Paxton.

Edwin Heeregrave, October 15th 2010, "Influence of CD4+ cell types on HIV-1 infection". Promotor is Prof. dr. B. Berkhout; co-promotor is Dr W.A. Paxton.

7. Curaçao

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

Since 2005, Stichting HIV Monitoring has collected data on HIV-infected patients in Curaçao. As of June 2011, a total of 746 patients had been registered; of those, 58% were still in outpatient clinical care. At the time of entry into care, 64% of the 746 patients already had AIDS or had CD4-cell counts below 350 cells/mm^3. This indicates that antiretroviral treatment was started for many patients only when the CD4-cell count was below the recommended threshold, but this situation has improved in the last few years. Approximately 80% of patients who started treatment in or after 2003 have achieved sustained viral suppression, probably as a result of improved treatment regimens in the past five years, with the majority of patients now being treated with a combination of tenofovir/emtricitabine and either lopinavir or efavirenz. Nevertheless, virologic failure has occurred in 20% of treated patients. For one third of those patients, the absence of resistance to any antiretroviral drug suggested that they did not take their prescribed medication. The frequency of follow-up was according to the recommended guidelines. Thus, on the whole, care and treatment of HIV-infected patients in Curaçao withstands comparison with settings having more resources.

Zes jaar geleden begon de Stichting HIV Monitoring met het verzamelen van data van HIV-geïnfecteerde patiënten in Curaçao. Begin juni 2011 waren er 746 patiënten geregistreerd van wie er 58% nog in (poli-)klinische zorg waren. Op het moment van in zorg komen, had 64% van deze patiënten AIDS of een CD4-celaantal van minder dan 350 cellen/mm^3. Antiretrovirale behandeling kon derhalve bij veel patiënten pas ingezet worden op een moment waarop hun CD4-celaantal onder de aanbevolen grens lag. Hierin is de laatste jaren wel enige verbetering te zien. Ongeveer 80% van de patiënten die sinds 2003 met therapie zijn gestart, slaagt erin langdurige virale onderdrukking te bereiken. Dit is zeer waarschijnlijk een gevolg van verbeterde behandelregimes in de laatste vijf jaar; de meerderheid van de patiënten wordt nu behandeld met een combinatie van tenofovir/emtricitabine plus lopinavir of efavirenz. Toch komt virologisch falen nog steeds bij 20% van de patiënten voor. Een derde van de patiënten met therapiefalen heeft tegen geen enkel antiretroviraal geneesmiddel resistentie ontwikkeld. Dit duidt erop dat zij hun voorgeschreven medicatie hoogstwaarschijnlijk niet innemen. De klinische, immunologische en virologische monitoringfrequentie volgt de aanbevolen behandelrichtlijnen, zodat over het algemeen genomen de zorg en behandeling van HIV-geïnfecteerden in Curaçao vergelijkbaar is met die in rijkere landen.

Introduction

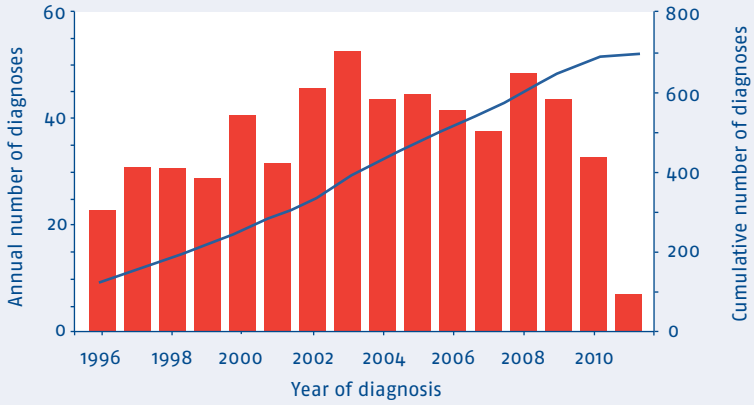
Since 2005, Stichting HIV Monitoring (SHM) has collected demographic and clinical information on all HIV-infected patients who are in follow-up at the St. Elisabeth Hospital in Willemstad in Curaçao. Such an extensive monitoring and registration system is unique in the Caribbean and has offered many new insights into the local HIV epidemic and the effects of clinical care and treatment [224]. In this special report, we present a concise overview of the population registered in Curaçao.

HIV-infected population in care

As of June 2011, a total of 746 HIV-infected patients were registered in Curaçao, of whom 590 (79%) were still alive and 156 (21%) had died since initial registration. This is an increase of 73 patients, or 11%, compared to last year's report in which 673 patients were registered [1]. The total follow-up for the entire group of 746 patients was 4862 person-years. Of the 590 patients who were assumed to be still alive, meaning they were not registered as having died, 432 (73%) were still in clinical care and had at least one contact with the treating physician in Curaçao in the year prior to June 2011.

In total, 223 (30%) of the registered patients were diagnosed with HIV in or before 1999; 66 (30%) of those patients died before June 2011 (*Web Appendix Table 7.1*). Between 2000 and June 2011, 474 patients were diagnosed, but no information was available for the remaining 49 patients regarding the date of their first positive HIV test (*Figure 7.1*). By far, the majority of the patients were infected with HIV-1; two patients were infected with HIV-2, and four other patients had antibodies to both HIV-1 and HIV-2. Almost three-quarters of the registered population originated from the former Netherlands Antilles, and two-thirds reported being infected via heterosexual contact (*Table 7.1*).

Figure 7.1: Annual and cumulative number of HIV diagnoses amongst 746 HIV-infected patients in Curaçao registered by Stichting HIV Monitoring as of June 2011. In total, 109 patients were diagnosed prior to 1996, whilst for 49 patients the year of diagnosis was unknown or not yet recorded.



Legend: Bars=annual number of diagnoses; line=cumulative number of diagnoses since the start of the HIV epidemic.

Table 7.1: Characteristics of the HIV-infected population in Curaçao registered by Stichting HIV Monitoring as of June 2011.

	Alive, N=590		Dead, N=156		Total, N=746	
	N / median	% / IQR	N / median	% / IQR	N / median	% / IQR
Gender, male	358	61	108	69	466	62
Transmission						
MSM	108	18	15	10	123	16
Heterosexual	394	67	98	63	492	66
Other/unknown	88	15	43	28	131	18
Country of birth						
Antilles	408	69	139	89	547	73
Haiti	76	13	7	4	83	11
Dominican Republic	48	8	6	4	54	7
Treated with cART	438	74	97	62	535	72
Diagnosis						
CD4 (cells/mm^3)	332	124–504	114	53–352	313	94–476
RNA (log$_{10}$ copies/ml)	4.5	3.9–5.0	4.8	3.9–5.4	4.5	3.9–5.1
Age (years)	38	30–46	40	32–54	38	31–47
AIDS	34	6	32	21	66	9
Time to cART (years)	1.5	0.3–5.0	0.8	0.2–4.1	1.4	0.3–4.9
Follow-up (years)	6.1	2.1–11.1	2.5	0.3–7.1	5.3	1.6–10.5
Start of cART						
CD4 (cells/mm^3)	164	58–277	79	14–189	141	49–264
RNA (log$_{10}$ copies/ml)	5.0	4.4–5.4	4.8	4.3–5.5	4.9	4.4–5.4
Age (years)	42	34–49	46	38–56	43	35–51
AIDS	62	11	50	32	112	15
Follow-up (years)	4.4	1.8–8.6	1.8	0.2–4.3	3.6	1.3–8.0
Present (June 2011)						
CD4 (cells/mm^3)	413	276–553	-	-	413	276–553
RNA <500 copies/ml	294	62[a]	-	-	294	62[a]
Age (years)	47	39–54	-	-	47	39–54

[a] *percentage of 478 patients with a viral load measurement.*

Legend: *N=number; IQR=interquartile range; MSM=men having sex with men; cART=combination antiretroviral therapy.*

Children and adolescents

At the time of diagnosis, 13 patients were younger than 13 years of age ('children') and 16 were aged 13 to 18 years ('adolescents'). Most of the children, 10 in total, were infected by mother-to-child transmission (MTCT). Most of these infections occurred before 1995, when universal testing of pregnant women was introduced in Curaçao. Nevertheless, occasional infections via MTCT still occur. Adolescents were mainly infected via heterosexual (11 patients) or homosexual (4 patients) contact.

Since 2005, eight children and one adolescent have died, whereas 16 children and adolescents have reached adulthood. All eight children died before combination antiretroviral therapy (cART) was available. As of June 2011, three children and five adolescents were still registered with HIV infection, but the only data available in the preceding year were for just two of the adolescents.

Country of infection

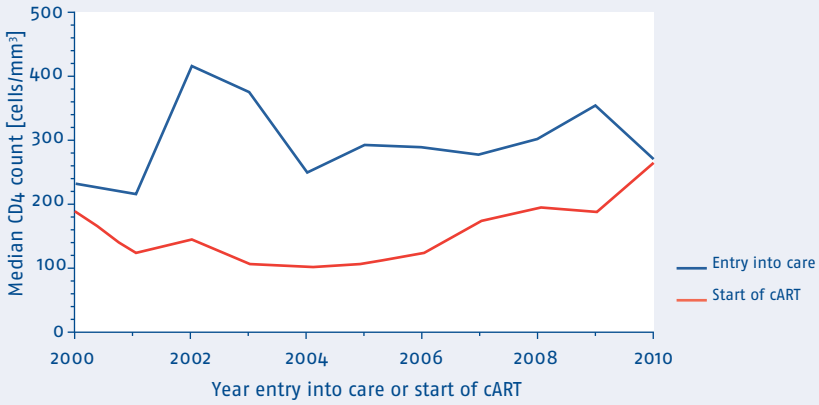
For 433 patients, or 58% of the registered population, the most likely country of infection was known. For 392 (86%) of those patients, the country of infection was the former Netherlands Antilles. This percentage was even higher (95%) amongst the 348 patients who were also born in the Antilles. Of the 433 patients, 17 patients were infected in the Netherlands, 14 in Haiti, and 8 in the Dominican Republic. All but four of the 226 patients with a known HIV-1 subtype were infected with a subtype B virus, which is the most prevalent subtype in the Caribbean and in the Netherlands amongst patients of non-African origin.

Late presentation and start of treatment

At the time of the first visit to the hospital, 349 (64%) of the 549 patients who could be classified presented in a late stage of their infection, that is, with a concurrent AIDS diagnosis or with CD4-cell counts below 350 cells/mm^3 [225]. For 198 (57%) of these 349 patients, CD4 counts were below 200 cells/mm^3. Hence, in general, it can be concluded that patients only enter care rather late in the course of their infection, which probably reflects a combination of late testing and a delay between HIV diagnosis and entry into care (*Figure 7.2*).

As a result of late entry into care, median CD4-cells counts at the start of cART were also low (141 cells/mm^3), which is well below the threshold of 200 cells/mm^3 at which treatment definitely should be started. Nevertheless, only 15% of the patients had experienced an AIDS-defining event by the time treatment was started. In recent years, however, there has been an increase in CD4 counts at the start of cART to 260 cells/mm^3 in 2010 *(Figure 7.2)*.

Figure 7.2: Median CD4-cell counts at the time of entry into care and at the start of combination antiretroviral therapy (cART) amongst HIV-infected patients in Curaçao. At the time of entry, median CD4-cell counts were 280 cells/mm³ (interquartile range [IQR], 99-451), whilst at the start of cART, CD4-cell counts were 141 cells/mm³ (IQR, 49-264). Whereas there were no statistically significant changes in CD4 counts at the time of presentation, CD4 counts at start of cART clearly increased in recent years indicating more timely treatment.



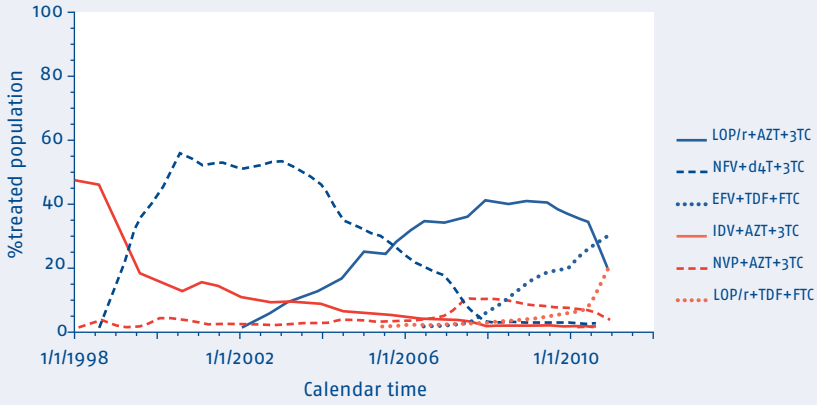
Patient monitoring

Current guidelines recommend monitoring HIV-infected patients two or three times a year, depending on CD4 count and treatment status [4]. In most recent years, these guidelines have been generally well followed. Between 2002 and 2010, on average, 1.9 immunology measurements were performed annually per patient, with an increase from 1.6 in 2002 to 2.5 in 2010. During the same period, viral load was monitored 1.8 times per year, and the frequency increased from 1.5 per year in 2002 to 2.4 in 2010. Finally, follow-up visits for each patient averaged 2.3 per year, with 1.9 visits annually between 2002 and 2006 and 3.3 in 2010.

Combination treatment

In total, 535 (72%) patients started cART. Of the 333 who did so between 2004 and 2011, 62% started with a combination of combivir and ritonavir-boosted lopinavir and 22% with a combination of tenofovir/emtricitabine and efavirenz. Over time, there have been clear shifts in the treatment regimens (*Figure 7.3*). Since 2008, a combination of tenofovir/emtricitabine with either efavirenz or lopinavir has become more popular. Of the 363 patients who had started cART and were still in follow-up as of June 2011, 65% were receiving tenofovir/emtricitabine, 42% ritonavir-boosted lopinavir, and 33% efavirenz.

Figure 7.3: Percentage of patients treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. The proportion of patients taking IDV+AZT+3TC decreased from 47% 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; 36% of the patients on cART were on this regimen at the beginning of 2010. The use of EFV+TDF+FTC and LOP/r+TDF+FTC increased from 2008 onwards, and at the beginning of 2011, 29% of the patients were receiving EFV+TDF+FTC, 18% LOP/r+TDF+FTC, and 18% LOP/r+AZT+3TC.

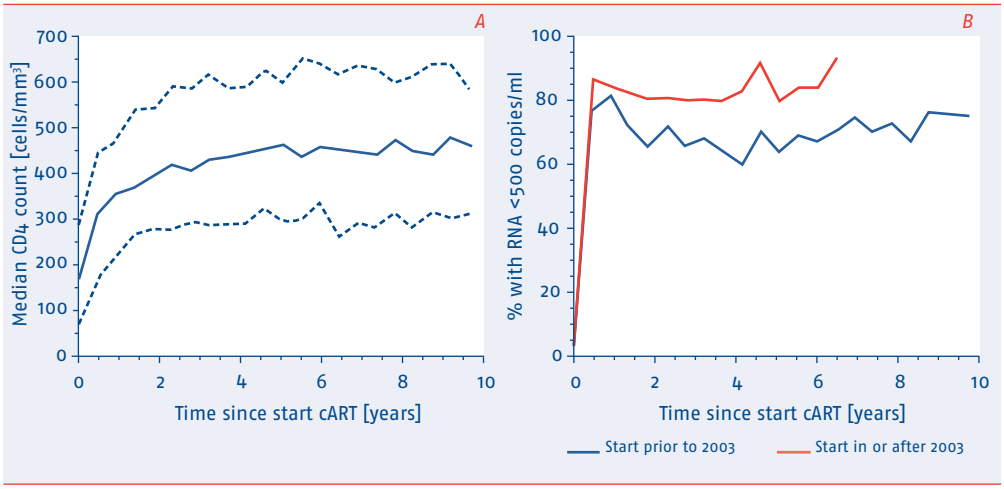


***Legend:** LOP/r=ritonavir-boosted lopinavir; AZT=zidovudine; 3TC=lamivudine; NFV=nelfinavir; d4T=stavudine; EFV=efavirenz; TDF=tenofovir; FTC=emtricitabine; NVP=nevirapine; IDV=indinavir.*

Treatment outcome

For 48% of the 497 antiretroviral therapy-naive patients who started cART, CD4-cell counts increased by at least 150 cells/mm^3 during the first six months of treatment; after two years, this proportion had increased to 80%. At the same time, 79% of the patients reached a viral load level below 500 copies/ml within six months after starting treatment. In the patients who were still in follow-up as of June 2011, CD4 counts appeared to reach a plateau between 450 and 500 cells/mm^3 after five years of cART (*Figure 7.4A*). During the same period, the proportion of patients with a viral load below 500 copies/ml decreased from 84% after 48 weeks to approximately 75% after five years of treatment. However, amongst those who started cART in 2003 or later, i.e., when more efficacious treatment combinations came into use, the proportion of patients who were able to retain viral suppression did not decrease (*Figure 7.4B*).

Figure 7.4: CD4-cell counts and viral load in 363 treated patients who were still in follow-up as of June 2011. (A) Median CD4-cell counts (solid line; dotted line: interquartile range [IQR]) increased from 163 (IQR, 58-278) cells/mm³ at the start of combination antiretroviral therapy (cART) to 309 (161-442) cells/mm³ after 24 weeks and reached a plateau between 450 and 500 cells/mm³ after five years. (B) The proportion of patients with HIV RNA <500 copies/ml was approximately 85% after 48 weeks, and it remained at a high level amongst those who started cART in 2003 or later, but gradually declined to levels between 60% and 75% after five years for those who started prior to 2003.



Less virologic failure

As viral suppression rates appear to have increased, one may presume that, conversely, rates of virologic failure have decreased. Indeed, by the definition of virologic failure in Chapter 4 (HIV RNA above 500 copies/ml despite at least four months of continuous treatment), the proportion of patients with virologic failure steadily declined from approximately 40% between 2000 and 2004 to 20% in 2010. Nevertheless, these failure rates are still higher than in the Netherlands.

Mortality and survival

Of the group of 658 patients who were still alive as of 1 January 2005 or were diagnosed after that date, 21 patients died within six months, whilst 77 patients had died by June 2011. Overall, the survival probability after six years of follow-up was 85%. Altogether, 286 patients started cART in or after 2005, and out of this group, 37 died, 17 of whom died within six months of starting cART, corresponding with a six-year survival probability of 82%.

Drug resistance

With so many patients experiencing virologic failure, it may be expected that some will have developed resistance to one or more antiretroviral drugs. In total, for 142 patients, one or more genotypic sequences of the protease and reverse transcriptase (RT) gene were examined after the start of treatment for resistance to protease inhibitors and nucleoside RT inhibitors. Altogether, 78 patients, or 56% of those sequenced, had high-level resistance to at least one antiretroviral drug, according to an interpretation algorithm developed by Stanford University [172, 173].

Of the 167 genotypic sequences obtained from the 142 patients when they were supposedly on treatment, 62% had high-level resistance to at least one antiretroviral drug, but 33% were fully susceptible to all drugs. This probably means that about one-third of patients who experienced treatment failure did so because they did not take their prescribed medication. Resistance to lamivudine and emtricitabine was observed in 43% of the sequences, and 8% of the sequences indicated resistance to at least one other nucleoside RT inhibitor. Altogether, high-level resistance to protease inhibitors was found in 32% of the sequences and to non-nucleoside RT inhibitors in 23%. However, there was a decreasing trend in the proportion of sequences resistant to protease inhibitors and a corresponding upward trend in resistance to non-nucleoside RT inhibitors, which presumably coincides with the changes in treatment regimens in recent years (*Figure 7.3*).

Infection with resistant virus

Infection with a resistant virus, and consequently the preclusion of certain drugs from the antiretroviral arsenal, does not seem to be a major problem at the moment. Infection with a resistant virus could be investigated in 67 patients who had a genotypic sequence within one year of diagnosis but before the start of treatment. Resistance-associated mutations were detected in only three patients. However, these mutations gave rise to high-level drug resistance in only one patient. Furthermore, in this particular patient, a pretreatment sample in which no resistance was found may have been confused with a sample with resistance mutations obtained after the start of treatment.

Conclusion

In recent years, the quality of care and treatment offered to HIV-infected patients in Curaçao has improved considerably and can now withstand a comparison with resource-rich settings. However, adherence to treatment and retention in care can be improved to reduce the number of patients failing on treatment or being lost to follow-up. Also, HIV infections need to be detected at an earlier stage, such that patients can start antiretroviral treatment in accordance with current recommendations. Currently, studies are ongoing to identify which groups have predominantly late testing and delayed entry into care.

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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Publications 2011

Publications

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Prenatale screening op hiv, hepatitis B en syphilis in Nederland effectief.
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Oral presentations

A Randomized Controlled Trial Comparing No Treatment with 24 or 60 Weeks of Temporary Antiretroviral Treatment during Primary HIV Infection (PHI).
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Combined antiretroviral therapy and the incidence of tuberculosis among HIV-positive individuals in high-income countries.
Del Amo J on behalf of the HIV-CAUSAL Collaboration. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Unified Methods for the Causal Analysis of HIV randomized trails and observational cohort studies.
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The effect of efavirenz versus nevirapine-containing regimens on all-cause mortality.
Cain LE for the HIV-CAUSAL Collaboration. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Sex differences in mortality rates among treated patients: the Antiretroviral Therapy Cohort Collaboration (ART-CC).
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Heterogeneity among ART-CC Cohorts before and after adjustment for patient and cohort level characteristics: AIDS Events, Mortality, and Effect of CD4.
Sterne J, May M for ART-CC. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Cumulative incidence of and risk factors for switching or interrupting first ART regimen and Death.
Ingle S, Abgrall S, May M, Sterne J for ART-CC. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Longer time on virological successful cART is independently associated with decreasing CD4-cell count in patients with <500 CD4-cells/mm³.
Gras L, Smit C, van Lelyveld S, Kesselring A, van Sighem A, de Wolf F; for the ATHENA national observational cohort. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Limited contribution to new infections from HIV-infected men who have sex with men on suppressive combination treatment.
van Sighem A, Bezemer D, Reiss P, Smit C, Gras L, de Wolf F, Fraser C. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Risk of progression to AIDS or death in relation to CD4-cell levels in HIV-infected patients with sustained viral response to cART.
Bucher HC for the Opportunistic Infections working group of COHERE in EuroCoord. *19th International Aids Conference, Rome, Italy, 17-20 July 2011*

Modelling response to antiretroviral therapy without a genotype as a clinical tool for resource-limited settings (Oral & Poster presentation).
Larder BA, Revell AD, Wang D, Hamers R, Tempelman H, Barth R, Wensing AMJ, Morrow C, Wood R, de Wolf F, Kaiser R, Pozniak A, Lane HC, Montaner JM. *International Workshop on HIV & Hepatitis Drug Resistance and Curative Strategies; Los Cabos, Mexico - 7th-10th June 2011*

Posters presentations

Faster CD4-cell Count Decline before the Start of Antiretroviral Therapy in Patients with HIV-1 Seroconversion in More Recent Calendar Years.
Gras L, Geskus R, van Sighem A, Bezemer D, Jurriaans S, Berkhout B, Fraser C, Prins J, Bakker M, de Wolf F. *18th Conference on Retroviruses and Opportunistic Infections, Boston MA, USA, 27 February- 2 March 2011*

Decreasing Community Infectiousness Is a Marker for Decreases in New HIV Infections among Dutch Homosexual Men.
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HCV treatment and CD4-cell count decline in HIV/HCV co-infected patients: European Cohort Collaboration.
Smit C, d'Arminio Montforte A, Puotti M, de Wolf F, Dabis F, on behalf of the HCV working group of Cohere. *18th Conference on Retroviruses and Opportunistic Infections, Boston MA, USA, 27 February- 2 March 2011*

Differences in mortality rates among treated patients according to geographical origin and ethnicity/race: the Antiretroviral Therapy Cohort Collaboration (ART-CC).
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Initiation of combined antiretroviral therapy for HIV infection and the risk of non-AIDS diseases.
Zhang S, van Sighem A, Gras L, Prins J, Kauffmann R, Richter C, Reiss P, de Wolf F. *18th Conference on Retroviruses and Opportunistic Infections, Boston MA, USA, 27 February- 2 March 2011*

Rising HIV-1 Viral Load Set-point at a Population Level Coincides with a Fading Impact of Host Genetic Factors on HIV-1 Control.
van Manen D, Gras L, Boeser-Nunnink B, van Sighem A, Maurer I, Mangas-Ruiz M, Harskamp A, de Wolf F, van 't Wout A, Schuitemaker H, and Dutch HIV Monitoring Fndn HIV-1 Host Genetics Study. *18th Conference on Retroviruses and Opportunistic Infections, Boston MA, USA, 27 February- 2 March 2011*

Dyslipidemia in HIV-infected children and adolescents treated with cART between 1997 and 2009: a longitudinal study.
Smit C, Hartwig NG, Geelen SPM, Schölvinck EH, vd Flier M, Scherpbier HJ, on behalf of the Dutch Paediatric HIV Treatment Centers (PHON). *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Are the reasons for switching or interrupting ART in the first 6 months different from those for late switches?
Abgrall S, Ingle S, May M, Sterne J on behalf of ART-CC. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

The use of data from multiple cohorts to develop an on-line HIV treatment selection tool.
Revell AD, Wang DW, Coe D, Mican, JM, Agan BK, Harris M, Torti C, Izzo I, Emery S, Boyd M, Ene L, De Wolf F, Nelson M, Metcalf JA, Montaner JSS, Lane HC, Larder BA. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Improving data quality in HIV cohort collaborations – exemplified by de D:A:D study.
Brandt RS, Rickenbach M, Hillebregt MMJ, Fontas E, Geffard S, McManus H, Fanti I, Delforge M, Ledergerber B an Kjaer J on behalf of de D:A:D study Group. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

How to identify patients enrolled in multiple cohorts – exemplified by the D:A:D study.
Kjaer J, Hillebregt MMJ, Brandt RS, Fontas E, Balestre E, McManus H, Fanti I, Delforge M, Rickenbach M on behalf of the D:A:D Study Group. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Cancers or not? Collection and preliminary assessment of non-AIDS-defining malignancies (NADMs) in de D:A:D Study
Worm S, Tverland J, Bruyand M, Reiss P, Fontas E, El-Sadr W, Kirk O, Weber R, d'Arminio Monforte, De Wit S, Ryom L, Friis-Moller N, Law M, Lundgren J and Sabin C. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

Calendar time trends in the incidence and prevalence of HIV-infected patients with triple-class virologic failure in Europe.
Nakagawa F, on behalf of the PLATO II Project Team of Cohere. *15th International Workshop on HIV Observational Databases, Prague, Czech Republic, 24-26 March 2011*

30 years of HIV among men who have sex with men in Switzerland.
van Sighem A, Vidondo B, Gebhardt M, Glass TR, Derendinger S, Bezemer D, Bucher H, Vernazza P, de Wolf F, Jeannin A, Staub R, Fraser C. *19th International Aids Conference, Rome, Italy, 17-20 July 2011*

Predicting response to antiretroviral therapy without a genotype: a treatment tool for resource-limited settings.
Revell AD, Wang D, Ene L, Tempelman H, Barth R, Wensing AM, Gazzard B, DeWolf F, Lane HC, Montaner JSS, Larder BA. *19th International Aids Conference, Rome, Italy, 17-20 July 2011*