# Monitoring Report 2013

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

## 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


### Colophon

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HIV Monitoring

# Monitoring Report 2013

## Human Immunodeficiency Virus (HIV) Infection in the Netherlands

## HIV Treatment Centres

The monitoring of HIV-infected adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 26 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 2013 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. Slotervaartziekenhuis — Amsterdam
7. Stichting Medisch Centrum Jan van Goyen — Amsterdam
8. VU Medisch Centrum — Amsterdam
9. 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. MC Zuiderzee — Lelystad
19. Academisch Ziekenhuis Maastricht — Maastricht
20. Universitair Medisch Centrum Sint Radboud — Nijmegen
21. Erasmus Medisch Centrum — Rotterdam
22. Maasstad Ziekenhuis — Rotterdam
23. St Elisabeth Ziekenhuis — Tilburg
24. Universitair Medisch Centrum Utrecht — Utrecht
25. Admiraal De Ruyter Ziekenhuis — Vlissingen
26. Isala — Zwolle

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

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


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# Introduction

The Monitoring Report 2013 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 13th in the series published by Stichting HIV Monitoring (SHM) since its founding in 2001. It provides a comprehensive review of trends over time in the HIV epidemic in the Netherlands and the effect of treatment.

Since 2002, SHM has officially been 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 anonymised data from HIV patients in care in the 26 officially acknowledged HIV treatment centres throughout the country, our work contributes significantly to the knowledge of HIV. Also, we make anonymised information available at both the centre and individual patient levels through a secure web-based environment, thereby enabling treating physicians to assess and improve patient care within their centres. Treating physicians, as well as national and international researchers, can also access data from all centres for scientific research purposes, once research proposals have been approved through appropriate procedures. Research conducted by SHM in collaboration with national and 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, the effects of combination antiretroviral therapy (cART), the development of resistance to antiretroviral drugs, and morbidity and mortality in the HIV-infected population. This section also contains information on specific patient populations, including those with viral hepatitis co-infections and HIV-1 infected children and pregnant women.

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

This is my first year as Director of SHM, and I am grateful to be able to build on the sound groundwork laid by my predecessor, Frank de Wolf. Given my clinical background, which includes practicing as an HIV treating physician, I have introduced a slightly new approach in compiling each chapter of this year's report. For the first time, a small group of HIV treating physicians and experts in public health with an in-depth knowledge on relevant chapter topics have been asked to help shape content and act as reviewers, with the intent of improving the report's clinical and public-health relevance. I thank them for their time and valuable input, and I hope to continue this fruitful collaboration in the years ahead.

Finally, 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. Without their ongoing motivation, tireless efforts and contributions, our work would be impossible. I also extend my gratitude to the patients with HIV who generously agree to provide data to SHM. It is only through this partnership between both professionals and patients that we can further improve our insight into the many facets of HIV and HIV treatment, and thereby, continue to not only improve care for people with HIV living in the Netherlands, but also provide guidance for prevention.

Professor Peter Reiss, MD

**Director, Stichting HIV Monitoring**

# Summary & recommendations

Peter Reiss

## The HIV epidemic in the Netherlands *(Chapter 1)*

As of June 2013, a total of 17,006 persons living with HIV in the Netherlands (16,813 adults, and 193 children and adolescents) were in care in one of the 26 designated HIV treatment centres. Of these 17,006, 87% (14,817) had started combination antiretroviral therapy (cART), and of these 14,817, 90% (13,369) had suppressed viraemia to below the level of quantification at the time of their last available HIV-RNA measurement. These results are impressive when compared to figures from other parts of the world. However, it is also important to realise that of the total 25,000 individuals that the Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates were living with HIV in the Netherlands in 2012, 27% are likely to be unaware of their infection; this means that about 6,750 infected persons have not yet been diagnosed or linked to care and, importantly, still contribute to fuelling the epidemic.

In 2012, an estimated 1,100 patients entered care, which is comparable to the annual number reported in the last 3 years. In 2012, the majority (67%) of newly diagnosed infections were in men who have sex with men (MSM), 27% were acquired through heterosexual contact, 1% through injecting drug use (IDU), and 5% through other or unknown modes of transmission. Although the rate of newly diagnosed cases stabilised in the key affected population of MSM, and even steadily declined amongst MSM 35 to 44 years of age, it continued to increase in MSM both 25 years and younger and 55 years and older, as well as in heterosexuals 45 years and older.

The rates of testing for HIV appear to be increasing in certain settings, and the proportion of patients who are identified and start cART earlier in their infection (including during primary HIV infection) has increased, particularly amongst MSM, but less pronounced in women and heterosexual men. However, 43% of newly diagnosed patients in 2012 presented late for care, that is, with AIDS or a CD4 count less than 350 cells/mm$^3$, and 26% presented with advanced HIV disease, that is, with a CD4 count less than 200 cells/mm$^3$ or AIDS. Generally, the likelihood of presenting late for care or with advanced HIV disease was greater for men with heterosexually acquired infection, for those originating from South and South-East Asia and sub-Saharan Africa, and for patients 45 years or older. This is also reflected in the fact that the median CD4 count at initiation of cART in 2012 was not higher than 320 cells/mm$^3$, although, fortunately, this count continues to rise gradually each year.

*Improved transdisciplinary strategies that target all factors sustaining the epidemic are clearly needed to achieve a significant decline in the rate of new infection. The aim of these strategies should be to simultaneously reduce the likelihood of HIV infection in key populations at risk and identify infected individuals early, whilst linking all infected persons to care.*

## Combination antiretroviral therapy in adults and quality of care *(Chapters 2, 3 and 7)*

Guidelines for use of first-line cART are adhered to extremely well in the Netherlands. Most patients who first initiated cART in 2012 did so with a once-daily regimen, with tenofovir/emtricitabine as the backbone; this was combined in approximately two thirds of patients with a non-nucleoside reverse transcriptase inhibitor (NNRTI) and in one third of patients with a ritonavir-boosted protease inhibitor (PI). Use of the integrase inhibitor raltegravir, which requires twice-daily dosing, as part of an initial regimen was rare.

Virological response to first-line cART has gradually improved during the era of cART and between 2010 and 2012, 85% of patients who first initiated cART achieved viral suppression to below the level of HIV-RNA quantification within 9 months. Patients originating from areas other than the Netherlands or western Europe or North America may have been less likely to achieve such a favourable early response, particularly when initiating cART at CD4 counts over 500/mm$^3$. Of the patients who first initiated cART from 1999 onwards and were continuously on treatment and still in follow-up at 12 years, 94% had suppressed viraemia to less than 50 copies/ml.

Overall, 8% of the same patients who first initiated cART from 1999 onwards have experienced virological failure (defined as time to the first of two consecutive plasma HIV RNA levels >200 copies/ml after 24 weeks on therapy) to first-line cART. Importantly, the annual proportion of patients experiencing virological failure has declined over time to less than 5%, but, as expected, remains associated with a substantial risk of emergence of drug resistance.

*Patients with heterosexually acquired infection originating from sub-Saharan Africa and the Caribbean or South America, and patients younger than 30 years were identified as being at increased risk of virological failure on both first- and second-line regimens. This suggests that measures aimed at supporting adherence specifically in these groups may be warranted.*

International collaborative cohort analyses of the prevalence and incidence of patients experiencing triple-class virological failure (defined as failure of at least two NRTIs, one NNRTI and one ritonavir-boosted PI), to which SHM contributes data, have demonstrated an important improvement in the prognosis of such patients over time, both in terms of their likelihood of achieving resuppression of viraemia and a reduced progression to AIDS and death. These trends are likely mainly driven by the availability of newer drugs with better tolerability, ease of use and limited cross-resistance, indicating the continued public health benefit of the introduction of new drugs.

The proportion of patients achieving a greater immunologic recovery on cART continues to improve year after year. Nonetheless, a substantial number of patients fail to achieve restoration of CD4 cells to levels above which the risk of both traditionally HIV-associated and non-AIDS-related morbidity may no longer be accentuated as a result of the infection.

This particularly holds true for those who commence treatment at a more advanced level of immunodeficiency. In 2012, 15% of patients in care had a last available CD4 measurement less than 350 cells/mm$^3$. Patients who start cART at a CD4 count of more than 350 cells/mm$^3$ and have sustained fully suppressed viraemia after 8 years, including patients more than 50 years old at the time of treatment initiation, are likely to achieve long-term CD4 counts similar to those in the general population. Similar trends were observed in the patients' ability to achieve a CD4/CD8 ratio greater than 1, which may be a marker of reduced residual immune activation whilst on suppressive cART. Future analyses (potentially in collaboration with other cohorts) are needed to address whether CD4/CD8 ratios independent of CD4 counts are associated with an increased risk of morbidity, including from non-AIDS events.

Although tolerability of cART has continued to improve with time and larger proportions of patients remain on their initial regimen for a longer time, drug intolerance or toxicity is still the most common reason for a change of initial treatment. MSM, women and patients who were older had a higher likelihood of changing their initial regimen because of toxicity. In MSM the risk was higher, especially when treatment was started at CD4 counts above 500/mm$^3$.

*As larger numbers of clinically asymptomatic, newly identified patients with HIV are expected to start treatment earlier, continued development of drugs that are better tolerated and improvements in individualized patient management remain necessary to further improve the durability of initial treatment.*

The monitoring by SHM of patients with HIV in care importantly facilitates the assessment of the quality of care provided by the treatment centres. It also supports the formal certification process for HIV treatment centres in the Netherlands, which is currently being prepared by Harmonisatie Kwaliteitsbeoordeling in de Zorgsector (HKZ, Harmonisation of Quality in the Healthcare Sector) in collaboration with the Dutch Association of HIV-treating Physicians (NVHB). Data from SHM can be used by treatment centres in collating and making available the key information required to support certification, which is planned to become operational in 2014. Simultaneously, SHM participates in a research project (the Q-HIV study), with additional support from the Aids Fonds, that aims to assess which patient-related, care provider-related and hospital-related determinants are importantly associated with quality of care. An early analysis from this study showed that the "cascade of care" appears to be remarkably similar in Dutch treatment centres caring for greater or fewer than 500 patients in terms of retaining patients in care, treating them and achieving undetectable viraemia.

## Morbidity and mortality *(Chapters 1, 2 and 4)*

Mortality rates remain low in HIV-infected patients in care in the Netherlands. There has been a sustained decline in death from AIDS, with a shift towards death from other causes.

Non-AIDS co-morbidities, including non-AIDS defining malignancies (NADM), cardiovascular disease (CVD) and chronic liver disease, comprise a sizable fraction of those other causes. Of note, however, the proportion of patients dying of AIDS (nearly 25%) remained substantial between 2007 and 2012. Once more, this seems to be largely driven by late presentation and entry into care, and it stresses the importance of identifying and linking individuals to care earlier in the course of the infection. Of note, a recent analysis by the Collaboration of Observational HIV Epidemiological Research Europe (COHERE), to which SHM is an important contributor, showed that the incidence of AIDS-defining illnesses was higher in individuals with a current CD4 count of 500 to 749 cells/mm$^3$ compared to those with a CD4 count of 750 to 999 cells/mm$^3$; in addition, the incidence did not decrease further at higher CD4 counts, even in patients suppressed on cART. These findings suggest that immune reconstitution may not be complete until the CD4 count increases to more than 750 cells/mm$^3$.

Similarly high CD4 counts that are achieved on cART, such as by commencing treatment at higher levels than the current average in the Netherlands, will contribute to preventing the most frequently observed non-AIDS co-morbidities, but the extent of that contribution is yet to be determined. Our analyses of the most recent SHM dataset generally show that prior AIDS and/or low nadir or current CD4 count are independently associated with an increased risk of cardiovascular disease, diabetes mellitus, chronic kidney disease and non-AIDS malignancies.

As expected, older age was also found to be an important risk factor for these co-morbidities, which are traditionally associated with aging. In this context, it is important to note that the average age at which individuals with newly diagnosed HIV enter care in the Netherlands has gradually increased over time; 20% were more than 50 years of age in 2012. At the same time, the age distribution of the overall patient population with HIV in care in the Netherlands has also changed, with 37% currently older than 50 years. Of particular concern is the increasing proportion of patients with multiple co-morbidities. Nearly 20% of those now in care who are more than 65 years of age have two or more of the following, reliably documented co-morbidities: hypertension, myocardial infarction, stroke, diabetes mellitus, chronic kidney disease, and non-AIDS defining malignancies. Data from the AGEhIV Cohort Study, in which SHM collaborates with the Academic Medical Center, the Amsterdam Institute for Global Health and Development and the Public Health Service (GGD) in Amsterdam, show that both the presence of multiple co-morbidities and individual cases of hypertension, CVD, peripheral artery disease and chronic kidney disease are significantly more prevalent amongst those with HIV than in an uninfected control population of a similar age distribution. Besides older age, smoking and a positive family history (for hypertension, myocardial infarction, diabetes mellitus, or hypercholesterolaemia), duration of time spent with a CD4 count less than 200 cells/mm$^3$, increasing levels of markers of inflammation and innate immune activation, central obesity and longer prior exposure to ritonavir at total doses of ≥800 mg were independently associated with the prevalence of co-morbidity.

Interestingly, an algorithm by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study group that includes SHM indicates stability in the percentage of patients in care at Dutch treatment centres with a high or very high risk of coronary heart disease in the next 5 years, despite the increase in proportion of older individuals on cART. This may well suggest that cardiovascular-risk management has improved over time, as also shown by the initiation of treatment with statins at less elevated lipid levels and the reduced use of the cART regimens associated with increased cardiovascular risk.

Whilst the overall incidence of non-AIDS-defining malignancies in the population with HIV in care has remained stable over time since the introduction of cART, the absolute number and proportion of deaths due to these malignancies has increased. Future analyses will focus on individual malignancies, of which those addressing anal cancer will be particularly pertinent and informative. In addition, collaborative analyses conducted on much larger datasets as part of the D:A:D study will provide the statistical power to address the possible contribution of prolonged exposure to particular antiretrovirals.

*Awareness of the role of modifiable, often lifestyle-related risk factors, like smoking, and their management by both physicians and HIV-infected patients, particularly those who are older or otherwise at high a priori risk of certain co-morbidities, offers important hope of ensuring a lower co-morbidity burden and healthy aging. This applies not only to conditions such as cardiovascular disease and diabetes mellitus, but also to measures to prevent cancer, chronic kidney disease and bone loss.*

## Hepatitis B and C co-infections *(Chapter 5)*

Screening for hepatitis B (HBV) and C (HCV) co-infection has, with time, increasingly become part of the standard-of-care in the Netherlands. As a result, the presence or absence of HBV or HCV infection is now documented for nearly all HIV-infected patients in care in the Netherlands. Approximately 12% of patients had evidence of ever having been exposed to HCV, 5% were documented as having chronic infection and 1% had acute infection. Eight percent of patients were shown to have chronic HBV infection.

HCV genotype 1 infection was the most common genotype in patients with either chronic or acute HCV infection, and most patients with HCV infection were male and from the Netherlands or other European countries. Acute HCV infection is seen mainly in MSM, with the incidence steadily increasing over time from 0.47 cases per 1,000 person-years in 2003 to 4.5 cases per 1,000 person-years in 2011, indicating the need for continued preventive efforts in these men.

*An estimated 28% of HIV-infected patients overall and 22% of MSM either had not been exposed to HBV or had not been successfully vaccinated and may remain at risk of acquiring HBV. Thus, it is important that efforts are undertaken to increase successful vaccination rates amongst this subgroup of patients.*

Co-infected patients with a longer duration of infection were at increasing risk of progressing to chronic liver disease, including hepatocellular carcinoma (HCC). Ten years after a known diagnosis of viral hepatitis, HCC had developed in 1% of patients with chronic HCV and 1% of patients with chronic HBV. Of note, the likelihood of dying from chronic liver disease from 2000 onwards had declined in patients with chronic HBV, likely as the result of increasing use of tenofovir as part of combination therapy for HIV.

The uptake of treatment for HCV has markedly increased in recent years, with 62% of patients having received treatment by 2012. However, currently available treatment still remains associated with considerable toxicity and suboptimal efficacy. Amongst patients treated with a combination of pegylated interferon alfa (peg-IFN alfa) and ribavirin (RBV), only 39% overall could be considered cured. Thus, a substantial number of patients in care co-infected with HIV and HCV either remain untreated or have not yet been successfully treated for HCV. The direct-acting antivirals boceprevir or telaprevir became available in the Netherlands early in 2012. When added to peg-IFN alfa and RBV for HCV genotype 1 infection, they have shown improved response rates, but their use remains limited because of high cost and association with clinically significant toxicities and drug-drug interactions with cART.

*The availability of combinations of direct-acting pan-genotypic antivirals against HCV that are much better tolerated and more efficacious is eagerly awaited. It is hoped that these combinations, which will potentially allow the use of interferon-free regimens, will contribute to further reducing the burden of severe chronic liver disease, hepatocellular carcinoma and liver-related mortality amongst persons living with HIV.*

## HIV in pregnant women and in children *(Chapter 6)*

Universal screening for HIV in pregnant women and the increasingly effective use of cART during pregnancy, fortunately, has made perinatal transmission of HIV extremely rare in the Netherlands. *Nonetheless, the observation that approximately 20 to 30% of HIV-infected pregnant women do not have fully suppressed viraemia around the time of delivery indicates the need for continued vigilance.*

Treatment outcomes for children living with HIV in the Netherlands and receiving care in one of the four designated paediatric treatment centres are generally favourable. These outcomes include long-term immunologic responses to cART, particularly in children who have started treatment soon after birth. *More and more of these children, however, are transitioning into adult care, and as many as a third do not have fully suppressed viraemia at the time of transition. Optimization of long-term care for this particularly vulnerable and difficult to manage group of young individuals is needed.*

## The Amsterdam Cohort Studies *(Chapter 8)*

The Amsterdam Cohort Studies on HIV infection and AIDS (ACS) are unique prospective longitudinal cohort studies started in 1984-1985 and focused on MSM and IDU with HIV or at risk for HIV infection. As of 31 December 2012, more than 2,500 MSM and more than 1,600 IDU had been enrolled. The ACS continues to provide important insights into both viral and host factors that play a role in the transmission and pathogenesis of HIV and other (sexually transmitted) infections, including HCV, and that assist in rational design of public health interventions. Importantly, the ACS continues to provide reliable information on HIV and HCV incidence over time in the key affected populations. Amongst MSM, incident HCV infections are being observed only amongst men who are infected with HIV; following a rise in infections after 1999, they have levelled off to approximately 10 cases per 1,000 person-years. Data on risk behaviour collected within the framework of the ACS demonstrate that HIV-uninfected participants in the cohort increasingly report unprotected anal intercourse, particularly with casual partners. Likewise, MSM who were recently prescribed post-exposure prophylaxis against HIV had a higher HIV incidence compared with MSM participating in the ACS, indicating ongoing sexual risk behaviour.

Other highlights of recent research include the identification of a gene polymorphism that affects the ability of HIV-1 to replicate in macrophages to be associated with the risk of HIV-associated dementia, the demonstration that cross-reactive neutralizing antibodies may appear much faster after HIV-1 infection than previously thought, and the finding that viruses with a particular envelope N-glycosylation site may be preferentially transmitted.

## HIV on Curacao *(Chapter 9)*

SHM continues to provide assistance to Stichting Rode Kruis Bloedbank with data collection and monitoring of patients with HIV in care at the St Elisabeth Hospital in Willemstad on the Caribbean island of Curacao. A temporary discontinuation in data collection followed the retirement of the previous data collector on the island. However, with the help of SHM, a new data collector has recently been trained, and this is expected to result in a proper update of available data. Although the quality of care for HIV-infected patients in Curacao has improved since the start of the new millennium, the number of patients presenting late for care and not being retained in care remains considerable.

# Monitoring programme report

## 1. The HIV epidemic in the Netherlands

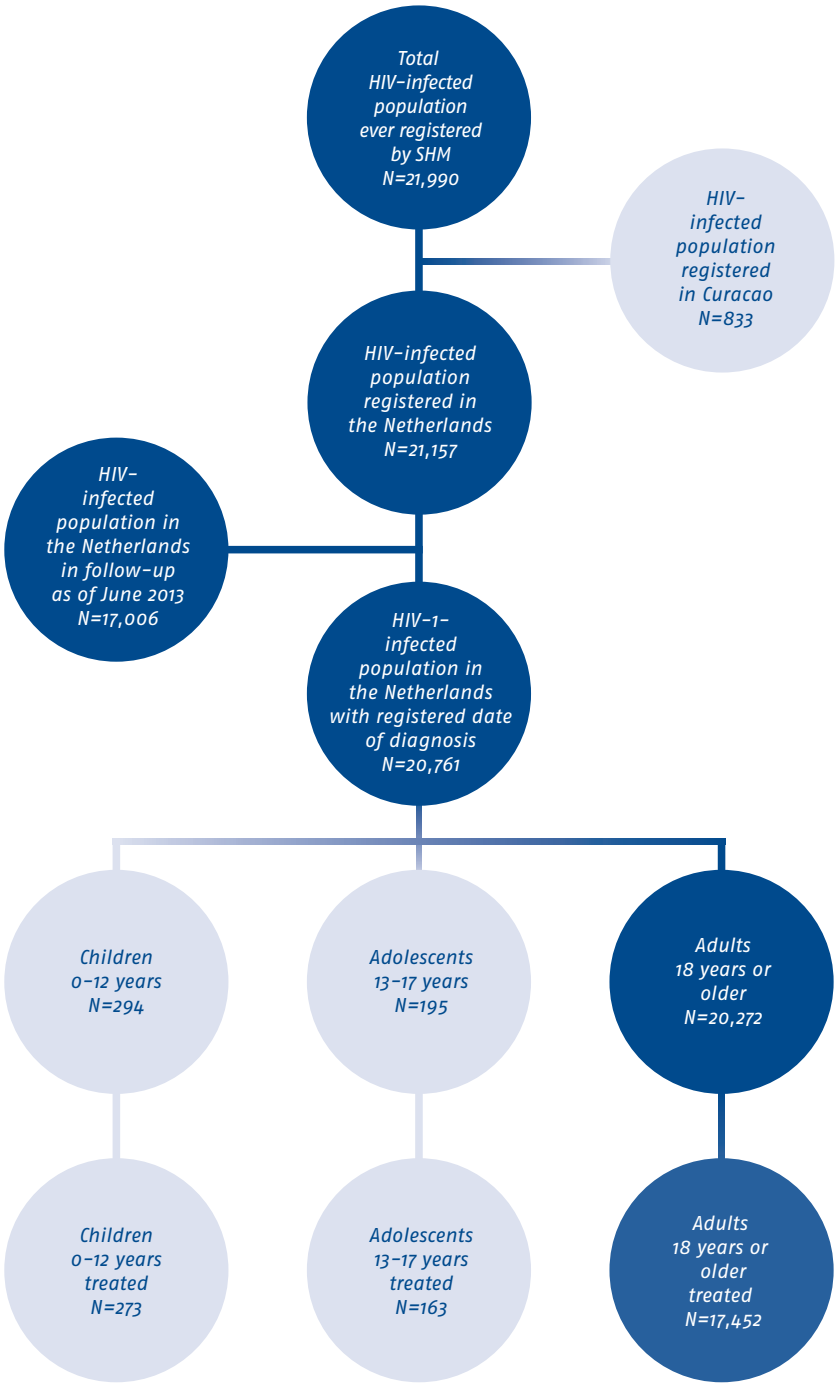
Ard van Sighem, Eline Op de Coul

### Introduction

For more than 10 years, Stichting HIV Monitoring (SHM) has collected demographic and clinical information from almost all patients infected with human immunodeficiency virus (HIV) who have been in care in one of the 26 HIV treatment centres in the Netherlands. One of SHM's main achievements is the development of a detailed knowledge of the characteristics of the HIV-infected population and its evolution over time. This chapter will focus mainly on the adult HIV-infected population, whilst children and adolescents are described in more detail in *Chapter 6*.

As of June 2013, 21,990 HIV-infected patients were ever registered by SHM; of those, 21,157 were followed in one of the HIV treatment centres in the Netherlands (*Figure 1.1*), with a total follow-up time since diagnosis of 183,583 person-years. The remaining 833 patients were registered in the St. Elisabeth Hospital in Willemstad, Curacao, and are discussed in more detail in *Chapter 9*. Of the 21,157 patients, the majority were infected with HIV-1 (20,829; 98%). A small group of patients, 92 in total, were infected with HIV-2, whilst 69 patients had antibodies against both HIV-1 and HIV-2. Serologic results were not yet available in the SHM database for 167 patients. Although the majority of the patients newly registered since June 2012 were diagnosed in 2012 or 2013, 18% of those newly registered were diagnosed in or prior to 2011.

*Figure 1.1: Overview of the HIV-infected population registered by Stichting HIV Monitoring (SHM) as of June 2013.*



## Population – in care

### Patients in clinical care

In total, 17,006 (80%) of the 21,157 registered patients, including 16,813 adults and 193 minors (less than 18 years of age), were still under clinical observation (*Figure 1.1; Table 1.1; Web Appendix 1.1*). Of the 4,151 patients who were no longer in clinical care, 2,104 (51%) had died, and 836 (20%) had moved abroad. Patients were considered to be in clinical care if data were available in 2012 or 2013 and if the patients were still alive. This definition was first adopted in SHM's Monitoring Report 2012 and better reflects present-day clinical practice, in which some patients who respond well to treatment and have no complications on treatment are seen only once a year by their treating physician [1].

*Table 1.1: Characteristics of the 17,006 HIV-infected patients in clinical care as of June 2013. An extended version of this table is available on the SHM website (Web Appendix Table 1.1).*

| | Men (N= 13,610, 80%) | | Women (N=3,396, 20%) | | Total (N=17,006) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Transmission | | | | | | |
| MSM | 10,161 | 75 | – | – | 10,161 | 60 |
| Heterosexual | 2,208 | 16 | 2,953 | 87 | 5,161 | 30 |
| IDU | 260 | 2 | 95 | 3 | 355 | 2 |
| Blood (products) | 132 | 1 | 83 | 2 | 215 | 1 |
| Other/unknown | 849 | 6 | 265 | 8 | 1,114 | 7 |
| Current age (years) | | | | | | |
| 0–12 | 65 | 0 | 60 | 2 | 125 | 1 |
| 13–17 | 32 | 0 | 37 | 1 | 69 | 0 |
| 18–24 | 276 | 2 | 93 | 3 | 369 | 2 |
| 25–34 | 1,661 | 12 | 714 | 21 | 2,375 | 14 |
| 35–44 | 3,489 | 26 | 1,164 | 34 | 4,653 | 27 |
| 45–54 | 4,885 | 36 | 888 | 26 | 5,773 | 34 |
| 55–64 | 2,354 | 17 | 321 | 9 | 2,675 | 16 |
| ≥65 | 848 | 6 | 119 | 4 | 967 | 6 |
| Region of origin | | | | | | |
| The Netherlands | 9,108 | 67 | 983 | 29 | 10,091 | 59 |
| Sub-Saharan Africa | 1,021 | 8 | 1,449 | 43 | 2,470 | 15 |
| Western Europe | 816 | 6 | 129 | 4 | 945 | 6 |
| Latin America | 900 | 7 | 301 | 9 | 1,201 | 7 |
| Caribbean | 518 | 4 | 173 | 5 | 691 | 4 |
| Other | 1,199 | 9 | 357 | 11 | 1,556 | 9 |
| Unknown | 48 | 0 | 4 | 0 | 52 | 0 |

| | Men (N= 13,610, 80%) | | Women (N=3,396, 20%) | | Total (N=17,006) | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Years aware of HIV infection | | | | | | |
| <1 | 649 | 5 | 112 | 3 | 761 | 4 |
| 1–2 | 1,764 | 13 | 310 | 9 | 2,074 | 12 |
| 3–4 | 1,810 | 13 | 336 | 10 | 2,146 | 13 |
| 5–10 | 3,866 | 28 | 1,043 | 31 | 4,909 | 29 |
| >10 | 5,388 | 40 | 1,555 | 46 | 6,943 | 41 |
| Unknown | 133 | 1 | 40 | 1 | 173 | 1 |

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

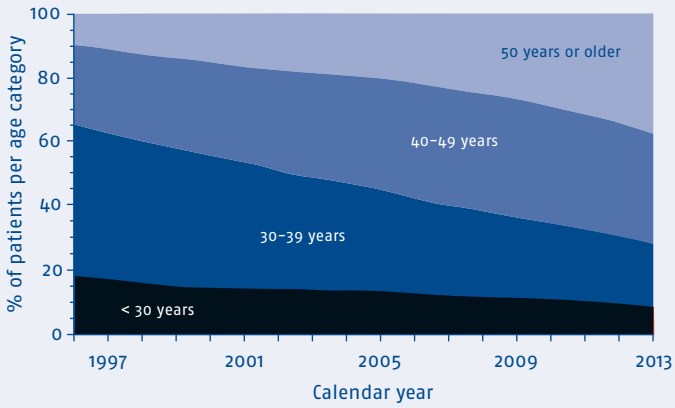
### Retention in care

Amongst the 15,249 patients who enrolled in HIV care in 2002 or later, 891, or 6%, disappeared from clinical care before 2012 and were not reported as having died or moved abroad. Levels of retention in care were highest for patients of Dutch origin; 96% were estimated to be still in care after 10 years. Amongst patients of sub-Saharan African origin, 75% of men and 79% of women were still in care after 10 years, as were 85% of men and 88% of women originating from other regions. Retention in care improved with increasing age, and for every additional 5 years of age at the time of entry into care, patients were 10% less likely to disappear from clinical care.

### Ageing population

The median age of the population in clinical care was 47 years (interquartile range [IQR], 39-54) and has been increasing since 1996 (*Figure 1.2*). This increase in age is mainly a result of the improved life expectancy of HIV-infected patients after the introduction of combination antiretroviral therapy (cART). In addition, patients are being diagnosed at increasingly older ages, as will be discussed later in this chapter. As a result, more than one third of the patients currently in clinical care, 37%, are 50 years or older, including 40% of the men and 24% of the women (*Web Appendix Table 1.1*). As a result, it is to be expected that in coming years the number of patients with age-related comorbidities will increase, thereby complicating the management of their HIV infection (see *Chapter 2*).

*Figure 1.2: The age of the HIV-infected population in clinical care 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 2013, these proportions were 9% and 37%, respectively. The proportion of patients in clinical care as of 1 June of each calendar year is shown according to those <30 years of age, 30 to 39 years, 40 to 49 years, and 50 years or older.*




## Duration of infection

On average, patients in clinical care as of June 2013 received their HIV diagnosis 9.6 years previously. However, a large group (41%) of those in care had lived with HIV for more than 10 years, whilst 8% had done so for more than 20 years. The average time since diagnosis was 9.4 years for men who have sex with men (MSM), 8.9 years for heterosexual men, and 9.7 years for heterosexual women. The majority of injecting drug users (81%) received their HIV diagnosis more than 10 years ago, which reflects the decreasing number of infections occurring via that route.

## Treatment combinations

Most of the patients in care (87%) were treated with cART. The most frequently prescribed regimens, which accounted for 57% of all treatment combinations, were a combination of tenofovir/emtricitabine and either efavirenz (26%), nevirapine (15%), ritonavir-boosted atazanavir (8%), ritonavir-boosted darunavir (7%), or rilpivirine (3%). A backbone of tenofovir/emtricitabine was used by 70% of the patients, whilst 12% used abacavir/lamivudine and 8% zidovudine/lamivudine. Additional drugs in the regimen included efavirenz that was used by 32%, nevirapine by 25%, atazanavir by 13%, darunavir by 13% and rilpivirine by 3%.

## Clinical condition

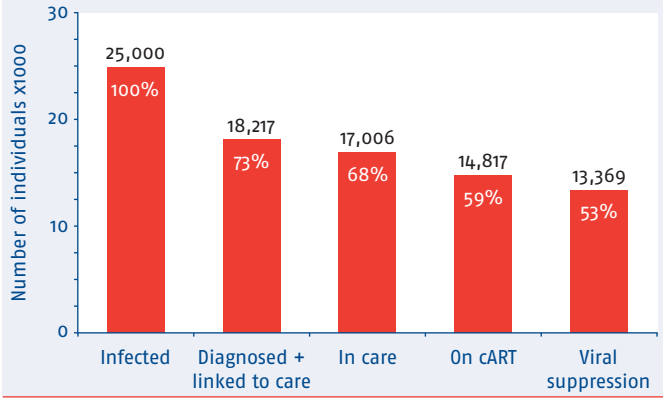
The median CD4 counts were relatively high at 570 (IQR, 428-750) cells/mm$^3$, partly as a result of treatment and partly as a result of earlier diagnosis as shown later in this chapter. CD4 counts were similar between men and women, although men infected via heterosexual

contact had lower CD4 counts than their female counterparts (*Web Appendix Table 1.1*). For all patients in care, the most recent viral load measurement was below 500 copies/ml for 82% and below 100 copies/ml for 79%. About one fifth (22%) of the patients were diagnosed with an AIDS-defining disease; 56% of these patients were diagnosed concurrently with AIDS and HIV.

### Cascade of HIV care

According to recent estimates by the Joint United Nations Programme on HIV/AIDS (UNAIDS), approximately 25,000 people were living with HIV in the Netherlands in 2012 [2]. From this total number of infected people, a "cascade of HIV care" was constructed, which is currently a way of depicting engagement in HIV care across a few key indicators, the last one being the number of individuals with suppressed viral load (*Figure 1.3*) [3]. It should be noted that in the Netherlands the total number of diagnosed HIV-infected individuals is unknown; only the number of diagnosed patients who are linked to care and registered by SHM can be reliably determined. Patients are considered to have viral suppression if their most recent measurement of HIV RNA was below 100 copies/ml. With such low RNA levels, the probability of transmission of HIV is very low, so new infections would be prevented [4]. Overall, 53% of the total infected population and 73% of those diagnosed and linked to care had a suppressed viral load. Likewise, 56% of the infected population had RNA levels below 500 copies/ml (*Web Appendix Figure 1.1*).

*Figure 1.3: Cascade of HIV care for the total HIV-infected population in the Netherlands as of June 2013. According to UNAIDS, 25,000 patients were living with HIV in the Netherlands in 2012. In total, 18,217 were ever linked to care and registered by SHM, still alive and not reported as having moved abroad (21,157 registered patients minus 2,104 patients who died minus 836 patients who moved abroad). Of these patients, 17,006 were still in care, whilst 14,817 had started combination antiretroviral treatment (cART). Altogether, 13,369 of the patients in care had a most recent RNA measurement below the limit of quantification or below 100 copies/ml.*




## Population – diagnosis

### HIV-1-infected individuals

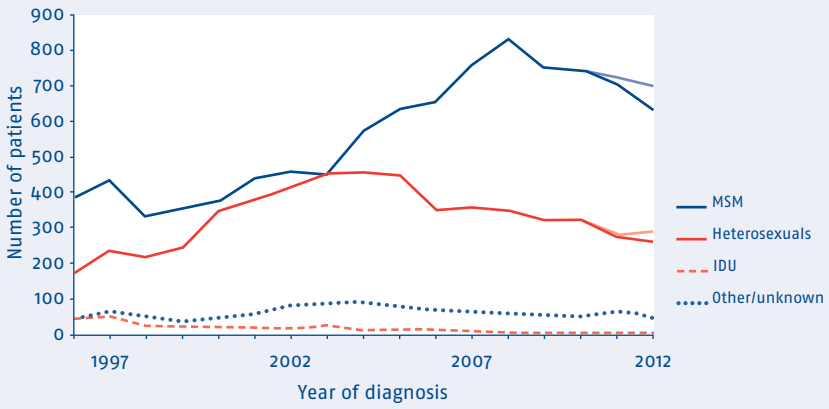
Having briefly discussed the HIV-infected population currently in clinical care, we will now focus on the 20,272 patients who were diagnosed with HIV-1 as adults with a recorded date of diagnosis (*Figure 1.1*). The majority of these patients were MSM (11,863, 59%); the rest were men (2,845, 14%) or women (3,461, 17%) infected via heterosexual contact (*Web Appendix Table 1.2*). For 736 (4%) of the patients, the reported mode of transmission was injecting drug use, whilst 235 (1%) patients were infected by exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 1,132 (6%) infections.

### No further increase

The annual number of diagnoses amongst MSM since the 1990s has steadily increased from around 400 to well above 800 in 2008 (*Figure 1.4*). From 2009 onwards, however, the registered number of diagnoses has been considerably lower, ranging between 700 and 750 per year and thus marking an end to the trend in an increasing number of diagnoses [1]. In fact, the increase may have slowed as early as 2006, since the number of new diagnoses in 2007 and 2008 may have exceeded the long-term trend because of the introduction of opt-out testing for HIV at sexually transmitted infections (STI) clinics across the country at about that time [5]. Nevertheless, it appears that the increase in frequency of testing and in the proportion of patients diagnosed early in the course of their infection, which is discussed later, has not yet

been sufficient to have induced a clear reduction in the number of new HIV infections and a resulting convincing decline in the number of new diagnoses.

***Figure 1.4:*** *Annual number of HIV-1 diagnoses per transmission risk group. In 2012, men who have sex with men (MSM) accounted for 67% of the diagnoses, infections via heterosexual contact for 27%, infections via injecting drug use (IDU) for 1%, and infections via other or unknown modes of transmission for 5% of the annual tally. The light coloured extending lines indicate the projected number of diagnoses when the backlog in registration of HIV cases (3% in 2011, 11% in 2012) is taken into account.*

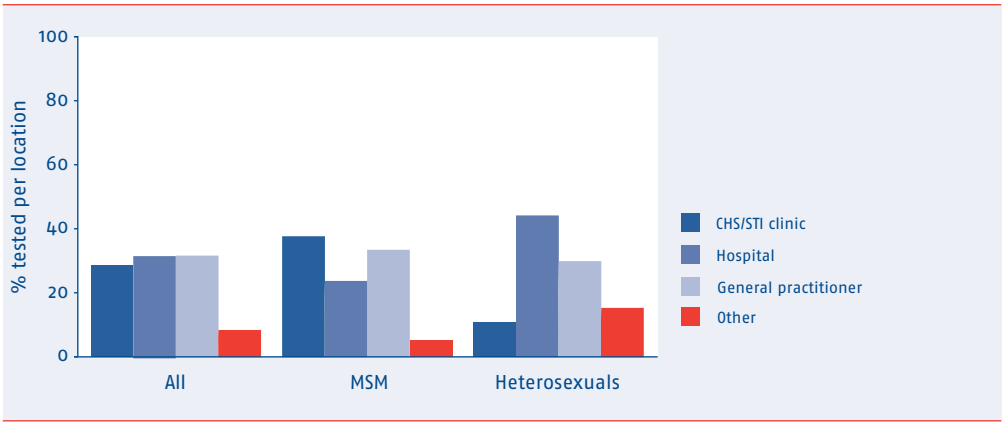



In the heterosexual population, the annual number of diagnoses has declined to approximately 300 cases per year in the last few years. This decline, as shown later in this chapter, is largely a result of a reduced number of diagnoses in migrant populations. Injecting drug use is rarely reported any longer as the most probable mode of transmission, which reflects the decreasing popularity of injecting drugs.

### Testing location

Information on the location of testing was available for 95% of patients diagnosed in 2008 or later. Altogether, 27% received their first HIV-positive test result at a community health service or STI centre, 30% at a hospital, and 30% at a general practice (*Figure 1.5*). Amongst those tested at community health services or STI centres, 89% were MSM, 5% were heterosexual men, and 5% were heterosexual women. These numbers are comparable with those directly reported by STI clinics in 2012: 85% MSM, 7% heterosexual men, and 8% women [(6)].

*Figure 1.5: Proportion of patients diagnosed from 2008 onwards stratified by location of testing and mode of transmission.*



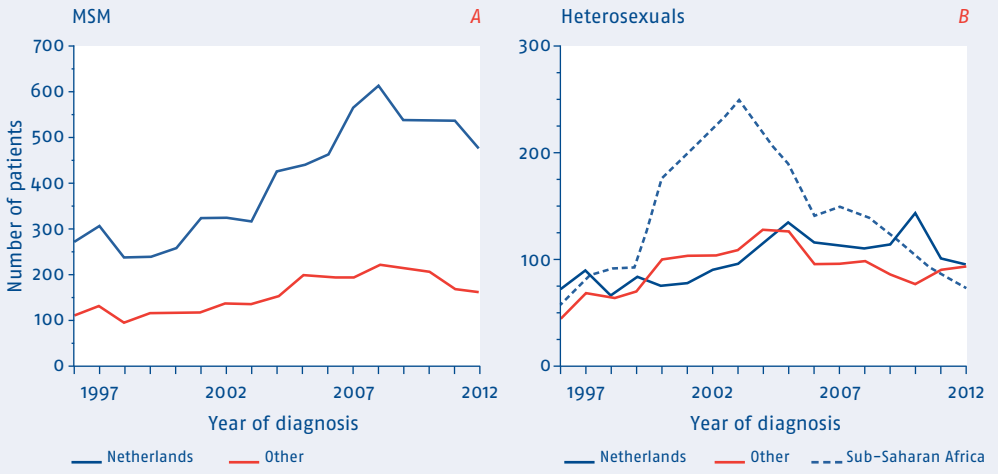

*Legend: MSM=men who have sex with men; CHS=community health service; STI=sexually transmitted infection.*

## More patients of Dutch origin

Overall, 72% of the patients infected via homosexual contact originated from the Netherlands, 10% originated from other European countries, 6% from Latin America, and 3% from the Caribbean (*Figure 1.6A*). In recent years, the proportion of MSM of Dutch origin has increased to 76% (*Web Appendix Table 1.3*). Minor changes over time have been observed in the proportion of patients from Latin America (7% of the annual tally in the period before 2011 and 4% afterwards) and in those of Western European origin (8% before 2011 and 5% thereafter).

In the heterosexual population, only 32% originated from the Netherlands, whilst 40% originated from sub-Saharan Africa, 10% from Latin America, 6% from the Caribbean, and 4% from South and Southeast Asia (*Figure 1.6B*). However, the number of diagnoses amongst sub-Saharan Africans dropped sharply after 2003, probably partially as a result of stricter immigration laws that came into effect in the Netherlands at approximately that time. After 2010, 37% of the diagnosed heterosexual population was of Dutch origin, and 29% originated from sub-Saharan Africa.

*Figure 1.6: Annual number of diagnoses amongst (A) men who have sex with men (MSM) and (B) patients infected via heterosexual contact stratified by country of origin. Of the 11,863 MSM, 72% originated from the Netherlands, 1,195 (10%) from other European countries, 764 (6%) from Latin America, and 394 (3%) from the Caribbean. Amongst the 6,306 heterosexual patients, 2,547 (40%) originated from sub-Saharan Africa, 2,004 (32%) from the Netherlands, 626 (10%) from Latin America, 351 (6%) from the Caribbean, and 264 (4%) from South and Southeast Asia. Note: data collection for 2011 and 2012 is not yet finalised.*




## Country of infection

For 14,796 (73%) of the diagnosed adult patients, the most likely country of infection was reported. The majority of the patients born in the Netherlands (93%) reported having been infected in the Netherlands (*Figure 1.7*). Most of the patients born in sub-Saharan Africa were infected in that region (82%), but 15% of those patients were probably infected in the Netherlands. Amongst patients from other regions, except those from South and Southeast Asia, the majority were infected in the Netherlands.

*Figure 1.7: 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.*

As may be expected from the heterogeneity in the geographic regions of origin, there were also major differences in the regions of infection between the major transmission groups. The majority of MSM (88%) were infected in the Netherlands. Also, the majority of patients infected via injecting drug use (81%) were infected in the Netherlands, whilst 10% of them reported having been infected in other western European countries. The reported distribution across regions of infection was compatible with the HIV-1 subtypes of the infected patients. Overall, 94% of MSM and 91% of drug users for whom the HIV-1 subtype was known were infected with subtype B virus, which is the dominant subtype found in Western countries.

Amongst heterosexual patients, 47% were infected in the Netherlands, whilst 36% reported having been infected in sub-Saharan Africa. Altogether, 72% of the 873 Dutch heterosexual men who reported a country of infection were infected in the Netherlands, 12% were infected in South and Southeast Asia, and 10% in sub-Saharan Africa. Amongst 728 Dutch women infected via heterosexual contact, 89% reported having been infected in the Netherlands and 6% in sub-Saharan Africa, whereas only 3 women were infected in South and Southeast Asia.

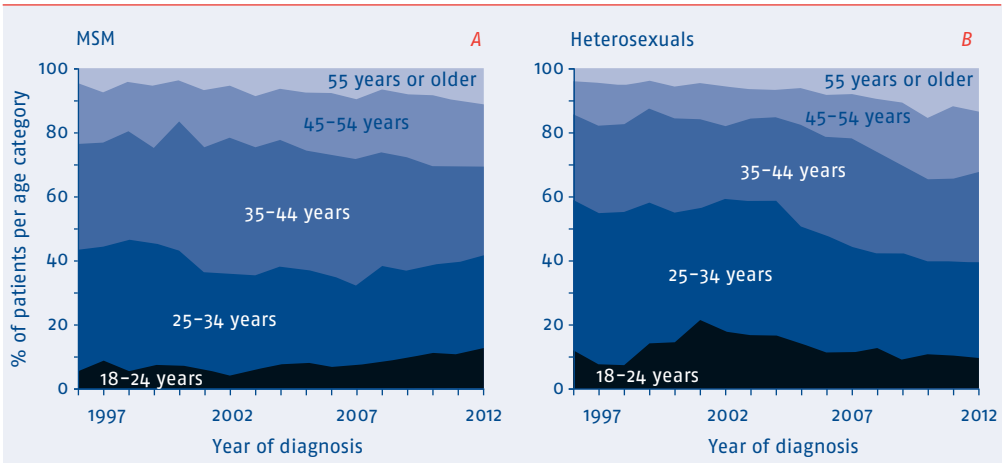
### Increasing age

The age at which patients are diagnosed with HIV has been slowly increasing over time. In 1996, the average age at the time of diagnosis was 36 years; in 2012, it was 39 years. Over the entire period from 1996 through 2012, 14% of adults who received a diagnosis of HIV were 50 years or older; in 2012, 20% were 50 years or older. There were, however, considerable age differences between MSM and heterosexual man 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. Amongst heterosexual patients of Dutch origin, the average age at the time of diagnosis was 38 years for women and 43 years for men. Heterosexual patients born in sub-Saharan Africa (women: 31 years; men: 35 years) or elsewhere (women: 35 years, men: 41 years) were substantially younger than their Dutch counterparts.

For MSM, the age distribution at the point of diagnosis gradually changed over time, whilst amongst heterosexuals there were no notable changes up to 2003 (*Figure 1.8*). Thereafter, the age of heterosexuals at diagnosis started to increase concomitantly with the decreasing number of diagnoses amongst patients from sub-Saharan Africa, who were generally younger than heterosexuals of Dutch or other origin.

***Figure 1.8:*** *Age distribution at the time of diagnosis amongst (A) HIV-1-infected men who have sex with men (MSM) and (B) heterosexual men and women. Between 1996 and 2012, the proportion of MSM aged 45 years or older at the time of diagnosis increased from 23% to 31%, whilst these proportions rose from 14% to 32% for heterosexuals. During the same period, the proportion of patients between 25 and 34 years of age decreased from 38% to 29% for MSM and from 47% to 30% for heterosexuals.*



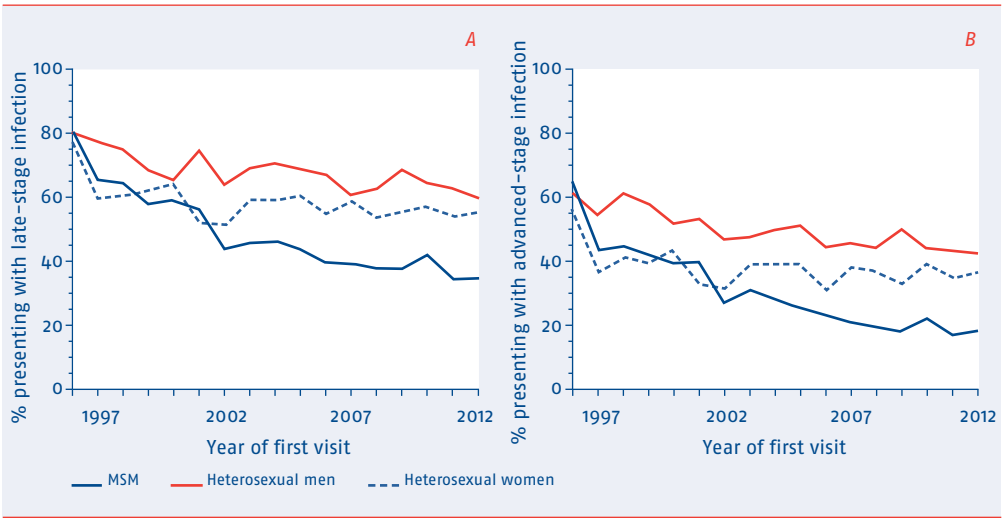

### Young adults

The number of diagnoses amongst young adults less than 25 years of age infected via heterosexual contact was approximately 75 in the early 2000s and decreased to 25 in 2012, or 10% of the annual tally (*Figure 1.8; Web Appendix Figure 1.2*). Amongst MSM, both the number and the proportion of diagnoses amongst young adults increased over time, and in 2012, young adults accounted for 12% of the annual tally, or 78 diagnoses.

## Late presentation

Overall, 54% of the patients were late presenters, i.e., individuals either presenting for care with a CD4 count below 350 cells/mm$^3$ or presenting with an AIDS-defining event regardless of CD4 count [7]. Although the proportion of late presenters has decreased over time, in 2012 43% of patients entered clinical care late in their infection (*Figure 1.9; Web Appendix Figure 1.3*). In recent years, between 10% and 15% of the patients already had AIDS at the time of entry into care. Also, the proportion of patients presenting for care with advanced HIV disease, i.e., with a CD4 count below 200 cells/mm$^3$ or AIDS, decreased over time and was 26% in 2012.

***Figure 1.9:*** *Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection at the time of entry into care. From 1996 onwards, 54% presented with late HIV disease: men who have sex with men (MSM) 47%, heterosexual men 67%, heterosexual women 56%, injecting drug users (IDU) 68%. Overall, 35% were advanced presenters: MSM 29%, heterosexual men 48%, heterosexual women 36%, and IDU 47%. Late stage infection: CD4 counts below 350 cells/mm$^3$ or having AIDS, regardless of CD4 count. Advanced stage infection: CD4 counts below 200 cells/mm$^3$ or having AIDS.*



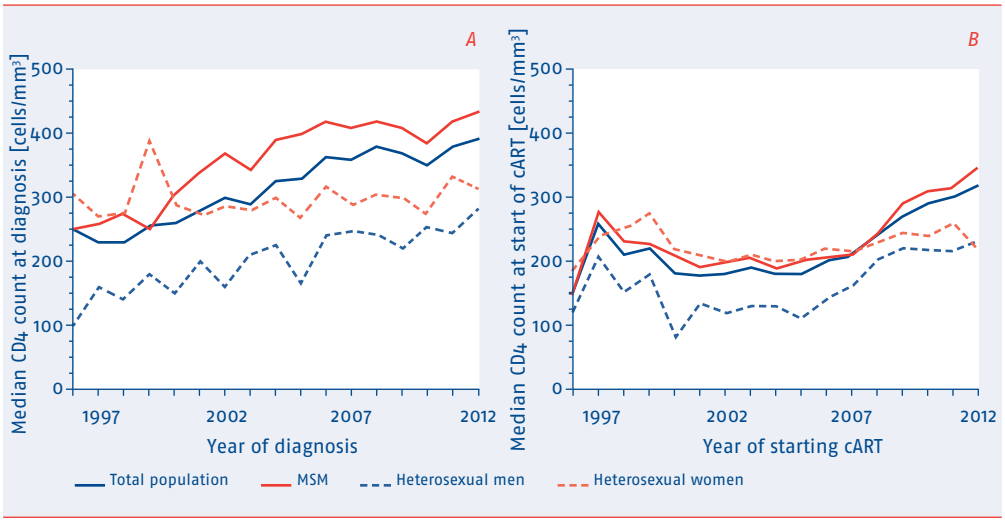

Amongst patients entering clinical care in 2009 or later, 37% of MSM, 64% of heterosexual men, and 55% of heterosexual women presented with late-stage HIV infection. Patients of sub-Saharan African origin infected via heterosexual contact were more likely to present with a late-stage infection, with 66% of this group presenting late compared to 53% of their peers of Dutch origin. Late-stage infection at the time of entry into care was most often found in heterosexual patients originating from South and Southeast Asia, of whom 70% were late presenters. In this same group, 61% presented for care with advanced HIV infection compared to 41% of sub-Saharan Africans and 37% of Dutch heterosexual patients.

Late presentation was also more common in patients entering care at older ages. Amongst those entering care at 45 years of age or older, 55% of MSM and 67% of heterosexuals were late presenters. In contrast, the proportion of late presenters was 28% amongst MSM and 44% amongst heterosexuals entering care at ages younger than 25 years. Although testing behaviour and frequency may differ between these two age groups, the relatively shorter duration of the sex lives of those diagnosed at younger ages also accounts for these observed differences. Late-stage infection was also observed more often in patients who received their HIV diagnosis in 2008 or later at a hospital (64%) compared to those who were tested at a general practitioner's office (43%), community health services or STI clinics (28%), or other testing locations (42%).

### Increasing CD4 cell counts

Between 1996 and 2012, median CD4 counts in the total adult population at the time of diagnosis increased from 239 to 390 cells/mm$^3$ (*Figure 1.10A*). This overall increase was mainly the result of a rise in CD4 counts in both homosexual and heterosexual men, whereas CD4 counts in women remained virtually unchanged. In recent years, CD4 counts in MSM seem to have reached a plateau.

*Figure 1.10: Changes over time in median CD4 counts (A) at HIV diagnosis and (B) at the start of combination antiretroviral therapy (cART). Between 1996 and 2011, CD4 counts at the time of diagnosis increased from 239 (interquartile range [IQR], 80–420) to 390 (IQR, 200–580) cells/mm³ in the total adult population. The increase was most apparent for men who have sex with men (MSM): 240 (IQR, 85–415) in 1996 and 433 (IQR, 280–610) cells/mm³ in 2012. During the same period, CD4 counts in heterosexual men increased from 110 (IQR, 30–380) to 287 (IQR, 60–500) 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, 130–396) cells/mm³ shortly after cART became available, decreased to a plateau around 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2012, CD4 counts were 320 (IQR, 180–430) cells/mm³ in the population, 347 (IQR, 250–460) cells/mm³ in MSM, 230 (IQR, 59–350) in heterosexual men, and 218 (IQR, 70–350) cells/mm³ in heterosexual women.*




## Earlier diagnosis

The increase in CD4 counts at diagnosis, in conjunction with a decreasing proportion of late presenters, suggests that, on average, patients are being diagnosed increasingly earlier in the course of their HIV infection. For individual patients, however, the CD4 count at diagnosis may not always be a reliable marker of time since infection. In a large European cohort of seroconverters, for instance, a quarter of newly infected patients had CD4 counts below 350 cells/mm³ within only 1 year after seroconversion [8].

A further indication of earlier diagnosis was the increase in the proportion of MSM who were diagnosed with a recent infection (*Web Appendix Figure 1.4*). A diagnosed infection was considered to be recent if the time between the last negative HIV test and the first positive test was 1.5 years, at most. Diagnosis with a recent infection was less common in older MSM. Amongst homosexual men diagnosed in 2009 or later, 50% of the infections in

those aged 18 to 24 years were classified as recent, whereas this held true for only 29% of those aged 55 years or older. No major changes were observed in the proportion of heterosexuals with a recent infection.

### Increasing frequency of testing

Since both the proportion of recent infections and CD4 counts at diagnosis have increased amongst those diagnosed with HIV, testing for HIV has apparently become more common. An additional indication for this is the increasing proportion of patients with a previously negative test for HIV (*Web Appendix Figure 1.4*). In 2012, 69% of MSM and 34% of heterosexuals diagnosed with HIV had a previous test with a negative result. The proportion with a previously negative test was highest, 78%, amongst those diagnosed at community health services or STI centres, whilst this proportion was 32% amongst those diagnosed in a hospital, 61% amongst those tested at a general practice, and 45% amongst those diagnosed elsewhere.

## Population – start of cART

### Treated population

Amongst the 20,272 adult patients with an HIV-1 infection, 17,452 patients had started cART by June 2013. The majority of these patients, 85%, started cART whilst being antiretroviral therapy-naïve. For the entire group of adults, the total follow-up time since start of cART was 130,612 person years.

### Treatment combinations

According to the current guidelines, the recommended preferred first-line antiretroviral regimens in therapy-naïve patients include tenofovir/emtricitabine in combination with efavirenz, ritonavir-boosted darunavir, or ritonavir-boosted atazanavir [9]. In 2012 and 2013, these regimens accounted for 59% of all first-line regimens: 35% included efavirenz, 15% boosted darunavir, and 9% boosted atazanavir. A further 15% of the patients started with a combination of tenofovir/emtricitabine and nevirapine, and 11% with tenofovir/emtricitabine and rilpivirine. Since last year, this rilpivirine-containing regimen has been available as a fixed-dose combination for patients with a viral load below 100,000 copies/ml [10-12], although the fixed-dose combination with efavirenz still accounted for 48% of the first-line regimens in last year's report [1], as rilpivirine is generally associated with fewer side-effects than the fixed-dose combination with efavirenz, many patients prefer to start with rilpivirine, despite the requirement of taking it with food.

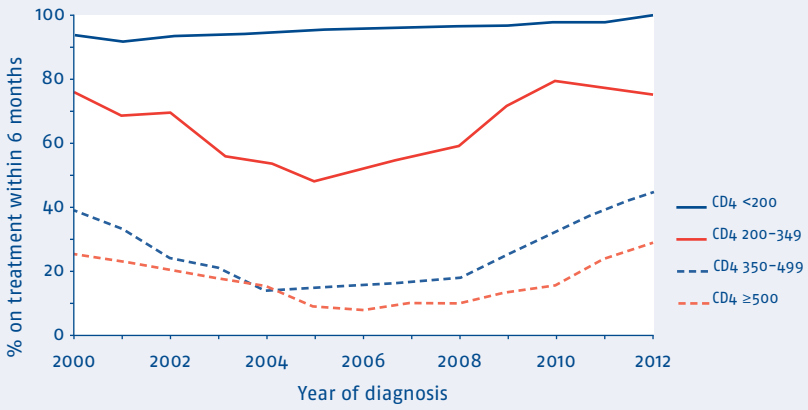
Altogether, 22 patients, or 2%, started tenofovir/emtricitabine in combination with raltegravir. Although this combination is included in preferred first-line regimens in the American guidelines, it is not recommended by the Dutch guidelines, because raltegravir is a twice-daily drug, and national guidelines favour once-daily regimens.

## Earlier start

In the past few 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 (*Figure 1.10B*). In 2012, median CD4 counts at the start of treatment had increased to 320 cells/mm$^3$. Altogether, 42% of the patients started treatment according to the current guidelines, which strongly recommend starting before CD4 counts cross the threshold of 350 cells/mm$^3$. On the other hand, a large group of patients (28%) still began treatment with CD4 counts already below 200 cells/mm$^3$, which is considered a late start.

The main reason for starting treatment so late appears to be late receipt of a diagnosis, because most patients who were able to start treatment on time did so. Patients with less than 200 CD4 cells/mm$^3$ at diagnosis almost immediately started treatment: within 6 months after diagnosis, more than 95% had started cART (*Figure 1.11*). The proportion of patients starting treatment within 6 months was smaller for those with higher CD4 counts, but it has increased in recent years, reflecting changes in treatment guidelines and a tendency to start treatment at higher CD4 counts.

***Figure 1.11:*** *Proportion of patients who started combination antiretroviral treatment (cART) within 6 months after HIV diagnosis stratified by CD4 count at the time of diagnosis. Patients were considered only if they had more than 6 months of follow-up after diagnosis. Of all patients diagnosed in 2011, 98% (100% in 2012) with CD4 counts less than 200 cells/mm$^3$ had started cART within 6 months after receiving their diagnosis, whilst 77% (75% in 2012) with counts between 200 and 349 cells/mm$^3$, 39% (45% in 2012) with counts between 350 and 499, and 24% (29% in 2012) with counts of 500 cells/mm$^3$ or above had begun cART within 6 months of diagnosis.*



### Immediate start of treatment

The most recent American guidelines recommend starting treatment irrespective of CD4 counts, mainly on the basis of expert opinion and indirect evidence [9]. The increase in the proportion of patients with more than 500 cells/mm$^3$ who were on treatment within 6 months of receipt of the diagnosis in recent years may be an indication that this strategy of immediate treatment is also being adopted in the Netherlands (*Figure 1.11*).

### Short-term treatment outcomes

In the entire group of patients who started cART, median CD4 counts increased from 228 cells/mm$^3$ at the start of treatment to 360 cells/mm$^3$ after 24 weeks. An increase of similar magnitude, albeit at higher CD4 counts, was observed in patients starting treatment in 2010 or later, that is, 300 cells/mm$^3$ at the start of cART and 440 cells/mm$^3$ at 24 weeks. Altogether, 88% of the patients achieved suppression of viral load to unquantifiable levels or below 500 copies/ml within 24 weeks, whilst 80% had HIV RNA levels below 100 copies/ml. A more comprehensive overview of treatment outcomes is presented in the next chapter.

## Conclusion

In recent years, the annual number of new HIV diagnoses in the Netherlands has hovered around 1,100. Meanwhile, the increasing trend in the number of diagnoses amongst MSM, which had been observed since the turn of the millennium, has come to an end. Amongst MSM between the ages of 35 and 44 years, the number of diagnoses is even in a steady decline. On the other hand, the number of diagnoses is still increasing amongst young adults and in MSM 55 years of age or older. Diagnoses in the group of patients infected via heterosexual contact show a decreasing trend, which is mainly due to reductions in immigration from HIV-endemic regions. However, amongst heterosexuals 45 years of age or older, the number of diagnoses is increasing.

HIV-infected patients are being diagnosed increasingly earlier in the course of their infection. A shrinking proportion of patients are diagnosed with CD4 counts below 350 cells/mm$^3$ and, conversely, the proportion diagnosed with a recent infection is on the rise. These changes are more pronounced, however, amongst MSM than amongst heterosexual men and women.

In addition, in recent years, testing for HIV has appeared to be more frequent, because patients with a positive test more often have had a previously negative test result. Testing rates appear to be highest amongst patients who received a positive test result at community health services or STI centres and lowest in those tested in a hospital. The population that tested positive for HIV in a hospital also had the highest proportion of late testers. These observations illustrate that patients tested at community health services or STI centres are more likely actively seeking testing for HIV on a regular basis than patients diagnosed in a hospital.

Patients tested early in their infection generally start treatment sooner and before CD4 counts have dropped below the threshold of 350 cells/mm$^3$. In most recent years, treatment uptake has increased in patients with CD4 cells above this threshold. As a result, 53% of the HIV-infected population, including those not yet diagnosed, have a suppressed viral load. The true percentage may even be higher because of reporting delays.

## Recommendations

Despite all these positive developments – more testing, earlier diagnosis, earlier start of treatment, and a large proportion with viral suppression – the number of HIV diagnoses is still not in a convincingly significant decline amongst either MSM or heterosexuals. To fully curb the epidemic, testing and treatment needs to be scaled up. However, reductions in sexual risk behaviour are expected to have a much greater impact on the number of new infections [13, 14].

# 2. Response to combination antiretroviral therapy (cART)

Luuk Gras, Kees Brinkman, Jan Prins, Peter Reiss

## Introduction

The primary goal of combination antiretroviral therapy (cART) is to prevent progression of HIV disease [15]. Studies in HIV-serodiscordant heterosexual couples have shown that HIV RNA levels and transmission of HIV are inversely correlated [16-18]. A recent randomized controlled trial in HIV-serodiscordant couples in which the HIV-infected partner had a CD4-cell count between 350 and 500 cells/mm$^3$ confirmed that starting cART immediately, as compared to deferring treatment until the CD4 count has dropped to ≤250 cells/mm$^3$, effectively prevents the transmission of HIV [19]. Thus, besides preventing disease progression in the HIV-infected individual, cART also benefits public health by preventing onward HIV transmission.

However, the strength of the recommended guidelines for the start of cART decreases at higher latest CD4-cell counts [9, 20]. Studies seem to agree that cART is beneficial when started between 350 and 500 CD4 cells/mm$^3$, but they have reported conflicting results regarding the benefit of starting cART when the CD4-cell count is still above 500 cells/mm$^3$ [21-24]. A disadvantage of an earlier start of cART may be longer exposure to antiretroviral drugs, some of which are associated with the development of cardiovascular disease [25-27], loss of bone density [28-30], renal disease [31-33], and liver disease [34, 35]. Short-term toxicity is less frequently seen with newer drugs [36-38], but certain complications may take a longer time to emerge. Another disadvantage of an early start of cART is the longer inconvenience of daily lifelong medication. Since these individuals have not yet experienced life-limiting effects of HIV infection and have high CD4-cell counts, these inconveniences and adverse events may lead to less than optimal adherence to therapy [39] and, thereby, to enhanced risk of virological failure, emergence of resistant virus [40-42] and, ultimately, HIV progression [43].

However, as untreated HIV increases the risk of several non-AIDS defining diseases, newer drugs are generally better tolerated, and early cART has a beneficial effect on prevention of HIV transmission, most guidelines recommend either starting or considering starting cART when CD4-cell counts are 500 cells/mm$^3$ or higher. United States (US) guidelines, which are generally followed by the Dutch Association of HIV-treating Physicians (NVHB), currently recommend starting cART in all HIV-infected individuals, regardless of CD4-cell count, which implies that all HIV-infected individuals should be offered treatment immediately after diagnosis [9].

The Strategic Timing of Anti-Retroviral Treatment (START) trial is an on-going randomized controlled trial to evaluate the role of immediate cART in patients with CD4 counts >500 cells/mm$^3$ versus delay of treatment until the count is ≤350 cells/mm$^3$. It will help to more robustly inform the question of the optimal timing of cART initiation, including the size of its effect on preventing different non-AIDS-defining morbidities [44].

In this chapter we describe trends over time in the virological and immunological response to cART and the management of complications of treatment, according to demographic and clinical characteristics at its start.

## Demographic and clinical characteristics at the start of cART

Of the 20,761 patients with an HIV-1 infection and a known date of diagnosis (*Figure 1.1*) registered by Stichting HIV Monitoring (SHM), 17,334 were 16 years of age or older when they started cART between January 1995 and December 2012. Of these, 2,560 were mono- or dual ART-experienced at the start of cART, and 14,774 were ART-naïve. We divided patients according to calendar year of starting cART: 5,228 started between 1995 and the end of 2000, 5,071 between 2001 and the end of 2006, 6,111 between 2007 and the end of 2011, and 924 started in 2012 (*Table 2.1*). Patients starting in 2013 are not included, as follow-up of these patients is currently too short to meaningfully report their virological and immunological response to cART.

***Table 2.1:*** *Baseline characteristics of 17,443 patients starting combination antiretroviral therapy (cART) between 1 January 1995 and 31 December 2012 as number (N) or percentage (%) unless stated otherwise.*

| | Year of starting cART | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1995–2000 | | 2001–2006 | | 2007–2011 | | 2012 | |
| | N | % | N | % | N | % | N | % |
| Total | 5,228 | | 5,071 | | 6,111 | | 924 | |
| **Demographic characteristics** | | | | | | | | |
| Male gender | 4,292 | 82.1 | 3,651 | 72.0 | 5,070 | 83.0 | 810 | 87.7 |
| Age at starting cART (median, IQR) | 37.6 | 32.2–44.5 | 37.9 | 31.5–45.1 | 40.6 | 33.2–47.9 | 41.4 | 32.8–49.8 |
| Transmission risk group | | | | | | | | |
| MSM | 3,137 | 60.0 | 2,296 | 45.3 | 3,899 | 63.8 | 624 | 67.5 |
| Heterosexual contact | 1,340 | 25.6 | 2,171 | 42.8 | 1,785 | 29.2 | 233 | 25.2 |
| IDU | 374 | 7.2 | 184 | 3.6 | 85 | 1.4 | 8 | 0.9 |
| Blood or blood products | 109 | 2.1 | 78 | 1.5 | 44 | 0.7 | 6 | 0.6 |
| Vertical transmission | | | 1 | 0.0 | 6 | 0.1 | 2 | 0.2 |
| Unknown | 268 | 5.1 | 341 | 6.7 | 292 | 4.8 | 51 | 5.5 |

| | Year of starting cART | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1995–2000 | | 2001–2006 | | 2007–2011 | | 2012 | |
| | N | % | N | % | N | % | N | % |
| Region of origin | | | | | | | | |
| Netherlands | 3,246 | 62.1 | 2,374 | 46.8 | 3,708 | 60.7 | 608 | 65.8 |
| W-Europe/N-America/Australia | 608 | 11.6 | 372 | 7.3 | 415 | 6.8 | 39 | 4.2 |
| Caribbean/S-America | 491 | 9.4 | 638 | 12.6 | 657 | 10.8 | 103 | 11.1 |
| Sub-Saharan Africa | 567 | 10.8 | 1,273 | 25.1 | 805 | 13.2 | 81 | 8.8 |
| Other | 316 | 6.0 | 414 | 8.2 | 526 | 8.6 | 93 | 10.1 |
| **Clinical characteristics** | | | | | | | | |
| CD4-cell count at start cART, cells/mm$^3$ (median, IQR) | 200 | 80–350 | 190 | 80–290 | 263 | 160–340 | 330 | 190–432 |
| HIV RNA at start cART, $\log_{10}$ cps/ml (median, IQR) | 4.80 | 4.11–5.30 | 5.00 | 4.45–5.34 | 4.94 | 4.41–5.37 | 4.93 | 4.40–5.38 |
| AIDS diagnosis at the start of cART | 1,732 | 33.1 | 1,406 | 27.7 | 1,057 | 17.3 | 151 | 16.3 |
| CD4 cell count <200 or AIDS at start of cART ***** | 2,810 | 58.8 | 2,799 | 59.1 | 2,152 | 37.2 | 272 | 31.5 |
| CD4 cell count <350 or AIDS at start of cART ***** | 3,775 | 79.0 | 4,084 | 86.2 | 4,517 | 78.1 | 514 | 59.5 |
| CD4 cell count <500 or AIDS at start of cART ***** | 4,374 | 91.5 | 4,426 | 93.4 | 5,398 | 94.3 | 736 | 85.2 |
| HCV** | | | | | | | | |
| Negative | 3,982 | 76.2 | 4,188 | 82.6 | 5,304 | 86.8 | 795 | 86.0 |
| Positive | 490 | 9.4 | 397 | 7.8 | 485 | 7.9 | 59 | 6.4 |
| Unknown | 756 | 14.5 | 486 | 9.6 | 322 | 5.3 | 70 | 7.6 |
| HBV*** | | | | | | | | |
| Negative | 4,329 | 82.8 | 4,422 | 87.2 | 5,480 | 89.7 | 831 | 89.9 |
| Positive | 503 | 9.6 | 383 | 7.6 | 408 | 6.7 | 44 | 4.8 |
| Unknown | 396 | 7.6 | 266 | 5.2 | 223 | 3.6 | 49 | 5.3 |
| **Treatment characteristics** | | | | | | | | |
| ART-naive at start cART | 3,080 | 58.9 | 4,765 | 94.0 | 6,014 | 98.4 | 915 | 99.0 |
| Other drug class next to NRTI in initial cART | | | | | | | | |
| NNRTI | 785 | 15.0 | 2,652 | 52.3 | 4,143 | 67.8 | 584 | 63.2 |
| PI | 4,325 | 82.7 | 1,946 | 38.4 | 1,585 | 25.9 | 276 | 29.9 |
| NNRTI+INSTI | | | 1 | 0.0 | 41 | 0.7 | 9 | 1.0 |
| PI+INSTI | | | | | 37 | 0.6 | 8 | 0.9 |
| INSTI | | | | | 80 | 1.3 | 22 | 2.4 |
| Other* | 118 | 2.3 | 472 | 9.3 | 225 | 3.7 | 25 | 2.7 |

| | Year of starting cART | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 1995–2000 | | 2001–2006 | | 2007–2011 | | 2012 | |
| | N | % | N | % | N | % | N | % |
| Daily frequency of initial cART intake | | | | | | | | |
| QD | 45 | 0.9 | 1,474 | 29.1 | 4,762 | 77.9 | 807 | 87.3 |
| BID | 2,362 | 45.2 | 3,457 | 68.2 | 1,320 | 21.6 | 115 | 12.4 |
| TID | 2,670 | 51.1 | 103 | 2.0 | 15 | 0.2 | | |
| ≥4× daily | 115 | 2.2 | 19 | 0.4 | 5 | 0.1 | | |
| Unknown | 36 | 0.7 | 18 | 0.4 | 9 | 0.1 | 2 | 0.2 |
| cART started during pregnancy | 93 | 1.8 | 395 | 7.8 | 232 | 3.8 | 16 | 1.7 |
| cART started during primary infection | 129 | 2.5 | 278 | 5.5 | 547 | 9.0 | 138 | 14.9 |
| **Other characteristics** | | | | | | | | |
| Current smoker or history of smoking | | | | | | | | |
| No | 1,400 | 26.8 | 1,733 | 34.2 | 2,304 | 37.7 | 302 | 32.7 |
| Yes | 2,807 | 53.7 | 2,050 | 40.4 | 3,035 | 49.7 | 513 | 55.5 |
| Unknown | 1,021 | 19.5 | 1,288 | 25.4 | 772 | 12.6 | 109 | 11.8 |
| CHD risk score**** | | | | | | | | |
| Low (<1%) | | | 485 | 57.0 | 1,065 | 54.4 | 135 | 52.5 |
| Moderate (1–5%) | | | 329 | 38.7 | 826 | 42.2 | 107 | 41.6 |
| High (5–10%) | | | 32 | 3.8 | 55 | 2.8 | 14 | 5.5 |
| Very high (≥10%) | | | 5 | 0.6 | 13 | 0.7 | 1 | 0.4 |

*Legend: cART= combination antiretroviral therapy; MSM=men having sex with men; IDU=injecting drug use; W-Europe=Western Europe; N-America=North 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; QD=once-daily; BID=twice-daily; TID=three times-daily; med=median; IQR=interquartile range*

* *Other includes regimens including only NRTIs, regimens including both PI's and NNRTI's and other combinations.*

** *By hepatitis C RNA or, if absent, antibody.*

*** *By hepatitis B surface antigen.*

**** *5-year risk of coronary heart disease (CHD) calculated with D:A:D (Data Collection on Adverse Effects of Anti-HIV Drugs) Study algorithm [45].*

***** *Percentage of patients with an available CD4-cell count.*

Of the 17,443 patients who started cART, 3,511 were women (20%), of whom 26% were born in the Netherlands. Of the 924 patients who started cART in 2012, 624 (68%) were MSM, a similar percentage to that of 2011. Amongst the 103 patients of Caribbean or South American origin who started cART in 2012, 25 were individuals originally from the former Netherlands Antilles (24%), and 46 were from Surinam (45%). The 93 individuals from other regions of origin who started in 2012 were from Central and Eastern Europe (n=37), Southeast Asia (n=36), North Africa and the Middle East (n=11), and Oceania and Pacific (n=7); for 2 patients the region of origin was unknown. Out of 114 women who started cART in

2012, 26% were born in the Netherlands.

## CD4-cell count at the start of cART

In 2007, the United States Department of Health and Human Services (US DHHS) treatment guidelines, which are generally followed by the NVHB, recommended starting cART when the CD4 cell count fell below 350 cells/mm$^3$, and in 2009 they recommended starting cART when the count fell below 500 cells/mm$^3$. More recently, these guidelines have recommended cART for all HIV-infected patients regardless of CD4 count [9,46]. Although the median CD4-cell count at the start of cART increased from 210 cells/mm$^3$ in 2007 to 304 cells/mm$^3$ in 2011 and to 330 cells/mm$^3$ in 2012 (Cuzick test for trend $p<0.0001$), in 2012, 514 out of 864 patients (59%) with an available CD4-cell count at the start of cART still started with either an AIDS diagnosis or a count of less than 350 cells/mm$^3$, a statistically significant decrease over the 78% of such patients between 2007 and 2011 ($p<0.0001$). *Figure 2.1* shows the percentage of men and women with a 'late' start of cART (defined as having an AIDS diagnosis prior to starting or a CD4 cell count of <200, <350 or <500 cells/mm$^3$). Amongst men, the percentage of patients with AIDS or <350 CD4 cells/mm$^3$ at the start decreased over time from 90% in 1996 to 57% in 2012. Amongst women, the decrease was less pronounced; it declined from 86% in 1996 to 71% in 2012.

Amongst women, the median CD4-cell count at the start of cART increased from 220 cells/mm$^3$ in 2007 to 270 cells/mm$^3$ in 2011, but decreased to 250 cells/mm$^3$ in 2012 (*Figure 2.2*). Median counts amongst men increased from 210 cells/mm$^3$ in 2007 to 330 cells/mm$^3$ in 2012. The increase was strongest amongst men from the Netherlands, western Europe and North America, who were infected mostly through homosexual contact. Amongst both men and women from the Caribbean and South America, the CD4-cell count at the start of cART was lower in 2012 compared to 2011. *Web Appendix Table 2.1* gives an overview of the number of men and women contributing to the trends shown in *Figures 2.1* and *2.2*. The percentage of patients with an AIDS diagnosis at the start of cART declined over time (test for trend $p<0.0001$). Nearly 15% of patients starting cART in 2012 did so during primary infection, similar to the number in 2011. Starting treatment during primary infection has been shown to result in a lower viral load set-point (associated with a slower rate of disease progression), a longer total time off therapy and a longer time to reaching CD4-cell counts of 350 cells/mm$^3$ or lower [47-49].

*Figure 2.1: Percentage of patients starting cART 'late' (defined as starting with AIDS or below three different CD4-cell count thresholds (<200, <350, and <500 cells/mm³) in men (A) and women (B).*

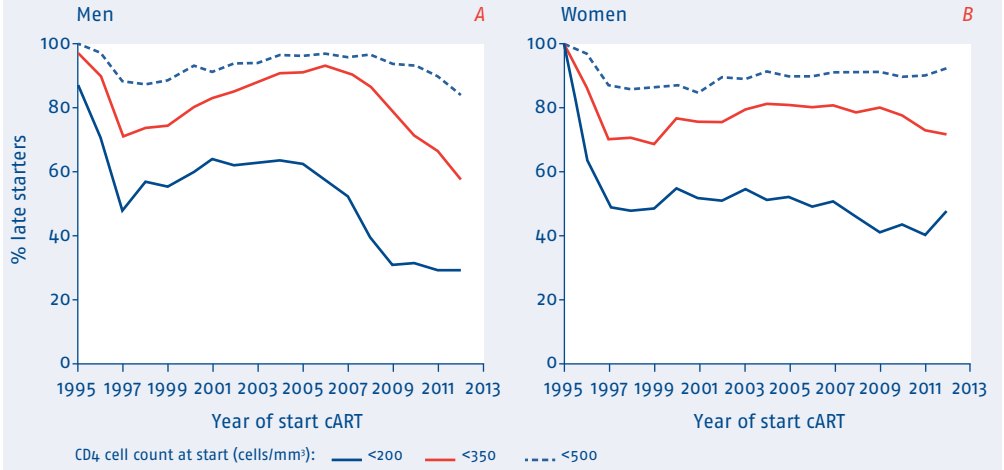
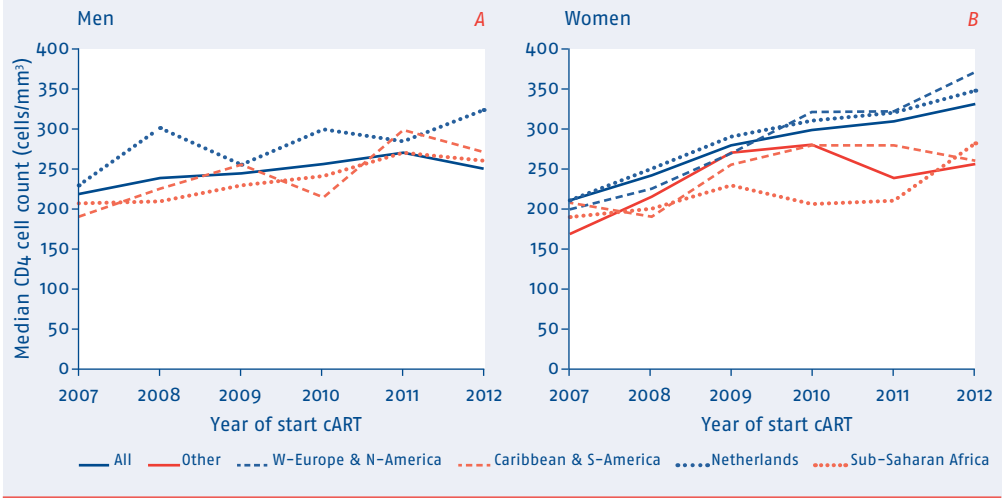



*Figure 2.2: Median CD4-cell count at the start of cART according to region of origin (2007-2011) for men (A) and women (B).*




*Legend: W-Europe=Western Europe, N-America=North America, S-America=South America.*

In a logistic regression analysis amongst the 924 patients starting cART in 2012 adjusted for the demographic characteristics listed in *Table 2.1*, as well as availability of a previous negative HIV test and pregnancy status at the start of therapy, the probability of starting at a CD4-cell count of 350 cells/mm$^3$ or more was lower among heterosexually infected individuals than among MSM (odds ratio [OR] 0.46, 95% confidence interval [CI] 0.31-0.69, p=0.0002) and also among individuals from the Caribbean and South America (OR 0.49, 95% CI 0.26-0.91, p=0.02), when compared to individuals from western Europe or North America. Also, repeatedly tested individuals (defined as having a negative test at 1.5 years prior to HIV diagnosis) had higher odds of starting with ≥350 cells/mm$^3$ (OR 1.86, 95% CI 1.34-2.59, p=0.0002), as well as those who started cART during a pregnancy (OR 3.36, 95% CI 1.12-10.06, p=0.03). Repeated testing for HIV is less frequent in the heterosexual population compared to the homosexual population (*Chapter 1*). It has already 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 [50]. HIV testing is part of routine screening for sexually transmitted infections (STI) in patients 25 years of age or older, unless they decline. The most frequently reported barriers for HIV testing are fear for the test result and no perceived risk for HIV infection [5, 51, 52].

## Initial regimens at initiation of cART

The percentage of patients starting cART with a regimen containing a first-line boosted protease inhibitor (PI) decreased slightly from 33% in 2011 to 29% in 2012. The percentage of patients starting with a regimen containing a non-nucleoside reverse transcriptase inhibitor (NNRTI) slightly increased from 60% to 63%. The five most frequently used starting regimens in 2012 were tenofovir plus emtricitabine, combined with efavirenz (36%), darunavir/ritonavir (15%), nevirapine (15%), atazanavir/ritonavir (9%) or rilpivirine (9%). The fixed-dose combination of tenofovir and emtricitabine was used in 92% of all starting regimens in 2012. The fixed-dose combination of abacavir and lamivudine, which according to current guidelines may be considered as a starting regimen in patients with <100,000 HIV RNA copies, without active HBV co-infection, low cardiovascular risk and because of its lower cost, was used in 2012 in only 4% of starting regimens.

Over time, initial regimens have increasingly shifted from requiring dosing three times a day (51% of regimens amongst patients starting cART between 1995 and 2000) to once-daily dosing (87% amongst those starting in 2012). 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 [46]. Once-daily regimens have been associated with a modestly improved adherence compared to twice-daily regimens [53]. Since 2009, the integrase inhibitor raltegravir, not recommended in starting regimens because it needs to be taken as part of a twice-daily regimen, was used in only 4% of starting regimens.

## Virological response to cART

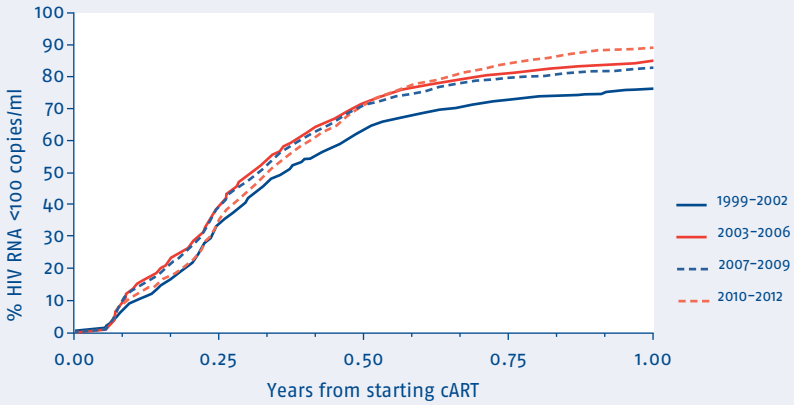
Out of the 17,443 patients who started cART from 1995 onward, 9,921 started cART from 1999 onward as ART-naïve, with at least two available plasma viral loads measured with an assay with a lower detection limit of 50 copies/ml or less after the start of cART. Data from these 9,921 patients are included in this section of *Chapter 2*, and results on the virological response to cART in this section are restricted to this group of patients.

### Short-term virological response

The short-term virological response to cART is an important marker for longer-term clinical outcome. We therefore monitored the time to virological suppression to below 100 copies/ml during the first year after the start of cART. The cut-off of 100 copies/ml was chosen, rather than the more conventional 50 copies/ml, because plasma samples tested with the Roche COBAS AmpliPrep COBAS TaqMan HIV-1 assay, version 2.0 (CAP/CTM v2.0) are known to give higher results for plasma viral load when the viral load is at levels close to the lower detection limit [54].

Overall, the Kaplan-Meier estimate of the percentage of patients with initial virological suppression to below 100 copies/ml (first of 2 consecutive measurements <100 copies/ml) increased from 71% (95% CI, 70-72%) at 6 months to 81% (81-82%) at 9 months and 85% (84-86%) at 12 months. The percentage of patients with a plasma viral load less than 100 copies/ml nine months after starting cART was 73% (95% CI, 71-75%) between 1999 and 2002, 80% (78-82%) between 2003 and 2006, 83% (95% CI 82-85%) between 2006 and 2008, and 85% (95% CI 84-87%) between 2010 and 2012 (*Figure 2.3*). Differences in time to initial suppression across the four periods for the start of cART were small, but significant (overall log rank test $p<0.0001$).

*Figure 2.3: Kaplan–Meier estimates of the percentage of patients with initial suppression to <100 copies/ml during the first year after starting combination antiretroviral therapy (cART).*




To study factors associated with a shorter time to initial suppression of HIV RNA to <100 copies, we performed Cox regression using demographic and clinical data from the 9,921 patients, as well as data on the frequency of daily ART intake (qd, bid, and tid or more) and type of initial regimen (NNRTI-based, PI-based, PI/r-based, triple-NRTI, and other), whether an integrase inhibitor was used (yes/no) and the type of viral load assay (CAP/CTM v2.0 vs. other assays). In adjusted analyses, female gender, a lower plasma viral load at the start and being co-infected with hepatitis C virus (HCV) were independently associated with a shorter time to viral suppression (*Table 2.2*).

Furthermore, having been born in the Caribbean/South America or sub-Saharan Africa (compared to the Netherlands) and being younger than 30 years of age when starting cART were associated with a longer time to initial viral suppression. Starting a regimen that included an integrase inhibitor was significantly associated with a shorter time to suppression, as was starting NNRTI-based cART as compared to PI/r-based cART. Including an interaction term between calendar year of starting and regimen type (results not shown in table) suggested that the shorter time to virological suppression for NNRTI-based regimens was apparent only for combinations started after 2002.

Starting at 500 CD4 cells or higher, which occurred in only 688 out of 9,921 patients (6.9%), was associated with a significantly longer time to viral suppression, compared to starting at 200-350 cells/mm$^3$. There was no significant difference in time to virological suppression when cART was started at ≥500 or 350-500cells/mm$^3$ (p=0.14). Closer inspection of the association between CD4 count at the start of treatment and time to suppression by including interaction terms in the model suggested that the difference in time to suppression between

those starting with ≥500 and 200-350 cells/mm$^3$ was largest and only significant when cART was started between 2003 and 2006 and for patients born in regions other than the Netherlands/western Europe/North America (*Table 2.3*). A possible explanation may be that adherence to cART was reduced in patients starting with CD4-cell counts ≥500 cells/mm$^3$ during 2003-2006 because of a lower perceived necessity for therapy and a reduced quality of life due to the toxic effects of antiretroviral drugs used at that time.

***Table 2.2:*** *Unadjusted and adjusted hazard ratios (95% confidence intervals) of time from cART initiation to a confirmed HIV RNA <100 copies/ml by Cox proportional hazard regression analysis. Time to a confirmed HIV RNA <100 copies/ml is shorter compared to the reference group when the hazard ratio is higher than 1.00.*

| | | Unadjusted | | Adjusted |
|---|---|---|---|---|
| | HR (95% CI) | (overall) p-value | HR (95% CI) | (overall) p-value |
| Gender | | | | |
| Male | 1.00 | | 1.00 | |
| Female | 0.98 (0.93-1.03) | 0.39 | 1.09 (1.00-1.18) | 0.04 |
| Transmission risk group | | (<0.0001) | | |
| MSM | 1.00 | | 1.00 | |
| Heterosexual | 0.90 (0.86-0.94) | <0.00001 | 0.89 (0.83-0.96) | 0.003 |
| IDU | 0.62 (0.53-0.72) | <0.0001 | 0.51 (0.42-0.62) | <0.0001 |
| Region of origin | | (<0.0001) | | |
| Netherlands | 1.00 | | 1.00 | |
| Caribbean & S-America | 0.81 (0.76-0.87) | <0.0001 | 0.91 (0.85-0.99) | 0.03 |
| Sub-Saharan Africa | 0.83 (0.79-0.88) | <0.0001 | 0.91 (0.84-0.99) | 0.03 |
| Western Europe / North America | 0.71 (0.65-0.77) | <0.0001 | 0.95 (0.86-1.05) | 0.29 |
| Age (years) | | (<0.0001) | | |
| 16-29 | 0.89 (0.84-0.95) | 0.0002 | 0.90 (0.84-0.96) | 0.003 |
| 30-39 | 1.00 | | 1.00 | |
| 40-49 | 1.10 (1.05-1.16) | 0.0002 | 1.04 (0.98-1.10) | 0.19 |
| ≥50 | 1.06 (1.00-1.13) | 0.06 | 1.00 (0.93-1.07) | 0.99 |
| CD4 cell count at cART initiation (cells/mm$^3$) | | (<0.0001) | | |
| <50 | 0.80 (0.74-0.85) | <0.0001 | 0.98 (0.90-1.06) | 0.55 |
| 50-200 | 0.85 (0.80-0.89) | <0.0001 | 0.94 (0.89-1.00) | 0.05 |
| 200-350 | 1.00 | | 1.00 | |
| 350-500 | 0.94 (0.88-1.01) | 0.07 | 0.92 (0.86-0.99) | 0.03 |
| >500 | 0.80 (0.73-0.87) | <0.0001 | 0.85 (0.77-0.93) | 0.0008 |
| HIV RNA at cART initiation ($log_{10}$copies/ml) | | (<0.0001) | | |
| <4 | 1.29 (1.20-1.39) | <0.0001 | 1.46 (1.35-1.57) | <0.0001 |
| 4-5 | 1.00 | | 1.00 | |
| ≥5 | 0.68 (0.64-0.71) | <0.0001 | 0.63 (0.60-0.67) | <0.0001 |

| | | Unadjusted | | Adjusted |
|---|---|---|---|---|
| | HR (95% CI) | (overall) p-value | HR (95% CI) | (overall) p-value |
| Year of starting | | (<0.0001) | | |
| 1999-2002 | 0.70 (0.65-0.74) | 0.006 | 0.90 (0.83-0.97) | 0.007 |
| 2003-2006 | 0.87 (0.83-0.92) | 0.74 | 1.01 (0.95-1.07) | 0.78 |
| 2007-2009 | 1.00 | | 1.00 | |
| 2010-2012 | 0.98 (0.92-1.03) | 0.61 | 0.99 (0.92-1.06) | 0.76 |
| HBV co-infection | | | | |
| - | 1.00 | | | |
| + | 1.03 (0.95-1.02) | 0.42 | | |
| HCV co-infection | | | | |
| - | 1.00 | | 1.00 | |
| + | 1.07 (0.99-1.16) | 0.10 | 1.13 (1.03-1.24) | 0.0095 |
| Type of starting regimen | | (<0.0001) | | |
| NNRTI | 1.00 | | 1.00 | |
| PI | 0.72 | <0.0001 | 0.94 (0.83-1.07) | 0.34 |
| PI/r | 0.88 | <0.0001 | 0.90 (0.85-0.95) | <.0001 |
| NRTI only | 0.89 | 0.08 | 0.92 (0.79-1.08) | 0.31 |
| Other | 0.83 | 0.004 | 0.92 (0.80-1.06) | 0.27 |
| Integrase inhibitor included in regimen | 1.49 (1.26-1.77) | <0.0001 | 1.69 (1.40-2.05) | <0.0001 |
| Start during primary infection | 0.89 (0.82-0.97) | 0.005 | 0.93 (0.85-1.02) | 0.13 |
| Start during pregnancy | 1.15 (1.04-1.27) | 0.005 | 1.09 (0.96-1.25) | 0.19 |
| HIV RNA Assay | | | | |
| CAP/CTM v2.0 | 1.02 (0.97-1.08) | 0.45 | 0.88 (0.81-0.95) | 0.0008 |
| Other assay | 1.00 | | 1.00 | |

***Legend:*** *MSM=men who have sex with men; IDU=injecting drug user; HBV=hepatitis B virus; HCV=hepatitis C virus; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; PI/r=ritonavir boosted protease inhibitor; CAP/CTM v2.0=COBAS AmpliPrep COBAS TaqMan HIV-1 assay, version 2.0; HR=hazard ratio; CI=confidence interval.*

*Table 2.3: Selected hazard ratios (95% confidence intervals of time from cART initiation to a confirmed HIV RNA <100 copies/ml) by Cox proportional hazard regression analysis, after inclusion of interaction terms between CD4-cell count at the start of cART and year of starting cART and region of origin. Region of origin categories shown in Table 2.3 were merged into Netherlands/Western Europe/North America, and Other to avoid small numbers of patients in categories. Time to a confirmed HIV RNA <100 copies/ml is shorter compared to the reference group when the hazard ratio is higher than 1.00.*

| | CD4 cell count at the start of cART (cells/mm³) | | | |
|---|---|---|---|---|
| | <200 | 200-350 | 350-500 | ≥500 |
| Region of origin | | | | |
| Netherlands/Western Europe/ | | | | |
| North America | 0.96 (0.90-1.03) | 1.00 | 0.95 (0.88-1.03) | 0.92 (0.82-1.03) |
| Other | 0.92 (0.84-1.01) | 1.00 | 0.83 (0.72-0.96) | 0.70 (0.58-0.84) |
| Year of starting cART | | | | |
| 1999-2002 | 1.00 (0.86-1.16) | 1.00 | 0.82 (0.66-1.02) | 0.83 (0.64-1.07) |
| 2003-2006 | 1.02 (0.92-1.13) | 1.00 | 0.88 (0.73-1.06) | 0.72 (0.56-0.91) |
| 2007-2009 | 0.91 (0.83-1.00) | 1.00 | 0.84 (0.74-0.95) | 0.86 (0.72-1.04) |
| 2010-2012 | 0.85 (0.76-0.95) | 1.00 | 1.03 (0.93-1.15) | 0.91 (0.79-1.06) |

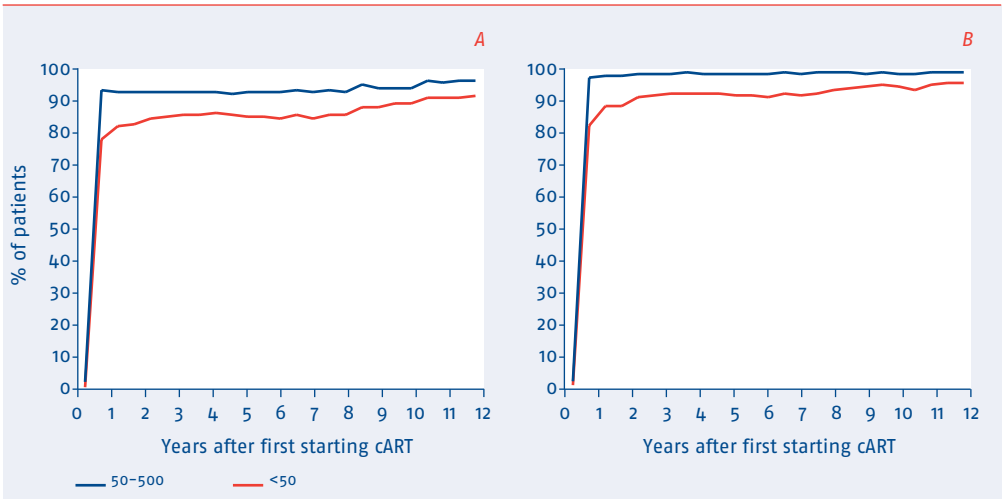
*Legend: cART= combination antiretroviral therapy.*

## Long-term virological response

After having achieved initial virological suppression, more than 30% of patients on cART experienced episodes of viraemia [55]. Monitoring of longer-term virological response is important, as high-level viraemia has been associated with a poorer clinical outcome and smaller increases in CD4-cell count [55-57]. In addition, frequent or persistent periods of low-level viraemia have been reported to be associated with emergence of drug resistance and treatment failure [58, 59]. The clinical significance of infrequent low-level viraemia remains less clear. Short-term low-level viraemia was not associated with AIDS, non-AIDS-defining events, death or CD4-cell count response [55, 60-63]. Although short-term low-level viraemia is assay-dependent [64] and has been found more frequently since new assays with a lower limit of detection were introduced [65, 66], resistance-associated mutations have been found in patients with plasma viral load levels below 50 copies/ml [59, 67]. Also, even at plasma viral load levels below 50 copies/ml, patients with low but detectable plasma viral load levels had a lower probability of sustained viral suppression than patients with completely undetectable viral loads [68]. Here we report on the long-term virological response in the same 9,921 ART-naïve patients starting cART from 1999 onward whose short-term response was described in the preceding section.

*Figure 2.4* shows that the percentage of patients with a viral load <50 copies/ml increased from 82% at 1 year to 92% at 12 years. These percentages were 88% to 94% for those continuously on cART. The increasing percentages with increasing time after start of cART are likely because of the selection of patients who do well and remain in follow-up.

*Figure 2.4: The percentage of patients with a plasma HIV RNA concentration <50 (red line) and <500 copies/ml (blue line) at months 9, 12, 18 and at every 6 months 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 first starting combination antiretroviral therapy (cART) and plot B shows a subgroup of patients continuously remaining on cART, allowing for a therapy interruption of <2 weeks. A total of 9,921 treatment-naïve patients starting cART were included, but this number diminished over time due to differences in length of follow-up.*




As these plots do not show the total percentage of patients with virological failure over time, we also analysed time to virological failure using Cox proportional hazard models. Virological failure was defined as time to the first of two consecutive plasma viral HIV RNA levels >200 copies/ml after 24 weeks on antiretroviral therapy, as defined in US guidelines [9]. cART interruptions shorter than 2 weeks did not count as an interruption. In total, 790 (8.0%) out of 9,921 treatment-naïve patients who started cART from 1999 onwards met the definition of virological failure.

The Kaplan-Meier estimate of the percentage of patients with virological failure within 12 year after first starting cART was 15% (95% CI 14-17%). Amongst MSM, the differences in time to virological failure between patients from western Europe (including the Netherlands) / North America, the Caribbean/South America and other regions of origin were borderline significant (plot A in *Figure 2.5*, overall log rank p=0.05). Amongst the heterosexual risk group, differences in the risk of failure were more pronounced.

The risk was higher among patients from sub-Saharan Africa and the Caribbean/South America compared to western Europe/North America and other regions (plot B in *Figure 2.5*, overall log rank p<0.0001).

*Figure 2.5: Kaplan-Meier estimates of the percentage and 95% CI of patients with virological failure according to transmission risk group (A: MSM, B: heterosexual) and region of origin.*

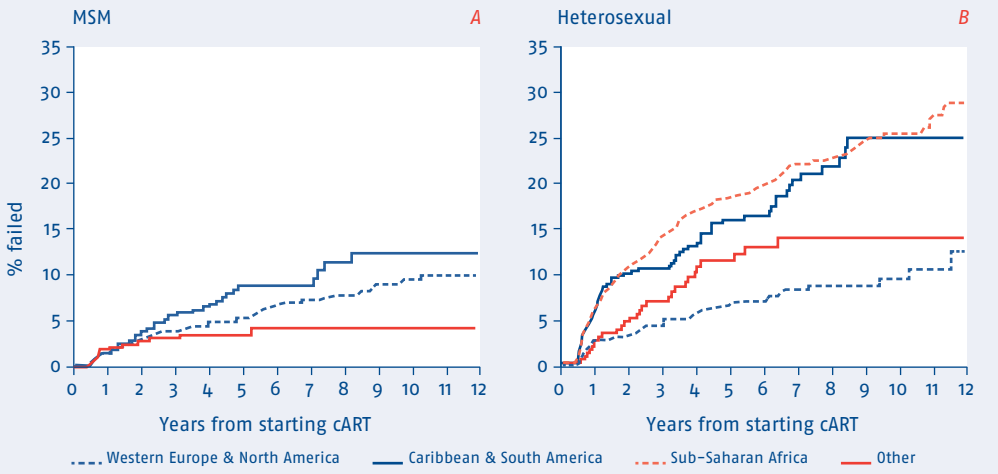



*Table 2.4: Adjusted hazard ratios (95% CI) of time to virological failure.*

| | HR (95% CI) | (Overall) P-value |
|---|---|---|
| Transmission risk group | | (0.001) |
| MSM | 1.00 | |
| Heterosexual | 1.36 (1.12-1.65) | 0.002 |
| IDU | 1.79 (1.18-2.70) | 0.006 |
| Region of origin | | (<0.0001) |
| Netherlands / Western Europe / North America | 1.00 | |
| Caribbean / South America | 1.82 (1.46-2.26) | <0.0001 |
| Sub-Saharan Africa | 2.12 (1.70-2.63) | <0.0001 |
| Age at the start (years) | | (<0.0001) |
| 16-29 | 1.47 (1.23-1.76) | <0.0001 |
| 30-39 | 1.00 | |
| 40-49 | 0.91 (0.75-1.10) | 0.32 |
| ≥50 | 0.85 (0.66-1.09) | 0.20 |
| CD4 cell count at the start (cells/mm$^3$) | | (<0.0001) |
| <50 | 1.82 (1.32-2.51) | 0.0003 |
| 50-200 | 1.60 (1.18-2.15) | 0.002 |
| 200-350 | 1.06 (0.78-1.43) | 0.73 |
| 350-500 | 1.00 | |
| >500 | 1.24 (0.83-1.85) | 0.29 |

| | HR (95% CI) | (Overall) P-value |
|---|---|---|
| HIV RNA at the start ($log_{10}$copies/ml) | | (<0.0001) |
| <4 | 0.85 (0.64-1.12) | 0.24 |
| 4-5 | 1.00 | |
| ≥5 | 1.47 (1.23-1.76) | <0.0001 |
| Year of starting | | (<0.0001) |
| 1999-2002 | 1.96 (1.58-2.43) | <0.0001 |
| 2003-2006 | 1.36 (1.12-1.67) | 0.002 |
| 2007-2009 | 1.00 | |
| 2010-2012 | 0.82 (0.61-1.11) | 0.21 |
| Starting regimen | | (<0.0001) |
| NNRTI | 1.00 | |
| PI | 1.66 (1.31-2.10) | <0.0001 |
| PI/r | 1.33 (1.13-1.57) | 0.0007 |
| NRTI only | 1.84 (1.31-2.57) | 0.0004 |
| Other | 1.37 (0.91-2.07) | 0.13 |

***Legend:*** *MSM=men who have sex with men; IDU=injecting drug user; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; PI/r=ritonavir boosted protease inhibitor; HR=hazard ratio; CI=confidence interval.*

In adjusted analyses, the risk of virological failure decreased with older age at the start of cART (*Table 2.4*). Those with a higher viral load at the start had an increased risk of failure. Patients starting with counts below 200 cells/$mm^3$ compared to those with higher counts had a significantly higher risk of failure. There was no significant difference in risk between starting between 350 and 500 CD4 cells/$mm^3$ and ≥500 (p=0.29). Starting with an unboosted PI, boosted PI, or a triple NRTI was associated with a higher risk of failure, and there was no evidence that differences in risk between drug classes had changed over time (test for interaction between starting year and starting regimen p=0.83). The risk of failure decreased with later calendar years of starting cART. Of note, the model was adjusted only for drug class, not individual regimens, suggesting that improvements within individual drug classes or other changes over time may have had a role in the decrease in risk. Risk of failure was not significantly different between men and women after adjustment for transmission risk group and region of origin.

## International collaborations

### The HIV-CAUSAL Collaboration:

Starting regimens containing 2 NRTI's combined with either efavirenz or nevirapine were compared for the 12-months change in CD4 cell count and virological failure (HIV RNA >50 copies/ml) at 12 months. Patients were ART-naïve at the start and started between 1998 and 2009. This analysis included data from SHM. Patients were censored when they started an ineligible drug. Models were adjusted for potential bias introduced by censoring via inverse probability weighting. Individuals on nevirapine regimens experienced a smaller 12-month increase in CD4 cell count by 11.5 cells/mm$^3$ and were 52% more likely to have virological failure at 12 months than those on efavirenz [69].

## Second-line cART

After confirmation of virological failure, therapy should be changed as soon as possible to avoid accumulation of resistance-associated mutations. The new regimen should contain at least 2, but preferably 3, fully active drugs. Apart from results of resistance testing, previous drug history should also be considered when selecting the new regimen because archived drug-resistance mutations may not be detected by standard drug-resistance tests [9]. The goal of second-line cART remains achieving durable suppression of plasma HIV-RNA to below 50 copies/ml [61], as it is much less likely, although appears to be possible, for drug-resistant strains to emerge below this level [67, 70, 71]. Persistent low level viraemia (defined as between 50 and 1000 copies/ml [72, 73], but also between 50 and 500 copies/ml [72, 73] is associated with drug resistance, although it is not clear whether this is due to the emergence of archived resistant viruses or viruses with new resistance-associated mutations generated during viral evolution [72, 73].

*Chapter 3* contains a more general discussion of virological failure and transmission of drug-resistant virus. Our objective in this section of *Chapter 2* is to describe characteristics of patients who start second-line cART after experiencing first-line virological failure, to describe the proportion of patients who also experienced virological failure on their second-line cART and to investigate characteristics associated with a poor virological response.

Of the 790 patients who met the definition for virological failure (see previous section on long-term virological response; note that the definition allows that patients could have modified their original initial cART regimen for reasons other than virological failure), 182 had not changed the regimen during follow-up (69 patients [38%] of these failed in or after 2011, 9 patients died, 17 were lost to follow-up), and a further 85 patients had managed to suppress viral load to levels below 200 copies/ml before a switch to a new regimen (most frequently recorded reasons for switching in this last group were toxicity [27%] and simplification [31%]). The characteristics of the remaining 523 patients who did change to a new second-line cART are shown in *Table 2.5*.

***Table 2.5:*** *Baseline characteristics of patients at the start of second-line cART, after virological failure of first-line cART.*

| | N | % |
|---|---|---|
| Total patients starting 2nd line cART | 523 | 100.0 |
| Male gender | 355 | 67.9 |
| Transmission risk group | | |
| MSM | 198 | 37.9 |
| Heterosexual | 268 | 51.2 |
| Other | 57 | 10.9 |
| Region of origin | | |
| Netherlands | 187 | 35.8 |
| Caribbean / South America | 90 | 17.2 |
| Western Europe / North America | 28 | 5.4 |
| Sub-Saharan Africa | 186 | 35.6 |
| Other | 32 | 6.1 |
| AIDS diagnosis prior to start 2nd line | 211 | 40.3 |
| HCV | | |
| Negative | 436 | 83.4 |
| Positive | 46 | 8.8 |
| Unknown | 41 | 7.8 |
| HBV | | |
| Negative | 441 | 84.3 |
| Positive | 60 | 11.5 |
| Unknown | 22 | 4.2 |
| Year start 2nd line cART | 53 | 10.1 |
| 1999-2002 | | |
| 2003-2005 | 135 | 25.8 |
| 2006-2008 | 151 | 28.9 |
| 2009-2013 | 184 | 35.2 |
| | **Median** | **IQR** |
| Age at starting 2nd line cART (years) | 38.2 | 30.8-46.3 |
| Years since start cART | 2.7 | 1.3-4.7 |
| Years since failure | 0.3 | 0.1-1.0 |
| CD4 cell count at starting cART (cells/mm$^3$) | 130 | 50-240 |
| CD4 cell count at failure (cells/mm$^3$) | 330 | 190-470 |
| CD4 cell count at start 2nd line cART (cells/mm$^3$) | 280 | 167-420 |
| HIV-RNA at starting cART ($log_{10}$copies/ml) | 5.00 | 4.70-5.44 |
| HIV-RNA at failure ($log_{10}$copies/ml) | 3.59 | 2.89-4.54 |
| HIV-RNA at start 2nd line cART ($log_{10}$copies/ml) | 3.99 | 3.00-4.73 |

***Legend:*** *cART=combination antiretroviral therapy; MSM=men who have sex with men; HCV=hepatitis C virus; HBV=hepatitis B virus; IQR=interquartile range*

The majority were men (68%), and there were more heterosexually infected patients than MSM. The median age at the start was 38 years. Second-line cART was begun with a median of 280 CD4 cells/mm$^3$ and 3.99 $\log_{10}$ HIV RNA copies/ml. The median time between the first cART initiation and the start of second-line cART and was 2.7 years, and it was 4 months (IQR 1-12) between the time of virological failure and the start of the second-line cART.

Compared to the characteristics of all patients who started cART (described in *Table 2.1*), the median CD4-cell count at the start of cART in patients who started second-line cART after first-line virological failure was lower (230 vs 130 cells/mm$^3$). This is because virological failure was more frequent before 2005 when cART was initiated at lower CD4-cell counts, and it was also more frequent amongst patients from sub-Saharan Africa, the Caribbean and South America, as they generally had lower median CD4-cell counts at the start of cART. In total, 63 patients used mono- or dual therapy at the time of virological failure. After having started first-line cART, these patients switched to mono- or dual therapy during follow-up for the following recorded reasons: decision of the patient or poor compliance in 20 patients (32%), end of pregnancy in 18 patients (29%), and toxicity in 8 patients (13%).

In total, 179 patients started a new NRTI, 182 started 2 new NRTI's and 12 patients started 3 new NRTI's. *Table 2.6* gives an overview of switching patterns for the 421 patients who started a new PI or NNRTI as part of second-line cART. In 33 patients raltegravir was included in the second-line cART and was the only change made in 5 patients. Maraviroc was started in 5 other patients. Changing the same drug from administration as a separate pill to part of a fixed-dose combination was not considered the start of a new drug.

***Table 2.6:*** *Overview of regimen changes in PI or NNRTI after failure of first-line cART.*

| | 2nd line cART | | | | |
|---|---|---|---|---|---|
| **Regimen at 1st line failure** | **NNRTI N (%)** | **PI N(%)** | **PI/r N(%)** | **NNRTI+PI N(%)** | **Total** |
| NNRTI-based cART | 11 (6) | 9 (5) | 138 (81) | 12 (7) | 170 (40) |
| PI-based cART | 16 (33) | 3 (6) | 21 (43) | 9 (18) | 49 (12) |
| PI/r-based cART | 21 (31) | 4 (6) | 37 (54) | 6 (9) | 68 (16) |
| 3 NRTI-based cART | 40 (52) | | 19 (25) | 18 (23) | 77 (18) |
| Mono/dual | 22 (43) | 4 (8) | 20 (39) | 8 (10) | 54 (13) |
| Other | 1 (33) | | 2 (67) | | 3 (1) |
| Total | 111 (26) | 20 (5) | 237 (56) | 53 (13) | 421 |

***Legend:*** *NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor, PI/r= ritonavir boosted protease inhibitor; NRTI=nucleoside reverse transcriptase inhibitor.*

When a viral sequence for resistance testing was available in the database (in 325, or 62%, of patients), we used a genotypic resistance interpretation algorithm [74] 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.

Of the 325 patients tested, 134 (41%) did not have or had only low-level resistance, 187 (58%) had intermediate or high-level resistance to NRTI (mainly to emtricitabine or lamivudine, see *Chapter 3*), 4 (1%) had both PI- and NNRTI-associated mutations, and 18 (6%) had mutations associated with all three major drug classes.

We scored the new second-line cART as the maximum score of all of the individual drugs in the second-line combination. According to this score, 184 (56%) patients harboured viruses with intermediate or high-level resistance to at least 1 of the NRTI's (also mainly emtricitabine or lamivudine) in the new second-line cART. Only five patients had intermediate or high-level resistance to one of the PI's or NNRTI's in the new regimen.

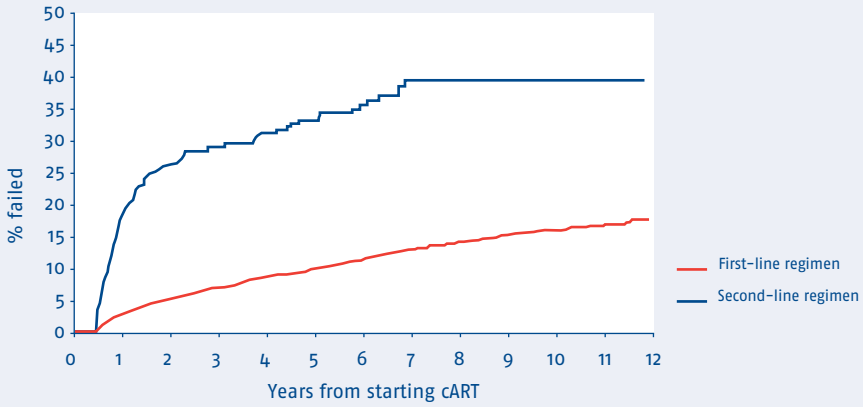
## Failure of second-line cART

Out of 523 patients, 145 (13%) met the definition for virological failure (confirmed viral load higher than 200 copies/ml whilst at least 24 weeks on cART) on second-line cART. *Figure 2.6* shows that within 1 year after starting second-line cART, 17% of the patients had again experienced virological failure. *Figure 2.6* also shows that the rate of failure on second-line cART was higher than that on first-line cART. This lower virological success rate of second-line regimens may be explained by cross-resistance between antiretroviral drugs used in consecutive regimens, but it is likely also due to a selection of patients with less than optimal adherence, which made them fail on first-line cART. In an adjusted Cox regression analysis, region of origin was the only variable associated with the risk of virological failure of the second-line cART. Patients from the Caribbean or South America (HR 1.97, 95% CI 1.22, 3.22; p=0.006) and from sub-Saharan Africa (HR 2.25, 95% CI 1.51, 3.34; p<0.0001) had a higher risk of virological failure of second-line cART, as compared to patients from western Europe (including the Netherlands) and North America.

Having a CD4-cell count of 500 cells/mm$^3$ or higher was borderline significantly associated with a longer time to failure compared to a CD4 count of 200 cells/mm$^3$ or less (HR 0.56, 95% CI 0.30-1.04, p=0.07). Other characteristics that have been found to be associated with virological failure, such as a high plasma HIV-1 concentration and the time between first-line virological failure and start of the second regimen, were not significantly associated with second-line failure in our analysis.

The risk was not significantly different between patients with or without an available resistance test (p=0.59). This may partly be explained by the currently incomplete collection of data on resistance.

*Figure 2.6: Kaplan-Meier estimates of the percentage of patients failing first-line cART or second-line cART.*




## International collaborations

### The Pursuing Later Treatment Options II (PLATO II) project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) Group:

The PLATO II project team estimated the incidence and prevalence of triple-class virological failure (TCVF), defined as failure of at least two NRTIs, one NNRTI and one PI/r. Data of the SHM are included in the analysis that includes patients starting ART between 2000 and 2009. The incidence of TCVF increased from 3.9 per 1,000 person-years of follow-up (95% CI 3.7 to 4.1) in 2000 to 8.8 (8.5 to 9.0) per 1,000 person-years in 2005, but then declined to 5.8 (5.6 to 6.1) per 1,000 person-years of follow-up by 2009. The prevalence was 0.3% in 2000 and then increased to 2.4% in 2005. However, since 2005, TCVF prevalence seems to have stabilized and has remained below 3%. The introduction of improved regimens and better overall HIV care is likely to have contributed to these trends.

Another report by the same group investigated trends in virological and clinical outcomes in patients with TCVF. The proportion of patients with virological response after TCVF increased from 19.5% in 2000 to 57.9% in 2009 (adjusted p<0.0001). The incidence of AIDS decreased from 7.7 per 100 person-years in 2000-2002 to 2.3 in 2008 and 2009 (adjusted p<0.0001). Mortality decreased from 4.0 per 100 person-years between 2000 and 2002 to 1.9 in 2007 and 1.4 in 2009 (adjusted p=0.22).The improvement in prognosis in patients after extensive failure with drugs from the three original drug classes was probably mainly driven by the availability of newer drugs with better tolerability, ease of use and limited cross-resistance, suggesting the public health benefit of the introduction of new drugs [75, 111].

## Immunologic response

After initiation of cART, most individuals suppress HIV viral load to levels below the detection limit of HIV RNA assays, and this is accompanied by an increase in CD4-cell count. Failure to suppress viraemia is associated with poorer recovery of CD4-cell count [76, 77]. However, incomplete immunological recovery may also occur when plasma viral load is sustained to levels below the limit of detection [78]. In the general population, a low CD4/CD8 ratio is associated with immunosenescence and all-cause mortality [79-81]. In untreated HIV infection, this ratio has been shown to independently predict immune restoration [82], AIDS [83] and non-AIDS-defining disease [84]. As the clinical benefit of cART is strongly related to the level of recovery of the immune status, in particular CD4-cell count (*Chapter 4*) [85-90], we report on the immune status in the treated population in the cART era, including descriptions of long-term CD4-cell count and CD4/CD8 ratio responses after the start of cART and of patients showing incomplete immunological recovery 3 years after having started cART.

## Immune status in the treated population by calendar year

*Figure 2.7* shows the immune status of patients in each calendar year after the start of cART. After starting cART, the percentage of patients with counts <350 cells/mm$^3$ (a level that puts them at higher risk of both AIDS and non-AIDS co-morbidity) dropped from 74% in 1996 to 15% in 2012. Likewise, the number of patients with CD4-cell counts <350 cells/mm$^3$ at the end of each calendar year decreased from 714 in 2003 to 446 in 2011. Due to currently incomplete data collection, the absolute number for 2012 is lower than that for 2011 and should be interpreted with caution. The trend of starting cART at higher CD4-cell counts, which was observed from 2007 onward, partly explains the drop in the absolute number of patients with low CD4-cell counts at the end of each calendar year.

*Figure 2.7: Last available CD4-cell count in each calendar year after the start of cART. The percentage (A) and the absolute number (B) of patients with CD4-cell counts are shown. For each patient the last available CD4-cell count between July and December of each year and after the start of cART was selected.*

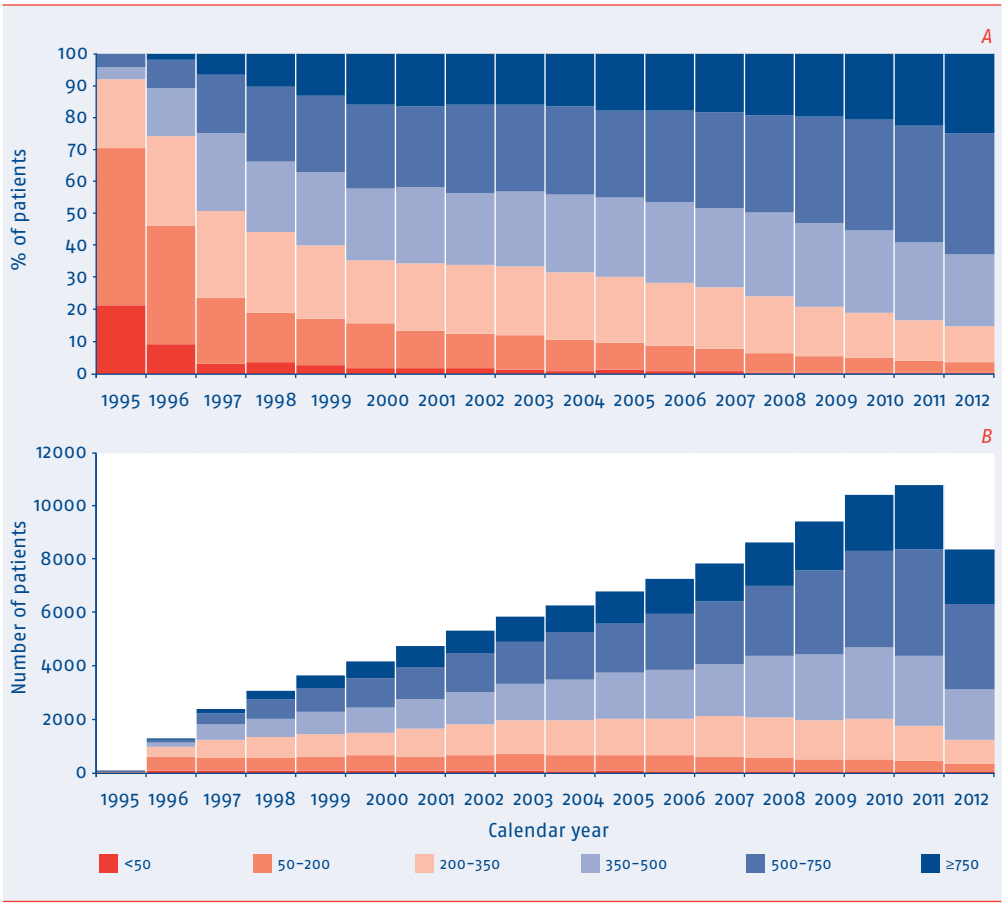
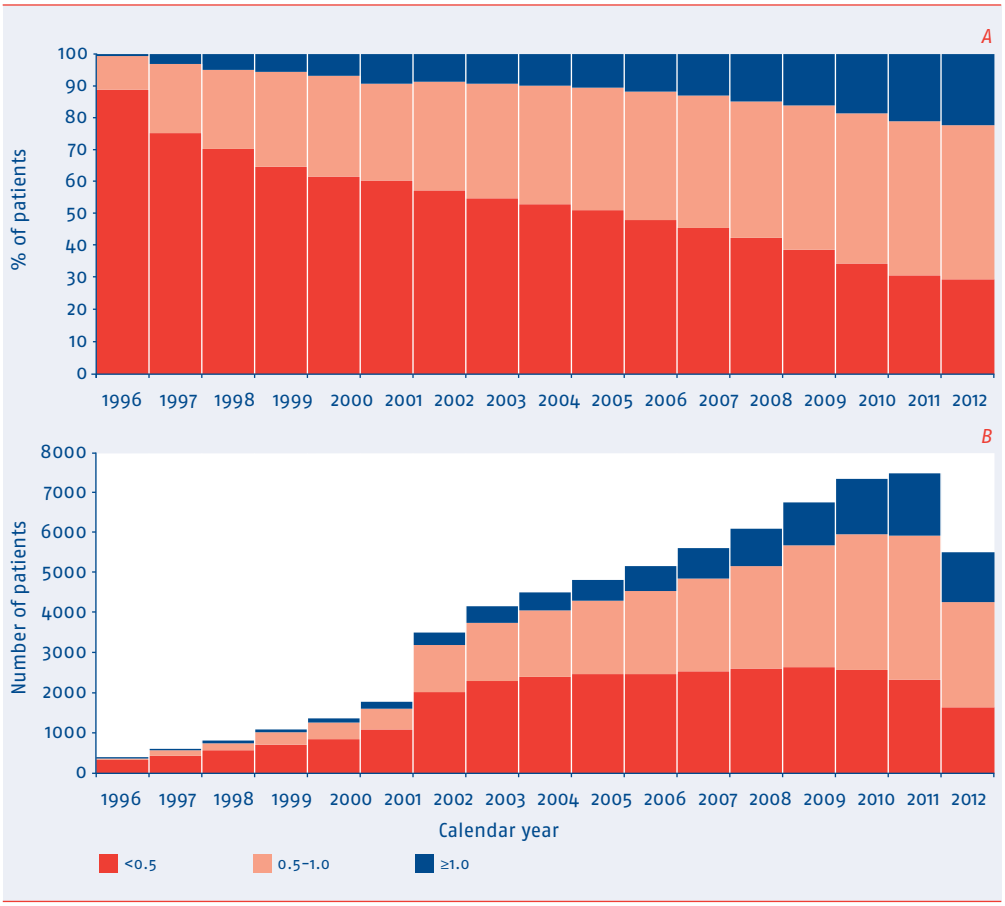



*Figure 2.8* shows that the percentage of patients with a CD4/CD8 ratio of 1 or higher increased from 1% in 1996 to 22% in 2012.

*Figure 2.8: Last available CD4/CD8 ratio in each calendar year after the start of cART. The percentage (A) and the absolute number (B) of patients with CD4/CD8 ratios. For each patient the last available CD4/CD8 ratio between July and December of each year and after the start of cART was selected.*

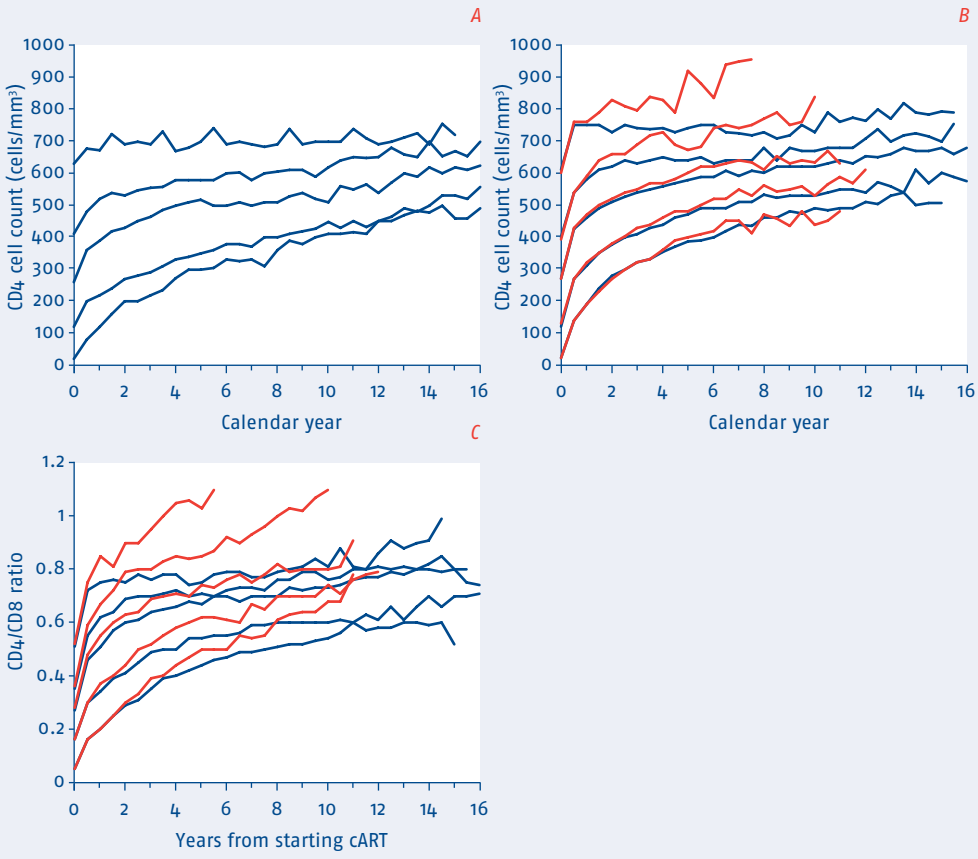


## Longitudinal CD4-cell count changes after starting cART

Out of the 17,334 patients (including both ART-naive and ART-experienced patients) who first began cART, a CD4-cell count at the start of therapy or thereafter was available for 15,722 (99.6%), and those 15,722 patients were included in further analyses. In this group, we studied CD4-cell count changes after starting cART, irrespective of whether patients had one or more therapy interruptions or were continuously on cART. In patients who received antiretroviral mono- or dual therapy before starting cART, median CD4-cell counts increased from 200 cells/mm$^3$ (IQR, 80-340) at the start to 320 CD4 cells/mm$^3$ (IQR, 180-490) at 1 year, 450 (IQR, 280-640) at 5 years, 510 (IQR, 330-720) at 10 years and 575 (IQR, 390-790) at 15 years.

The median CD4-cell count at the start of cART in ART-naïve patients was slightly higher compared to that in ART-experienced patients, with a median of 230 cells/mm$^3$ (IQR, 100-336) at the start of cART, and greater increases were also shown (to 410 [IQR, 270-570] at 1 year, 520 [IQR, 380-700] at 5 years, 580 [IQR, 420-780] at 10 years, and 640 [IQR, 480-854] at 15 years). *Figure 2.9* shows the median CD4-cell count after the start of cART stratified by the CD4-cell count at the start of cART. In the ART-experienced group (*Figure 2.9.A*), median CD4-cell counts for patients starting cART with <50 and 50-200 cells/mm$^3$ seemed to converge after 12 years. In the group of patients who started with low CD4-cell counts, this may partly be due to the death of patients with a poor immunological response after starting treatment, so that only patients surviving and doing well remained in follow-up.

*Figure 2.9: Median CD4-cell count according to the count at the start of combination antiretroviral therapy (cART) in ART-experienced patients (A) and ART-naïve patients (B) and CD4/CD8 ratio in ART-naïve patients (C), all stratified by CD4-cell count at the start of cART (<50, 50-200, 200-350, 350-500 and ≥500 cells/mm³). Blue lines in plot A and B show the median CD4-cell counts and CD4/CD8 ratio in plot C in all patients after starting cART, including patients on cART and those experiencing a therapy interruption. Red lines in plot B and C show the median CD4-cell counts and CD4/CD8 ratio for patients with an initial suppression to <50 copies/ml within 9 months after starting cART and with plasma HIV RNA concentration levels <50 copies/ml thereafter. In this subgroup, CD4-cell counts and CD4/CD8 ratio 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 40 patients.*



To study the maximum capacity of cART to restore CD4-cell counts, we performed an additional analysis that was restricted to therapy-naive patients who experienced sustained viral suppression (<100 copies/ml) on cART. Only patients were included who had reached HIV RNA levels of <100 copies/ml within 9 months after the start of cART. Patients were censored after virological failure (defined as two consecutive viral-load measurements >200 copies/ml), after a therapy interruption of 2 weeks or more or after the start of immunosuppressive therapy (chemotherapy or interferon). There was no restriction on the length of the period HIV RNA was undetectable in patients after initial suppression. This group, therefore, represents a highly selective group of patients with CD4-cell count changes showing the best possible response to cART. Median CD4 counts at 10 years were 440 cells/mm$^3$ for patients starting with <50 cells/mm$^3$, 530 cells/mm$^3$ for those starting between 50 and 200 cells/mm$^3$, 635 cells/mm$^3$ for those starting between 200 and 350 cells/mm$^3$ and 840 cells/mm$^3$ for patients starting between 350-500 cells/mm$^3$ (*Figure 2.9.B*, red lines). Because the number of patients remaining in follow-up was less when cART was started at a CD4 count of 500 cells/mm$^3$ or higher, data in this subgroup are reported up to only 7.5 years. 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 remaining virologically suppressed on cART. Median CD4-cell counts for subgroups of patients within each of the five CD4-cell count categories at the start of cART did not converge. For all patients starting cART with <50 CD4 cells/mm$^3$, the median CD4-cell counts (blue lines) did not differ greatly from the median CD4-cell counts for the restricted populations with suppressed viral load (red lines). The difference in median CD4-cell counts over time between all patients and those with a sustained suppressed viral load became more pronounced as the CD4-cell counts at the start of cART were higher. This may be because a substantial proportion of patients starting cART within the highest CD4-cell count strata either interrupted therapy or did not maintain a viral load <50 copies/ml whilst on therapy, as shown earlier.

*Figure 2.9.C* shows median CD4/CD8 ratio responses according to the 5 baseline CD4 cell count strata, <50, 50-200, 200-350, 350-500 and ≥500 cells/mm$^3$. Patients with lower CD4 cell counts at the start of cART also had lower CD4/CD8 ratios at the start. Similar to the CD4-cell count response, median CD4/CD8 ratios during sustained virological suppression on cART (*Figure 2.9.C*, red lines) in the 5 baseline CD4-cell count strata did not seem to converge. Importantly, the ability to achieve a CD4/CD8 ratio of 1 or higher seemed to be strongly related to the CD4-cell count at the start of cART. Median CD4/CD8 ratio reached levels higher than 1 after 3.5 years of suppressive cART when counts at the start were 500 cells/mm$^3$ or higher and after 8 years when counts were 350 to 500 cells/mm$^3$. When cART was started at counts below 350 cells/mm$^3$, median CD4/CD8 ratio levels of 1 or higher were not reached during 11 years of virologically suppressive cART. Although lower CD4/CD8 ratios have been suggested to be associated with increased immune activation markers during sustained viral suppression [91] and with subclinical atherosclerosis [92], the clinical significance of these findings remains to be determined.

In a mixed-effects analysis including all CD4-cell counts obtained during virologically suppressive cART, the following characteristics were associated with a smaller CD4-cell count recovery: female gender (estimated difference at 5 years with a male patient 65 cells/mm³), hepatitis C virus (HCV) co-infection at the start of cART (difference with HCV negative at 5 years 33 cells/mm³), lower HIV RNA at the start of cART (difference between 4-5 $\log_{10}$ copies/ml and ≥5 $\log_{10}$ copies/ml 37 cells/mm³), patients originating from sub-Saharan Africa (difference between patients from western Europe and North America, 63 cells/mm³), patients never having smoked (difference between ever versus never smoking, 38 cells/mm³), and patients older than 50 years at the start of cART (difference between those <50 years, 45 cells/mm³). Furthermore, there was evidence that the difference according to age depended on the CD4-cell count at the start of cART. The difference was larger when cART was initiated at lower CD4-cell counts (99 cells/mm³ when started at <50 cells/mm³, 39 cells/mm³ at 50-200 cells/mm³, 33 cells cells/mm³ at 200-350 cells/mm³, and 13 cells/mm³ at 350-500 cells/mm³; interaction between CD4-cell count at the start of cART and age p<0.0001).

## Incomplete immunological recovery

Incomplete recovery of CD4-cell counts despite long-term successfully suppressed viral load during cART is associated with an increased risk of mortality, AIDS and non-AIDS-defining diseases compared to achievement of higher counts [78, 93, 94]. We investigated the CD4-cell count response in patients who started cART with 350 cells/mm³ or less, were continuously on cART at 2 and 3 years (allowing for therapy interruptions less than 2 weeks) and were virologically successfully treated at 2 and 3 years (defined as having suppressed viral load of 100 copies/ml or less within 9 months from starting and not having had a confirmed viral load of more than 100 copies/ml after initial suppression, allowing for single blips between 100 and 500 copies/ml). The CD4-cell count between 1.5 and 2 years (closest to 2 years) and between 2.5 and 3 years (closest to 3 years) were selected. The median CD4-cell count at 2 years was 350 cells/mm³ (IQR 243-470) and at 3 years 400 (290-530). *Table 2.7* shows the distribution of CD4-cell counts at 2 and 3 years after starting cART, according to whether counts at the start of cART were below 200 or 350 cells/mm³.

***Table 2.7:** Number and percentage of patients with <200 and <350 CD4 cells/mm³ at the start of cART and their CD4-cell count at 2 years and at 3 years.*

| | | CD4 cell count at the start of cART (cells/mm³) | | |
|---|---|---|---|---|
| | | <200 | | <350 |
| CD4 cell count at 2 / 3 years | 2 years | 3 years | 2 years | 3 years |
| <200 | 265 (14%) | 120 (8%) | 273 (7%) | 129 (4%) |
| 200-350 | 658 (36%) | 476 (31%) | 840 (22%) | 587 (20%) |
| 350-500 | 543 (29%) | 484 (31%) | 1,218 (32%) | 889 (30%) |
| 500-750 | 312 (17%) | 376 (24%) | 1,195 (32%) | 1,093 (36%) |
| ≥750 | 71 (4%) | 90 (6%) | 259 (7%) | 307 (10%) |
| Total | 1,849 | 1,546 | 3,785 | 3,005 |

At 3 years, 31% of patients who started cART with <200 and 20% of those who started with <350 CD4 cells/mm$^3$ still had values <350 cells/mm$^3$ and thus remained at an increased risk for an AIDS or non-AIDS-defining event.

Independent risk factors significantly associated with still having <200 CD4 cells/mm$^3$ after 3 years of virologically suppressive cART, when cART was started with <200 cells/mm$^3$, were older age, lower CD4-cell count at the start of cART, HIV RNA <100,000 copies/ml at the start, transmission risk group, and having started cART during or before 2002 (*Table 2.8*). Starting cART between 1999 and 2002 was associated with an increased risk of incomplete immunological recovery as compared to starting between 2007 and 2009. There was no significant difference in the risk of incomplete recovery between starting with a boosted PI or an NNRTI-based regimen.

***Table 2.8:*** *Adjusted odds ratios (OR) of the risk of maintaining a CD4-cell count <200 cells/mm$^3$ after 3 years of virologically successful cART in patients starting treatment at <200 CD4 cells/mm$^3$.*

| | OR (95% CI) | (Overall) p-value |
|---|---|---|
| Gender | | |
| Male | 1.00 | |
| Female | 0.59 (0.32-2.07) | 0.08 |
| Age (per 5 years older) | 1.26 (1.14-1.40) | <0.0001 |
| CD4-cell count at the start of cART (per 50 cells/mm$^3$ increase) | 0.54 (0.44-0.66) | <0.0001 |
| Region of origin | | (0.44) |
| Netherlands | 1.00 | |
| Caribbean & South America | 0.92 (0.45-1.88) | 0.82 |
| Other | 0.53 (0.22-1.31) | 0.17 |
| Sub-Saharan Africa | 1.40 (0.73-2.69) | 0.32 |
| Western Europe / North America | 0.93 (0.43-2.03) | 0.86 |
| HIV RNA at the start of cART ($log_{10}$ copies/ml) | | (0.02) |
| <4 | 1.65 (0.77-3.51) | 0.19 |
| 4-5 | 1.00 | |
| ≥5 | 0.59 (0.37-0.93) | 0.02 |
| Initial regimen | | (0.28) |
| NNRTI | 1.00 | |
| PI | 1.07 (0.44-1.62) | 0.87 |
| PI/r | 0.97 (0.62-1.53) | 0.89 |
| 3 NRTI | 1.31 (0.36-4.75) | 0.68 |
| Other | 2.28 (1.06-4.92) | 0.04 |

| | OR (95% CI) | (Overall) p-value |
|---|---|---|
| Transmission risk group | | (0.007) |
| Homosexual | 1.00 | |
| Heterosexual | 1.32 (0.77-2.26) | 0.31 |
| Injecting Drug User | 4.31 (1.64-11.37) | 0.003 |
| Year of starting | | (0.18) |
| 1999-2002 | 1.75 (1.03-1.97) | 0.04 |
| 2003-2006 | 1.00 (0.61-1.64) | 0.99 |
| 2007-2012 | 1.00 | |

## Therapy switches and incidence of toxicity-driven regimen change during the first 3 years after the start of cART

Antiretroviral therapy may be associated with adverse clinical events and laboratory toxicities. This may lead to reduced adherence and treatment discontinuation, which are major reasons for treatment failure and emergence of antiretroviral-drug resistance [95-97]. In this section of *Chapter 2* we report on trends over time in treatment switches and especially treatment-limiting toxicities during the first 3 years after starting cART.

### Discontinuation of the initial regimen

Of the 17,334 patients who started cART, 12,994 discontinued the initial regimen. There was a trend over time towards a longer interval before discontinuation of the initial cART regimen, as *Figure 2.10* shows. However, a lower percentage of patients starting cART between 2010 and 2012 were still on the initial regimen 3 years after starting cART compared to those having started cART between 2007 and 2009. The percentage of patients still on the initial cART regimen 3 years after starting was 20% (95% CI, 19-22%) for those starting during 1995-1997, 29% (95% CI, 27-31%) during 1998-2000, 32% (95% CI, 30-34%) during 2001-2003, 36% (95% CI, 34-38%) during 2004-2006, 52% (95% CI, 50-54%) during 2007-2009, and 43% (95% CI, 41-46%) for those starting in or after 2010.

*Figure 2.10: Kaplan–Meier estimates of the percentage of patients still on the initial combination antiretroviral therapy (cART) regimen by period of initiation. Planned switches according to study protocol (in trial participants) and same-drug changes from individual components to part of fixed-dose co-formulations were not counted as a regimen change.*

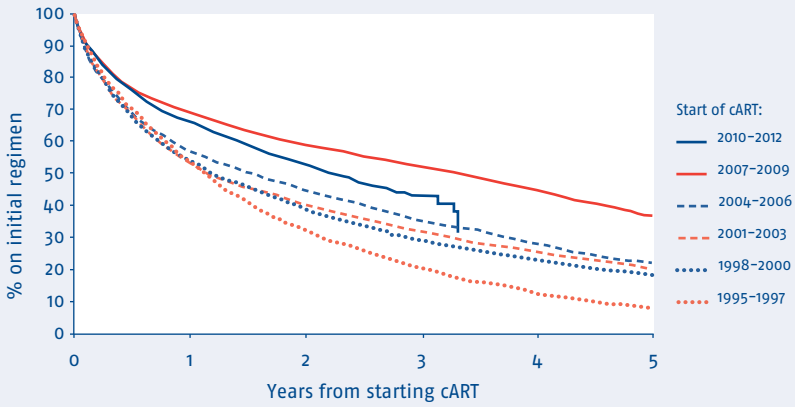
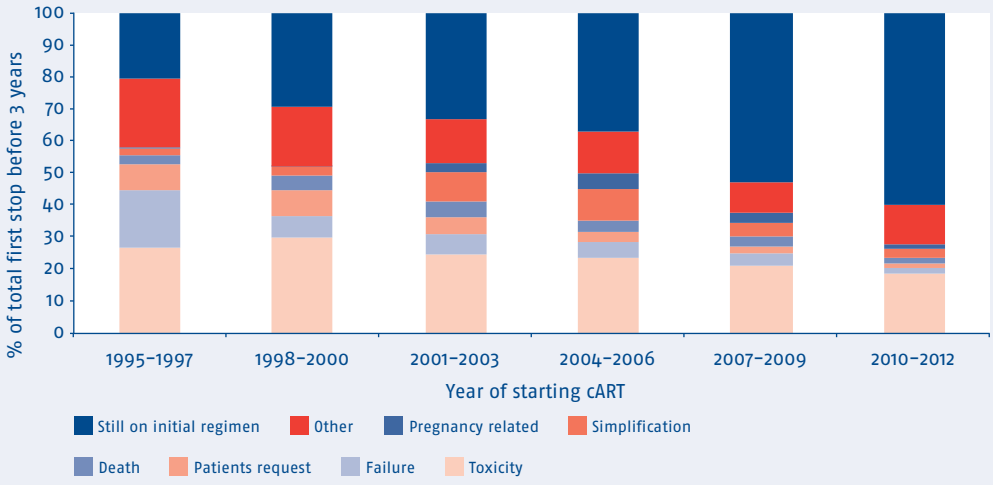



*Figure 2.11: Relative distribution of reasons for stopping or switching at least one of the drugs in the regimen within 3 years of cART initiation according to the starting year of cART. (Failure includes virological, immunological and clinical failure. Other reasons for stopping include new medication available, pharmacokinetic reasons, precautionary reasons [such as a high cardiovascular risk profile] and problems with adherence.)*



Overall, 10,316 patients discontinued the initial regimen within 3 years. The most common reasons for discontinuing were: toxicity (40%), treatment failure (11%), simplification (8%) and patient request (7%), which are similar to results reported by others [98, 99]. *Figure 2.11* shows trends over time in reasons for stopping. There was an increasing proportion of patients who were still on the initial regimen at 3 years. Figures for patients starting between 2010 and 2012 should be interpreted with caution, as most of these patients had not yet had 3 years of follow-up. Failure was the reason for stopping in 22% amongst those who had initiated cART between 1995 and 1997, but was lower thereafter (4% of all stops within 3 years of initiating cART between 2007 and 2009 were due to failure). Over time, the proportion of patients discontinuing their first regimen because of toxicity has gradually declined, but it still remains the major reason for stopping.

## International collaborations

### The Antiretroviral Therapy Cohort Collaboration (ART-CC):

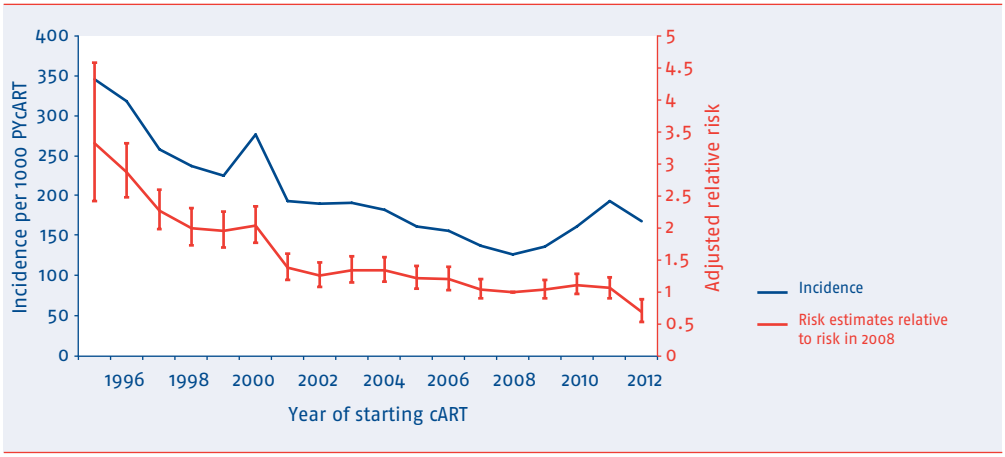
ART-CC estimated the incidence and risk factors for modifications to the first antiretroviral therapy regimen, treatment interruption and death. This analysis included data from the SHM. The study included regimens containing at least 2 NRTI's and either an NNRTI or boosted PI that was started in 2002-2009. The 3-year cumulative percentages of modification, interruption and death (prior to modification or interruption) were 47, 12 and 2%, respectively. Rates of modification and interruption were particularly high in the first year of ART. In adjusted analyses, rates of interruption were highest for injecting drug users and lowest for men having sex with men and higher for patients starting ART with CD4-cell counts above 350 cells/mm$^3$ than for other patients. Lower CD4-cell counts were associated with higher rates of modifications to another drug class or within the same drug class. Decreased rates of substitutions or switches to nonstandard regimens in recent years may be linked to greater use of well tolerated once-daily drugs [99].

### Toxicity-driven therapy changes

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 toxicity-driven therapy changes during the first 3 years of cART. Of note, these changes are importantly influenced by the extent to which options became available over time to replace regimen components associated with particular toxicities by less toxic alternatives.

During the first 3 years after the start of cART, patients were followed for a total of 41,571 person-years (PY), 97.7% of which totalled 40,612 person-years on cART (PYcART). The overall incidence of toxicity-driven regimen changes was 198 (95% CI, 194-203) per 1,000 PYcART. Patients could change the regimen more than once. During follow-up, 11,780 of the 17,334 patients (68.0%) did not change the regimen because of toxicity. The maximum number of changes because of toxicity in a single patient was 14.

*Figure 2.12: Toxicity-driven changes in therapy during the first 3 years after the start of cART. The incidence per 1,000 PYcART for each starting year of cART (blue line) and adjusted risk estimates (red line, reference year is 2008, vertical lines are 95% confidence intervals) obtained with logistic regression models including age, gender, region of origin, transmission risk group, weight, time after starting cART (0-6, 6-12, 12-24 and 24-36 months), HCV co-infection status, CD4 cell count and HIV RNA at the start of cART, initial regimen, and whether cART was started during primary infection.*




*Legend: cART=combination antiretroviral therapy; PYcART=person-years on cART during the first 3 years following the start of cART; HCV=hepatitis C virus.*

The incidence was highest (508 per 1,000 PYcART) during the first 3 months after the start of cART; it declined to 220 per 1,000 PYcART between 3 and 6 months, 178 per 1,000 PYcART between 6 and 12 months, and 128 per 1,000 PYcART between 24 and 36 months ($p<0.0001$). The incidence of toxicity-driven therapy changes during the first 3 years after cART initiation declined from 2000 to 2008 (*Figure 2.11*). The increase thereafter (from 2009 onwards) can be largely attributed to patients not yet having 3 years of follow-up after starting cART. In analyses adjusted for time after starting cART and other confounders, the risk for a toxicity-driven therapy change was not significantly different for those starting between 2010 and 2012 compared to those starting between 2007 and 2009 (*Figure 2.11* and *Table 2.9*).

*Table 2.9: Adjusted relative risk for toxicity-driven changes in therapy during the first 3 years after the start of cART.*

| | RR (95% CI) | (Overall) p-value |
|---|---|---|
| Gender | | |
| Male | 1.00 | |
| Female | 1.39 (1.28-1.51) | <0.00001 |
| Age (years) | | (<0.0001) |
| <30 | 1.00 (0.92-1.08) | 0.99 |
| 30-40 | 1.00 | |
| 40-50 | 1.11 (1.05-1.18) | 0.0002 |
| 50-60 | 1.16 (1.08-1.25) | 0.0001 |
| ≥60 | 1.29 (1.15-1.44) | 0.0000 |
| CD4-cell count at the start of cART (cells/mm$^3$) | | (0.03) |
| <200 | 0.96 (0.91-1.01) | 0.12 |
| 200-500 | 1.00 | |
| ≥500 | 1.09 (0.99-1.19) | 0.07 |
| Years after starting cART (months) | | (<0.0001) |
| 0-3 | 1.00 | |
| 3-6 | 0.43 (0.39-0.46) | <0.00001 |
| 6-12 | 0.33 (0.31-0.35) | <0.00001 |
| 12-24 | 0.25 (0.24-0.27) | <0.00001 |
| 24-36 | 0.19 (0.17-0.20) | <0.00001 |
| HIV RNA at the start of cART ($log_{10}$ copies/ml) | | (0.006) |
| <4 | 0.88 (0.81-0.95) | 0.003 |
| 4-5 | 1.00 | |
| ≥5 | 0.94 (0.89-0.99) | 0.04 |
| Initial regimen | | (<0.0001) |
| NNRTI | 1.00 | |
| PI | 0.83 (0.76-0.90) | <0.00001 |
| PI/r | 1.40 (1.32-1.48) | <0.00001 |
| 3 NRTI | 1.89 (1.71-2.09) | <0.00001 |
| Other | 2.22 (1.98-2.49) | <0.00001 |
| Transmission risk group | | (<0.0001) |
| Homosexual | 1.00 | |
| Heterosexual | 0.76 (0.65-0.88) | 0.0003 |
| Injecting drug users | 0.86 (0.80-0.92) | <0.00001 |
| Year of starting | | (<0.0001) |
| 1995-2000 | 2.05 (1.88-2.24) | <0.00001 |
| 2001-2003 | 1.26 (1.15-1.39) | <0.00001 |
| 2004-2006 | 1.20 (1.09-1.32) | 0.0002 |
| 2007-2009 | 0.99 (0.90-1.08) | 0.82 |
| 2009-2012 | 1.00 | |

| | RR (95% CI) | (Overall) p-value |
|---|---|---|
| Previous switch for toxicity | 1.42 (1.37–1.48) | <0.00001 |
| ART-naive at the start | 0.90 (0.83–0.96) | 0.003 |
| HCV-positive at the start | 1.25 (1.13–1.37) | <0.00001 |
| Start during primary infection | 1.22 (1.11–1.35) | 0.0001 |

***Legend:*** *RR=relative risk; CI=confidence interval.*

The risk was 39% higher in women than in men, independent of weight at the start of cART. The risk of toxicity was 9% (95% CI 0.99-1.19, p=0.07) greater when the CD4-cell counts at the start were 500 cells/mm$^3$ or higher, compared to 200-500 cells/mm$^3$. Independent of CD4-cell count at the start, initiation of cART during primary infection was also associated with an increased risk. Closer inspection of the association of a higher risk of a toxicity-driven therapy change with CD4-cell counts of 500 cells/mm$^3$ or higher revealed that this association was only significant among MSM (RR 1.17, 95% CI 1.05-1.31, p=0.005) but not amongst those with heterosexually acquired HIV (RR 0.70, 95% CI 0.36-1.35, p=0.29).

A previous toxicity-driven therapy change was associated with a 42% increased risk of a new toxicity-driven therapy change compared to no previous change. A possible explanation for this finding is that some patients may have had underlying conditions not accounted for in the analysis that may have predisposed them to drug toxicity [100]. The risk increased when patients were older than 40 years at the start of cART. Compared to patients aged 30 to 40 years, the risk was increased by 11%, 16% and 29% for patients aged 40 to 50, 50 to 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 [101]. Whether this is because of a higher likelihood of underlying predisposing conditions or the age-dependent pharmacokinetics of antiretrovirals requires further investigation [102]. There was no interaction between age and year of starting. Finally, patients with an HCV co-infection when cART was started had a 25% increased risk. MSM also had an increased risk compared to heterosexually infected patients, possibly because they have a higher awareness of other treatment options when they experience adverse effects than heterosexually infected individuals. The risk of a toxicity-driven therapy stop was also higher when cART was started with a boosted PI-based regimen as compared to an NNRTI-based regimen. However the risk changed over time as *Table 2.10* shows. Patients starting with a boosted PI-based regimen between 2010 and 2012 had a lower risk than those starting with an NNRTI-based regimen.

*Table 2.10: Adjusted relative risk (95% CI) of a toxicity-driven therapy stop within 3 years of starting cART, comparing NNRTI-based with boosted PI-based initial cART, according to year of starting cART.*

| | Starting year of cART | | | | |
|---|---|---|---|---|---|
| | 1998–2000 | 2001–2003 | 2004–2006 | 2007–2009 | 2010–2012 |
| NNRTI | 1.00 | 1.00 | 1.00 | 1.00 | 1.00 |
| Boosted PI | 2.31 (2.01–2.65) | 1.44 (1.26–1.66) | 1.34 (1.18–1.54) | 1.53 (1.35–1.74) | 0.70 (0.60–0.82) |

We have shown that although the incidence of toxicity-driven therapy changes has declined over time, toxicity remains the major reason for regimen change. In the next subsection we give an overview of adverse events associated with a toxicity-driven therapy changes

### Adverse events associated with a toxicity-driven therapy change

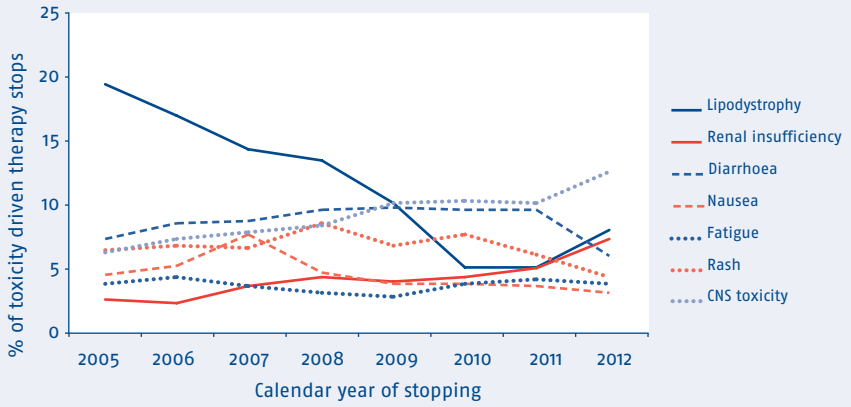
*Figure 2.13* shows the change in distribution of the seven most frequently registered adverse events associated with a regimen change over time. Most remarkable was the absolute and relative decline in treatment-limiting toxicity due to lipodystrophy (both peripheral fat loss and central fat accumulation) from 172 patients in 2005 (20% of all toxicity-driven therapy changes in 2005) to 52 (5%) in 2011. In 2012, there was a slight increase to 8%. For most of the changes due to lipodystrophy, lamivudine/zidovudine was stopped (in 27%), which was followed by stavudine (17%) and lamivudine/zidovudine/abacavir (15%). These were replaced by tenofovir/emtricitabine in 48% of the therapy changes that were followed by a new cART regimen, followed by tenofovir/lamivudine in 20% and abacavir/lamivudine in 17%.

The percentage of patients who stopped because of central nervous system (CNS) toxicity increased from 56 patients out of 882 (6%) with a toxicity-driven therapy stop in 2005 to 125 out of 986 (13%) in 2012. Amongst those 125, efavirenz was stopped due to CNS toxicity in 99 patients (79%). Of the 95 patients (96%) who subsequently switched to another cART regimen, 44% switched to rilpivirine, 27% to nevirapine, 9% to ritonavir-boosted darunavir, and 8% to ritonavir-boosted atazanavir.

The percentage of change because of renal insufficiency (both acute and chronic combined) was lowest (2%) in 2006 and increased to 7% in 2012. The percentage of therapy changes because of nausea, diarrhoea and fatigue was relatively stable between 2005 and 2012. The percentage of toxicity-driven changes because of rash was highest at 9% in 2008 and declined to 4% in 2012.

An overview of the number of other adverse events associated with a toxicity-driven therapy change is given in *Web Appendix Table 2.2*. The number of patients with at least one toxicity-driven therapy change remained relatively stable between 2005 and 2012. Numbers were highest in 2010 when 1,041 patients stopped a drug due to toxicity and lowest in 2005 when 882 patients did so.

*Figure 2.13: Relative distribution over time of the seven most frequently recorded adverse events associated with a toxicity-driven therapy change of at least one of the drugs in the cART regimen. For every toxicity-driven therapy change, one to three adverse events can be recorded, therefore percentages do not add up to 100%. CNS toxicity includes the following adverse events recorded in the database: dizziness, sleeplessness, nightmares, mood changes, concentration disorders and confusion.*



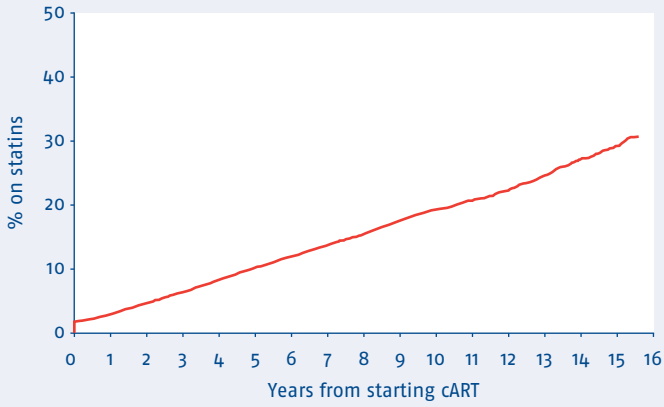

## Use of statins in the cART-treated population

Early in the course of HIV infection, levels of both high-density lipoprotein (HDL) and low-density lipoprotein (LDL) cholesterol decrease, and during more advanced stages of infection, triglyceride levels increase [103]. After starting ART, dyslipidaemia is typically manifested as a further increase in triglyceride levels whilst HDL cholesterol levels remain low and LDL cholesterol levels increase, usually higher than before HIV infection, depending on the drugs used in the regimen [104]. These changes may place patients with HIV at an increased risk for cardiovascular disease. Therapy with hydroxy-methylglutaryl coenzyme A reductase inhibitors (statins) in HIV-infected patients is well established in treating hyperlipidaemia, but it has not been formally proven to prevent cardiovascular disease. In addition, the anti-inflammatory properties of statins might also contribute to lowering the risk of age-associated non-AIDS-defining morbidity and mortality, including from cardiovascular disease.

Currently it is unknown whether the use of statins in HIV infection is associated with an increased risk of diabetes, as has been described in the general population. Furthermore, results from observational studies in non-HIV settings suggest there may be an increased risk of several adverse events, including musculoskeletal disease with the use of statins [105, 106]. Analyses of all of these issues are hampered by the observational nature of the available data. In this section we report on the use of statins, which we consider to be an indirect marker of clinically relevant hyperlipidaemia, after starting cART, and we look at the clinical and demographic characteristics of patients at the start of statin use.

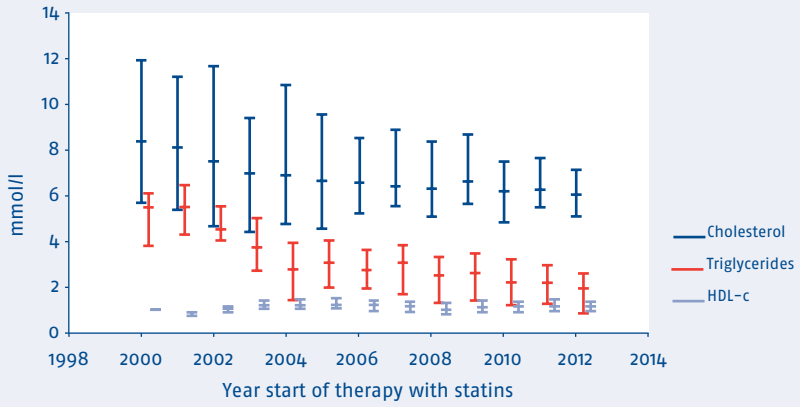
Out of 17,334 patients who started cART in or after 1995, 3% had started therapy with statins within 1 year, 6% within 3 years, 10% within 5 years, 19% within 10 years and 29% within 15 years (*Figure 2.14*).

***Figure 2.14:*** *Kaplan–Meier estimates of the percentage of patients who started therapy with statins. For patients with an unknown start date for statin therapy, but for whom it was known that statin therapy changed at a later date, the time to statin therapy was included as a left censored endpoint.*




The median age at which therapy with statins was started increased from 45.2 years (IQR 39.2-53.9) in 1997 and 1998 to 52.1 (47.6-60.2) between 2011 and 2013. Also median CD4-cell counts when statin therapy was started increased over time; they were 355 cells/mm$^3$ (270-650) in 1997 and 1998 and rose to 560 cells/mm$^3$ (410-786) when statins were started in or after 2011. Ten percent of patients starting statin therapy had a previous diagnosis of diabetes mellitus.

*Figure 2.15: Median and IQR of lipids at the start of statin therapy according to year of starting. Information on whether levels were obtained during fasting was not available.*




Over time we observed a trend of starting statins at lesser degrees of dyslipidaemia over time (*Figure 2.15*). Also, levels of HDL cholesterol increased over time from 1.00 mmol/l in 1997 to 1.12 mmol/l (0.94-1.40) in 2012. The percentage of patients with hypertension (indicated either by use of anti-hypertensive therapy, with a latest recorded systolic blood pressure of >140 mmHg, or hypertension reported in the patient's medical file in the year prior to the start of statins) was 18.5% between 2011 and 2013. At the start of statin therapy, the percentage of patients with a prior diagnosis of diabetes mellitus increased from 12% in 2001 and 2002 to 22% from 2011 to 2013. The percentage of patients with a prior myocardial infarction increased from 9% in 2001 and 2002 to 12% in 2007 and 2008. However the percentage decreased thereafter and was 3% from 2011 to 2013. In the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study, abnormal triglycerides, total and HDL cholesterol were all independently associated with an earlier start of lipid-lowering medication [107]. Furthermore, a higher body mass index (BMI), previous diagnosis of diabetes mellitus, previous cardiovascular event or a family history of cardiovascular disease also were independently associated with an earlier start.

As the patient population with HIV continues to age, management of patients at risk for dyslipidaemia and other cardiovascular disease will become increasingly important. Given that statins are usually prescribed for prolonged use, monitoring patients for adverse effects of statins, such as severe musculoskeletal toxicity and possibly diabetes mellitus, is important [105, 106].

*Figure 2.16: Estimated 5-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the Data Collection on Adverse Effects of Anti-HIV Drugs (D:A:D) study [45]. Calculation of the risk involves, amongst other variables, total cholesterol, HDL cholesterol and systolic blood pressure. Values for these variables were estimated on the basis of a last observation carried forward approach. The algorithm as published by the D:A:D study distinguishes between current and ex-smokers, but given that longitudinal assessment of an individual's smoking status with the current method of data collection is incomplete, we treated these two groups as one. The published estimates of the contribution to the risk for current and ex-smokers were averaged. Plot A shows the percentage and plot B the number of patients. An accurate assessment of an individual's risk requires recent measurements of lipid levels and blood pressure. Recent HDL-cholesterol measurements were often lacking or absent completely. Risk could not be estimated especially in younger patients because of missing data. Hence, the reported absolute number of patients is smaller than the number of patients in active follow-up at the end of each calendar year and older patients are over represented.*

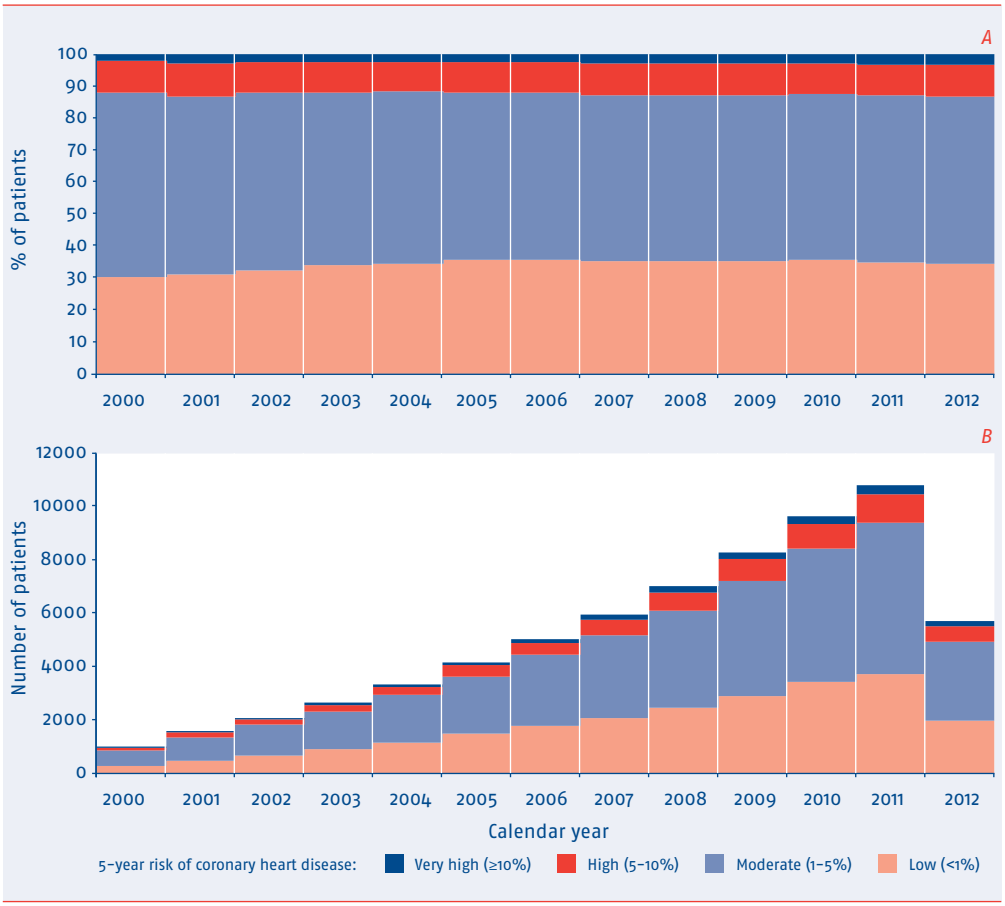


*Figure 2.16* gives an overview of the estimated risk of the development of coronary heart disease (CHD) in the cART-treated population over time, calculated using the D:A:D study algorithm [45]. Over time, the percentage of patients at high risk (5-10%) or very high risk (≥10%) remained stable; it was 12.8% in 2011. Median age of the population for whom the risk could be estimated increased from 42.6 years at the end of 2000 to 47.8 years at the end of 2012. Older age, male gender, current smoking or smoking in the past, current use of abacavir, longer cumulative exposure to lopinavir, a family history of cardiovascular disease, a diagnosis of diabetes mellitus, lower HDL cholesterol, a higher total cholesterol and a higher systolic blood pressure all contributed to an increased risk. The relatively stable risk level and the aging of the population under study suggests better management of lipid and blood pressure levels over time and/or a decrease in the use of abacavir and lopinavir. In individuals under the age of 40 years, the percentage at low risk increased from 62.3% in 2000 to 83.4% in 2011. Hardly any individuals at high or very high risk of CHD were less than 40 years of age. Amongst individuals aged 40 or more, the percentage at high or very high risk decreased slightly from 19.1% to 16.9%.

## Summary and Conclusions

### CD4-cell count at the start of cART

In summary, CD4-cell counts at the time of cART initiation have increased since 2007, with a median of 330 cells/mm$^3$ in 2012. CD4-cell counts at the start were lower among men from sub-Saharan Africa and women. cART is currently recommended for all HIV-infected patients, and 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 ≥350 CD4 cells/mm$^3$ or more, as normal cell counts with virologically successful cART are approached only after 8 years of continuous therapy. Although patients currently start cART at higher CD4-cell counts than ever before, a considerable proportion (71% of women and 57% of men) continue to be late-presenters (having either AIDS or <350 CD4 cells/mm$^3$) at the time they start cART. Repeated testing for HIV will inevitably result in an early diagnosis of HIV and render a timely start of cART more likely. Testing rates are especially low and need to be improved in the heterosexual-transmission risk group. Fear of a positive test result is the most important barrier to testing for HIV in high risk populations [5, 51, 52]. The five most frequent starting regimens in 2012 were tenofovir plus emtricitabine, combined with efavirenz (36%), darunavir/ritonavir (15%), nevirapine (15%), atazanavir/ritonavir (9%) or rilpivirine (9%). The fixed-dose combination of tenofovir and emtricitabine was used in 92% of all starting regimens in 2012, either combined with efavirenz (36% of all starting regimens), darunavir/ritonavir (15%), nevirapine (15%), atazanavir/ritonavir (9%) or rilpivirine (9%).

### Virological response

Within 9 months, 85% of patients who started cART between 2010 and 2012 reached initial virological success (a confirmed HIV RNA <100 copies/ml). Ensuring a quick suppression of plasma viral load and maintaining suppression 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 emergence of drug resistance. Time to success was longer in younger patients, male patients and patients from sub-Saharan Africa and the Caribbean and South America.

The risk of virological failure after initial success declined over time but was increased in younger patients (<30 years) and heterosexually infected patients from sub-Saharan Africa and the Caribbean and South America. Patients from sub-Saharan Africa and the Caribbean and South America continue to be at higher risk of failure on subsequent second-line cART. Each of the factors that may have contributed to failure of an initial regimen need to be addressed before prescribing a subsequent regimen, most notably adherence (especially, but not solely, in patients from sub-Saharan Africa and the Caribbean and South America), genotypic testing for resistance at the time of failure and prior ART history.

### Immunological response

A timely start of cART is important because CD4-cell counts levels approach those seen in the general population after 8 years of virologically suppressive cART only when cART is started at 350 CD4 cells/mm$^3$ or higher. Increases in CD4-cell counts were less in older patients; however, increases in CD4-cell count were similar between patients of <50 and ≥50 years of age at the start of cART when it was initiated at counts of 350 cells/mm$^3$ or higher. Increases were also smaller in patients born in sub-Saharan Africa, patients with HCV co-infection and male patients.

Despite virologically successful cART, 31% of patients starting cART at CD4-cell counts lower than 200 cells/mm$^3$ and 22% of patients starting at counts lower than 350 cells/mm$^3$ still had counts lower than 350 cells/mm$^3$ at 3 years and thus remained at an increased risk of AIDS and non-AIDS-defining morbidity.

Similar to CD4-cell count changes, normalization of the CD4/CD8 ratio towards levels of 1 or higher seemed to be strongly related to the CD4-cell count at the start of cART. Median CD4/CD8 ratio reached levels higher than 1 after 3.5 years of suppressive cART when CD4 cell counts were 500 cells/mm$^3$ or higher and after 8 years when counts at the start were between 350 and 500 cells/mm$^3$. However, patients starting at lower CD4-cell counts did not reach median levels higher than 1 during follow-up. Although lower CD4/CD8 ratios have been suggested to be associated with increased immune activation markers during sustained viral suppression and with subclinical atherosclerosis, the clinical significance of these findings remains to be determined.

### Durability and toxicity

Lifelong use of ART requires tolerable and durable regimens. Approximately 50% of patients currently starting cART are able to remain on their first-line regimen for more than 3 years. Toxicity remains the main reason for changing treatment, although the incidence of

therapy changes driven by toxicity has dramatically declined since the introduction of cART. MSM had a higher risk for a toxicity-driven therapy change compared to heterosexuals, as did women and older patients. Among MSM, the risk was higher when cART was started at CD4 cell counts of 500 cells/mm$^3$ or higher. Amongst patients changing therapy because of toxicity, the most frequently recorded adverse events in 2012 was CNS toxicity, which in many patients led to efavirenz being substituted for rilpivirine, and likely explains the observed increasing rate of discontinuation of first-line cART in the last 2 years. Better tolerated drugs, such as rilpivirine and more individualized patient-management strategies, are needed to continuously improve the durability of cART regimens.

Despite the increasing age of the HIV-infected population on cART, the proportion of patients at high cardiovascular risk has remained stable. This suggests that cardiovascular risk management has improved over time, as illustrated by the initiation of statins at less elevated lipid levels and the preferred use of cART regimens without known cardiovascular risk.

Optimized prospective longitudinal monitoring of lipid levels, smoking status, blood pressure and other risk factors will be important to continue reliable assessment of cardiovascular risk in our increasingly aging HIV-1 infected population and to study the impact of interventions such as the use of statins in modifying disease risk.

# 3. Virological failure and resistance

Ard van Sighem, Anne Wensing, Jan Prins, Kees Brinkman, Peter Reiss

## Introduction

Treatment with combination antiretroviral therapy (cART) generally results in sustained suppression of HIV viral load to levels below the threshold of quantification. It is generally believed that viral replication has been halted in individuals on cART, although some studies of treatment intensification suggest that active replication persists in some infected individuals [108]. Also, patients may have difficulty maintaining optimal adherence to the treatment regimen because of, for example, drug-related toxicities, resulting in drug concentrations that 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 (SHM) and the extent to which resistant virus strains are transmitted to uninfected individuals.

## Resistance during treatment

### Low-level viraemia

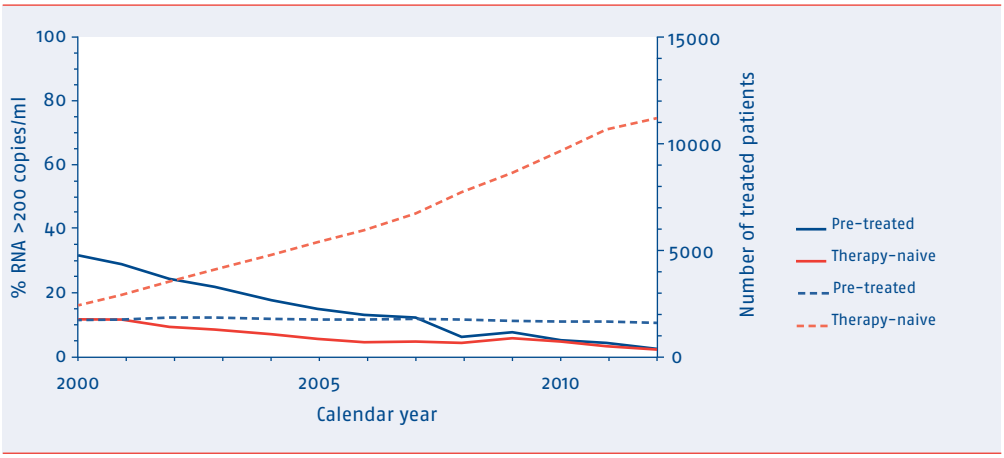
In clinical practice, low-level replication of HIV despite cART usually betrays itself by quantifiable viral loads, typically above 50 copies/ml. Many patients, however, who have viral loads consistently below 50 copies/ml may occasionally have a single measurement above 50 copies/ml [109, 110]. The 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 necessarily herald the presence of resistance-associated mutations [55, 62]. Moreover, rates of low-level viraemia appear to have increased since 2008, when a new quantification assay was introduced in several treatment centres across the country. With this new assay, HIV RNA levels below 50 copies/ml measured with earlier assays are frequently found to be greater than 50 copies/ml (see also *Chapter 2*).

### Less virological failure

To minimise the effect of blips and the new quantification assay, we used a viral-load threshold of 200 copies/ml as a marker of virological failure [9]. Since 2000, the annual proportion of patients with virological failure has decreased to approximately 3%. During the same time, the difference between patients pre-treated with mono- or dual therapy and patients starting cART whilst antiretroviral therapy-naïve has disappeared (*Figure 3.1*; *Web Appendix Figure 3.1*). From 2008 onwards, approximately equal proportions of patients in these two groups had virological failure, coinciding with the introduction of new antiretroviral drugs. These drugs are able to suppress viral load, even in patients who have

had multiple episodes of virological failure and harbour virus strains that are resistant to many of the older drugs. Improvements in virological response over calendar time after extensive failure were also found by the Pursuing Later Treatment Options II (PLATO II) project team, in which SHM participates [111].

*Figure 3.1: Annual number of treated patients with a viral load measurement (dashed lines) and the proportion of patients with virological failure (solid lines), i.e., a viral load above 200 copies/ml whilst on treatment and measured at least 4 months after start of cART or 4 months after resuming treatment following a treatment interruption. Amongst approximately 1700 pre-treated patients, the proportion with failure with use of a threshold of 200 copies/ml decreased from 31% in 2000 to 2% in 2012. Amongst previously therapy-naïve patients, failure was less common and decreased from 12% to 3% during the same period, whilst the number of naïve patients increased from approximately 2,350 to 11,250.*




## Scanning for drug resistance

In patients who experienced virological failure, resistance to antiretroviral drugs was ascertained by scanning genotypic sequences of the reverse transcriptase (RT) and protease genes obtained at the time of the failure for specific mutations known to be associated with resistance to the three originally most commonly used classes of drugs, including lamivudine and emtricitabine, other nucleoside RT inhibitors (NRTI), non-nucleoside RT inhibitors (NNRTI), and protease inhibitors (PI) [112]. In recent years, new drug classes have been introduced, including integrase and entry inhibitors. Genotypic sequences of the relevant genes are increasingly being obtained during routine clinical care, but only approximately 30 sequences of the integrase gene were available in the SHM database and were not considered for further analysis. A genotypic resistance interpretation algorithm 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 [74].

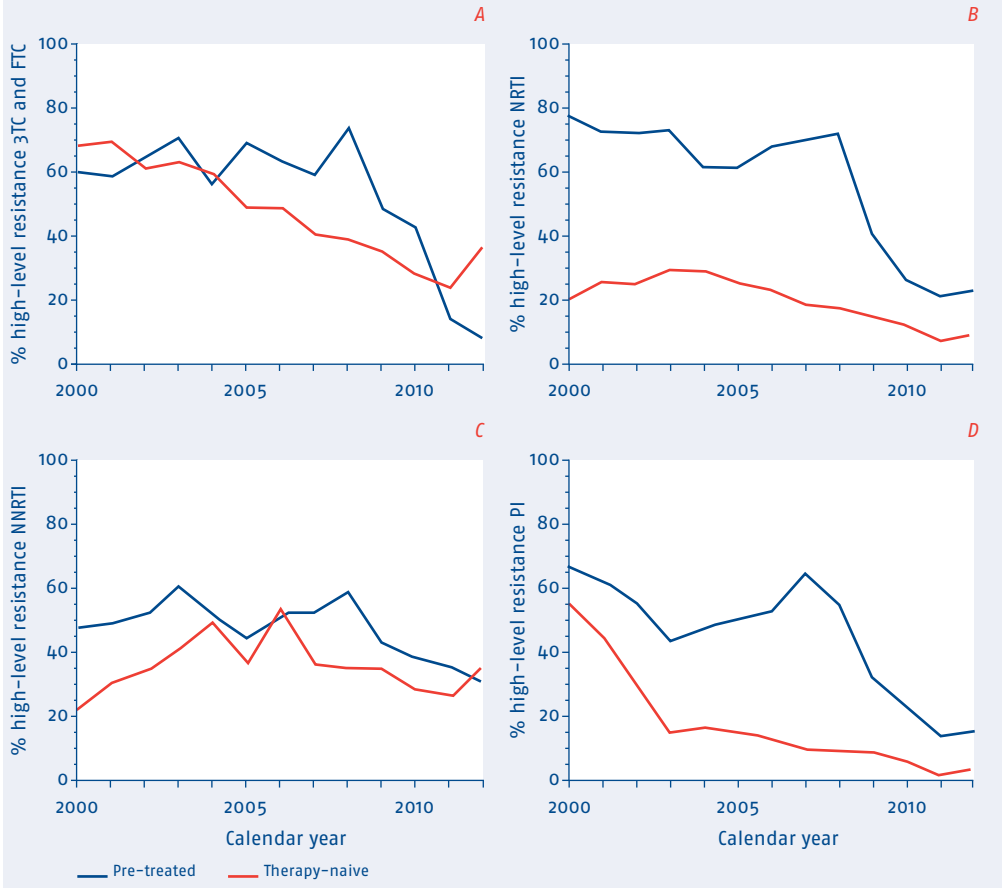
### Sequences

In total, 4,113 sequences were obtained after the start of cART from 2,495 patients who started in 1996 or later. Pre-treated patients were disproportionally represented with 1,609 sequences (39%). From 2008 onwards, however, only 16% of the sequences were from pre-treated patients, whereas 12% of all treated patients in clinical care were pre-treated. Altogether, 3,363 sequences (82%) were obtained whilst patients were receiving treatment. In 74% of these 3,363 sequences, high-level resistance to at least one antiretroviral drug was found, including in 88% of the sequences obtained from pre-treated patients and in 63% of those from patients who started cART whilst antiretroviral therapy-naïve. Of note, 8% of the sequences from pre-treated patients and 24% of those from previously therapy-naïve patients were susceptible to all antiretroviral drugs, likely indicating that the patients did not take their prescribed medication at the time the blood sample was obtained.

### Less resistance

Altogether, the proportion of sequences with high-level resistance at the time of virological failure decreased from 91% in 2000 to 47% in 2012 (*Web Appendix Figure 3.2*). Generally, patients who were pre-treated with mono- or dual therapy had higher levels of resistance at the time of failure compared to previously therapy-naïve patients. Differences in proportions with resistance were most apparent for PIs and NRTIs, whereas the proportions with resistance to lamivudine and emtricitabine and to NNRTIs were comparable between pre-treated and previously therapy-naïve patients (*Figure 3.2; Web Appendix Figure 3.3 and 3.4*). From 2008 onwards, the proportion of sequences with resistance showed a sharp decrease for pre-treated patients, which was concomitant with the decrease in the proportion with virological failure.

*Figure 3.2: Annual proportion of sequences with high-level resistance to (A) lamivudine (3TC) and emtricitabine (FTC), (B) other nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), (C) non-nucleoside reverse transcriptase inhibitors (NNRTI), and (D) protease inhibitors (PI). In total, 3,363 sequences were obtained from patients on treatment, distinguishing between patients who started combination antiretroviral therapy (cART) whilst being antiretroviral therapy-naïve and patients who were pre-treated with non-cART regimens. High-level resistance was found in 2,474 (74%) sequences, including 1,231 (88%) sequences from pre-treated patients and 1,243 (63%) sequences from previously therapy-naïve patients.*




## Type of regimen

In total, 271 sequences were obtained from previously antiretroviral therapy-naïve patients who started cART from 2000 onwards and were still on their first-line regimen at the time the sequence was obtained. The proportion of sequences with high-level resistance to at

least one antiretroviral drug was similar for patients on NNRTI-based regimens (61%) and for patients on PI-based regimens (55%). In 61% of the patients on an NNRTI-based regimen, high-level resistance to an NNRTI was found, whilst 38% were fully susceptible to all NNRTIs. In contrast, only 18% of the patients on a PI-based regimen were resistant to a protease inhibitor, and 60% were fully susceptible to all PIs. Resistance to lamivudine and emtricitabine was found in 50% of patients on a PI-based regimen and in 44% of those on NNRTI-based regimens, whilst resistance to other NRTIs was observed in 4% and 17%, respectively.

### Overall prevalence of resistance

Altogether, as of June 2013, resistance-associated mutations had been found in 2,062 HIV-infected patients, or 12%, of the 17,006 who were still in clinical care [112]. For 1,544 patients, or 9%, including 619 patients who were pre-treated with non-cART regimens, these mutations resulted in high-level resistance to at least one antiretroviral drug. Since resistance tests were available for only 25% of patients with virological failure in or after 2002, probably the true prevalence of resistance is higher. A crude estimate would put the true prevalence at approximately 40%, which would be more in line with findings in other European countries [113, 114].

Of the 1,544 patients with evidence of high-level resistance, 72% had resistance to lamivudine and emtricitabine, whilst 50% had resistance to at least one other NRTI. Resistance to at least one PI was found in 30% and to at least one NNRTI in 60%. High-level resistance to drugs from one drug class was observed in 41% of patients, resistance to two classes in 44%, and resistance to all three original drug classes in 15%. Predicted levels of resistance for each antiretroviral drug are shown in *Web Appendix Tables 3.1 and 3.2*.

## Transmission of drug resistance

### Limited treatment options

Treatment options may be more limited when patients are infected with a strain of HIV virus 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, and as a result, patients may experience delayed viral suppression or have an increased risk of virological failure. It is, therefore, important to screen patients for the possible presence of drug resistance so that the initial treatment regimen can be optimised [115, 116].

### Back mutation

Although a resistant virus strain may evolve to a drug-susceptible virus (a process sometimes referred to as back mutation), tiny concentrations of resistant variants remain dormant in resting CD4 cells and other reservoirs, awaiting more favourable conditions for replicating after treatment is started. The presence of resistance, therefore, needs to be established as close to the moment of infection as possible [117-119]. In particular, the M184V mutation in RT,

which is associated with high-level resistance to lamivudine and emtricitabine, can disappear relatively quickly after transmission. Other mutations disappear at a much slower pace or do not disappear at all, depending on the extent to which the virus becomes capable of replicating or whether its evolution is constrained by fixation through compensatory mutations [120].

### Screening for resistance

In 2003, screening for resistance at the time of entry into care was incorporated in the Dutch treatment guidelines. Since that time, a total of 4,609 patients have been screened for transmitted drug resistance, which comprises 40% of all 11,541 patients diagnosed with HIV during that period. To reduce a possible effect of back mutation on observed levels of resistance, only patients who had a genotypic sequence within 1 year of diagnosis and who had not started antiretroviral treatment were included in this total number. In addition, patients were divided into two complementary groups, one including patients with a recent infection (32%) and another including those with non-recent infection (68%). An infection was considered recent when the time between the last negative HIV test, if available, and the first positive test was, at most, 1.5 years. These two groups were quite different regarding patient characteristics. Dutch homosexual men represented 69% of the recently infected group, but only 42% of the group with long-standing infections. In contrast, sub-Saharan Africans accounted for 18% of those with long-standing infections, but only 3% of those with recent infections.

### Transmitted drug resistance

Overall, at least one resistance-associated mutation was found in 11% of the 4,609 patients with a genotypic sequence within 1 year of diagnosis, including 4% with NRTI mutations, 5% with NNRTI mutations, and 2% with mutations in the protease gene [112]. Between 2003 and 2012, there were no significant changes in these proportions nor were there changes in specific mutations. Last year, we reported a possible increase in the percentage of patients with a K103N/S mutation in RT, which confers resistance to efavirenz and nevirapine, but this increase appeared not to persist [1]. In 2012, only one patient, or 0.4% of 270 with a sequence, had this specific mutation compared to 1.2% in 2010 and 2011.

In total, 87 patients had high-level resistance to drugs from one class, 13 patients to drugs from two classes, and 4 patients to drugs from 3 classes. It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. All classes include drugs with little cross-resistance between them. Moreover, other classes of drugs have become available in recent years. As a result, even for patients with resistance to all four classes, there may still be fully efficacious cART combinations [111].

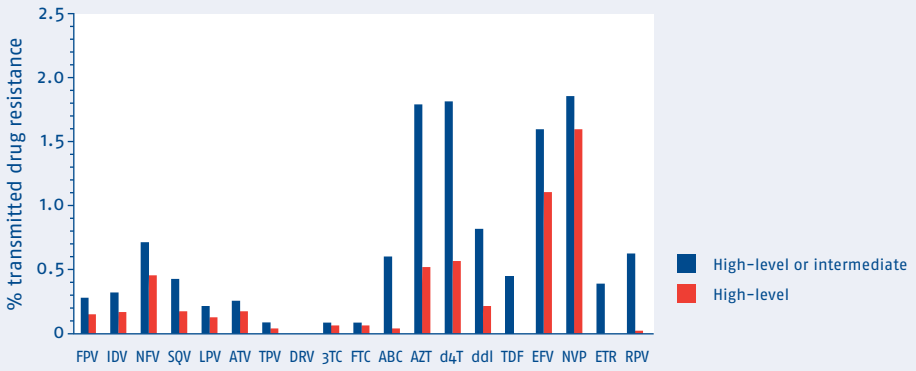
High-level resistance to at least one antiretroviral drug was found in 2.3% of the diagnosed patients, whilst 2.0% had intermediate levels of resistance (*Table 3.1*). The proportions of patients with resistance who had a recent infection were similar to those with a long-

standing infection, although resistance to NNRTIs appeared to be somewhat more common amongst those with long-standing infection. Overall, intermediate or high-level resistance to zidovudine and stavudine were most frequently observed, but both drugs are no longer commonly used (*Figure 3.3*). In addition, 1.1% of the patients had high-level resistance to efavirenz, whilst 1.6% were resistant to nevirapine. In recent years, no changes were observed in the proportion of patients with predicted high-level resistance.

***Table 3.1:*** *Number of diagnosed patients with intermediate or high-level resistance to any drug, protease inhibitors (PI), lamivudine (3TC) and emtricitabine (FTC), other nucleoside reverse transcriptase inhibitors (NRTI), or non-nucleoside reverse transcriptase inhibitors (NNRTI), according to the Stanford genotypic interpretation algorithm [74]. Only patients diagnosed in 2003 or later are included. A diagnosed infection was considered to be recent if the time between the last negative HIV test and the first positive test was, at most, 1.5 years.*

| | Recent infection, N=1,491 | | Non-recent infection, N=3,118 | | All diagnoses, N=4,609 | |
|---|---|---|---|---|---|---|
| | N | % | N | % | N | % |
| Any drug | | | | | | |
| Intermediate | 32 | 2.1 | 62 | 2.0 | 94 | 2.0 |
| High-level | 31 | 2.1 | 73 | 2.3 | 104 | 2.3 |
| PI | | | | | | |
| Intermediate | 5 | 0.3 | 9 | 0.3 | 14 | 0.3 |
| High-level | 7 | 0.5 | 14 | 0.4 | 21 | 0.5 |
| 3TC and FTC | | | | | | |
| Intermediate | 1 | 0.1 | 0 | 0.0 | 1 | 0.0 |
| High-level | 2 | 0.1 | 1 | 0.0 | 3 | 0.1 |
| NRTI | | | | | | |
| Intermediate | 21 | 1.4 | 44 | 1.4 | 65 | 1.4 |
| High-level | 8 | 0.5 | 20 | 0.6 | 28 | 0.6 |
| NNRTI | | | | | | |
| Intermediate | 9 | 0.6 | 13 | 0.4 | 22 | 0.5 |
| High-level | 18 | 1.2 | 56 | 1.8 | 74 | 1.6 |

*Figure 3.3: The predicted proportion of patients with high or intermediate levels of transmitted drug resistance, according to the Stanford interpretation algorithm, was 1.8% for AZT and d4T (two drugs that are no longer commonly used) and 1.9% for NVP and 1.6% for EFV [74]. High-level or intermediate resistance to other drugs was observed in less than 1% of new infections. Only patients with an HIV diagnosis in 2003 or later were included.*




*Legend: FPV=fosamprenavir; IDV=indinavir; NFV=nelfinavir; SQV=saquinavir; LPV=lopinavir; ATV=atazanavir; TPV=tipranavir; DRV=darunavir; 3TC=lamivudine; FTC=emtricitabine; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddI=didanosine; TDF=tenofovir; EFV=efavirenz; NVP=nevirapine; ETR=etravirine; RPV=rilpivirine.*

### Gender and viral subtype

The proportion of HIV infections with evidence of intermediate or high-level resistance was similar between men and women. However, transmission of virus strains with predicted full susceptibility to all NRTIs was less frequent amongst men (91%) than amongst women (97%). In contrast, virus strains susceptible to all PIs were observed in 87% of men, but in only 65% of women. These differences between the sexes can largely be explained by which HIV-1 subtype infected the patients. When consideration was given to patients infected with either a subtype B virus or with any other subtype, differences in levels of resistance between men and women disappeared.

Altogether, 2.5% of subtype B viruses had intermediate or high-level resistance to NRTIs, whereas this was true for only 0.3% of non-B viruses. These higher levels of resistance to NRTIs were largely due to strains of subtype B with revertant mutations in RT such as 215S or 215D, which have established themselves as subepidemics [121]. Revertant mutations at position 215 in RT were found in 195 (6%) subtype B infections, but in only 4 out of 1,076 non-B infections. Over time, there has been a clear increase in the proportion of patients infected with a virus strain with a 215S mutation in the absence of any resistance-associated mutations. In 2011 and 2012, 5% of all sequences had this specific mutation compared to 1% before that time. Due to a backlog in data collection, it is not possible to determine if this increase was a regional phenomenon or occurred on a national level. Full susceptibility to

all protease inhibitors was found in 94% of subtype B sequences, but in only 53% of non-B viruses. This difference is likely due to naturally occurring polymorphisms at minor resistance-associated positions in the protease gene, which are not considered clinically relevant [112].

## International collaborations

### EuroCoord Collaborative HIV and Anti-HIV Drug Resistance Network (CHAIN):

EuroCoord-CHAIN studied the effect of transmitted drug resistance on outcome in the first year of combination antiretroviral therapy (cART) in 10,056 patients combining data from 25 cohorts, including the SHM [122]. After 12 months, 4.2% of patients without transmitted drug resistance-associated mutations had experienced virological failure. This proportion was similar (4.7%) for patients with at least one mutation and a fully active cART regimen. Virological failure was much more frequent (15.1%) amongst patients with at least one mutation and resistance to at least one of their prescribed drugs. These findings confirm present treatment guidelines for HIV, which state that the initial treatment choice should be based on resistance testing in treatment-naive patients.

The Pursuing Later Treatment Options II (PLATO II) project team studied trends between 2000 and 2009 in virological and clinical outcomes in 2,476 HIV-infected individuals after triple-class virological failure [111]. Viral suppression rates increased from 19.5% in 2000 to 57.9% in 2009. This was accompanied by a decrease in incidence of AIDS and mortality. These improvements in outcomes were probably mainly driven by the availability of newer drugs with better tolerability, ease of use and small cross-resistance profiles.

## Conclusions

In terms of percentages, virological failure is less common nowadays than it was in 2000, thanks to improvements in combination treatment itself and the availability of treatment options. This appears to be true even for patients pre-treated with mono- or dual therapy who now have the same rates of virological failure as previously therapy-naïve patients. Nevertheless, due to a growing volume of treated HIV-infected patients, approximately 300 to 400 patients per year still experience virological failure.

Resistance patterns in sequences obtained at approximately the time of failure seem to indicate that in one quarter of previously therapy-naïve patients, virological failure is the result of patients not taking their prescribed medication, which could be due to, for instance, drug-related toxicity. In patients with a sequence obtained whilst failing on a PI-based or an NNRTI-based first-line regimen, overall levels of drug resistance are similar. However, PIs appear to be more resilient to the development of drug resistance than NNRTIs, most likely as a consequence of the larger number of mutations necessary to render the virus fully

resistant [123]. In patients on a PI-based regimen, resistance to lamivudine and emtricitabine is most commonly observed, whereas in patients on NNRTI-based regimens, resistance to NNRTIs and, to a lesser extent, to lamivudine and emtricitabine is most frequent.

Unfortunately, sequences are available for only approximately 25% of the patients with virological failure. Without a thorough understanding of the conditions under which sequences are available, it is difficult to draw firm conclusions on the prevalence of resistance in the entire HIV-infected population. Also, for some patients, virological failure may be caused by resistance to integrase or entry inhibitors, but sequences of the genes involved in this type of resistance are not yet routinely available in all treatment centres. In order to determine the true prevalence of resistance in treated patients with virological failure, SHM is investigating the possibility of developing a nationwide study to obtain sequences and plasma drug concentrations at the time of failure in a randomly selected sample of patients.

Even though the prevalence of resistance may be as high as 40% in the entire population in care, only 11% of patients are infected with a virus that harbours resistance-associated mutations. Most likely, this proportion is relatively low because the majority of patients on antiretroviral treatment have well suppressed viral loads, even in the presence of resistance-associated mutations. This implies that transmission takes place mainly via HIV-infected individuals who are not yet treated [13, 14]. The transmitted mutations give rise to intermediate or high-level resistance to at least one antiretroviral drug in only 4% of the patients, such that a suitable first-line treatment regimen will be available for most patients.

## Recommendations

Until now, data collectors in HIV treatment centres have not routinely collected protease and RT sequences, mainly due to the complex infrastructure and data management processes. This is one of the reasons why sequences are available for only a small proportion of patients with virological failure. The collection of sequencing data needs to be improved to permit monitoring resistance. The first steps to achieve this have already been taken, and further progress is expected in the coming months.

With the introduction of new drug classes in recent years, including integrase and entry inhibitors, the collection of data on sequences should be extended to other parts of the viral genome. Increasingly, genotypic sequences of the relevant genes are being obtained during routine clinical care, but not enough sequences are currently available in the SHM database to give a clear picture of resistance to these new drug classes.

Further, obtaining a sequence at the time of diagnosis or entry into care needs to be continued as a standard procedure. Clearly, without information on resistance before the start of treatment, patients could start with a partially active cART regimen that might lead to virological failure. Also, even though no resistance-associated mutations are currently found in many patients, there is no guarantee that this situation will not change. Monitoring these changes

will be nearly impossible without pre-treatment resistance profiles. A concomitant advantage of having genetic information of HIV sequences is that it allows identification of transmission networks, which will help to formulate tailor-made intervention strategies to reduce HIV incidence.

# 4. Mortality, AIDS-defining and non-AIDS-defining events in patients with HIV-1 infection

Anouk Kesselring, Ard van Sighem, Annelot Schoffelen, Ferdinand Wit, Peter Reiss

## Introduction

Of the 20,761 adult patients currently in the national HIV registration and monitoring database in the Netherlands, 87% are currently on combination antiretroviral therapy (cART). The life expectancy of HIV-infected patients has markedly improved since the introduction of cART; in a subgroup of recently diagnosed, effectively treated patients, it was shown to be similar to that of the general population in the Netherlands [124].

As a result of these marked improvements in life expectancy, HIV-infected patients in the Netherlands have become eligible for long-term life insurance to cover a mortgage, which is supported by a recently published analysis from the Antiretroviral Therapy Cohort Collaboration (ART-CC) [125].

Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased [126], morbidity and/or mortality related to non-AIDS-related diseases such as renal and liver disease, diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies has increased amongst HIV-1-infected patients in the cART era [89, 127-133].

Various reports suggest that the risk of non-AIDS morbidity may be higher amongst HIV-infected individuals treated with ART than amongst uninfected individuals of comparable age [134, 135]. For example, pulmonary hypertension [136], bone disease and non-traumatic bone fractures [137-139] have been reported to be more common in HIV-infected patients. There is also a concern that neurocognitive impairment may persist, or even progress, despite otherwise effective long-term cART [140-142]. Traditional risk factors (e.g., tobacco use [143], alcohol abuse and viral hepatitis co-infections [144] are likely to also importantly contribute to the increased risk of co-morbidities in HIV, similar to in uninfected individuals.

Importantly, one of the most prevalent co-morbidities in HIV is cardiovascular disease (CVD). Next to traditional risk factors such as smoking, probable additional risk factors amongst HIV-infected patients are metabolic abnormalities, including dyslipidaemia, insulin resistance, diabetes, and changes in body fat (lipodystrophy), which may partly be driven by use of cART, as well as sustained HIV-associated immune activation and inflammation [127, 145].

In this chapter, we report on rates of mortality and causes of death for HIV-1-infected patients on cART based on updated Stichting HIV Monitoring (SHM) data. In addition, we report the incidence of AIDS and non-AIDS co-morbidities, particularly diabetes mellitus, cardiovascular disease, chronic kidney disease (CKD), and non-AIDS malignancies in HIV-1-infected patients on cART. Incidence rates and, where possible, risk factors are presented.

## Definitions

**AIDS** is defined as the presence of any Centers for Disease Control (CDC) category C condition, including the presence of any AIDS-defining malignancy (Kaposi's sarcoma, non-Hodgkin's lymphoma, and invasive cervical cancer) [146]. A CD4 count less than 200 cells/mm$^3$ in the absence of AIDS-defining condition does not qualify as AIDS in these analyses.

**Diabetes mellitus** was defined according to criteria established by the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study *(http://www.cphiv.dk/DAD / StudyDocuments/tabid/112/Default.aspx)*.

**Cardiovascular diseases** including myocardial infarction, stroke, coronary artery by-pass grafting, coronary angioplasty or stenting and carotid endarterectomy were defined according to criteria established by the D:A:D study *(http://www.cphiv.dk/DAD / StudyDocuments/tabid/112/Default.aspx)*.

**Non-AIDS-defining malignancies**, excluding precancerous stages of anal and cervical cancer, basal-cell carcinoma, and squamous-cell carcinoma of the skin, were defined according to criteria established by the D:A:D study *(http://www.cphiv.dk/DAD /StudyDocuments/tabid/112/Default.aspx)*.

Histological confirmation of malignancies is part of standard clinical practice in the Netherlands, and therefore, pathology reports have been used as much as possible for the purpose of establishing the definitive presence of any malignancy.

**Chronic kidney disease (CKD)** was defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min (with the Cockcroft-Gaul equation), confirmed after 3 months or longer. End-stage renal disease (ESRD) was defined according to criteria established by the D:A:D study *(http://www.cphiv.dk/DAD /StudyDocuments/tabid/112/Default.aspx)*.

## Methods

For the analyses of incidence per calendar year and period, we consider all events after an individual started cART and after routine data collection was begun for the reported condition, whichever occurred most recently. For instance, data on chronic kidney disease (CKD) were used from 2007 onwards, because at that time laboratory data became available electronically for entry into the database. In the analyses presented, we also exclude patients who experienced the event of interest before they started cART or before routine data collection was started.

When constructing regression models, we used the parameters described and categorized in *Web Appendix Table 4.1* as covariates. We also included the time-updated number of years on cART as a covariate using the following categories: less than 1 year; 1 to 5 years, 5 to 10 years; and more than 10 years. HIV viral load and CD4 counts were included as time-updated variables in the models. We performed univariate analyses on each of the covariates and then included the covariates with a univariate p-value smaller than 0.1 in a multivariate analysis and performed a stepwise backwards model selection procedure, eliminating one variable per step until all variables had a p-value of 0.05 or less.

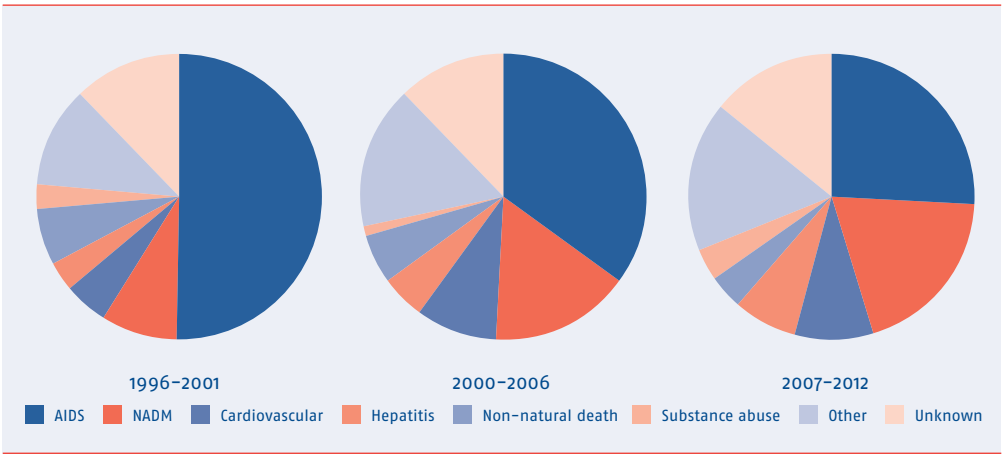
## Mortality and AIDS

From 1996 onwards, the overall mortality in all 20,761 HIV-1-infected patients ever recorded in the database and with a recorded date of HIV diagnosis was 12.0 (95% confidence interval [CI], 11.5-12.5) per 1,000 person-years, which declined over time to 9.3 (7.8-11.0) per 1,000 person-years in 2012 (*Web Appendix Figure 4.1.A; Web Appendix Table 4.2*). Despite this decline, the mortality rate, taking into account gender and age, was still 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 partly explained by patients who already had AIDS at the time of their HIV diagnosis. When these patients were excluded, the average mortality rate decreased to 10.4 per 1,000 person-years. The average mortality rate was even lower, 9.5 per 1,000 person-years, in patients who were diagnosed with HIV in 1996 or later. Generally, these patients quickly and durably suppressed HIV replication after they received a potent cART regimen as their first treatment regimen, instead of first having been treated with mono- or dual NRTI therapy in the period before cART first became available. In the same group of 20,761 patients, the incidence of AIDS decreased sharply to approximately 10 cases per 1,000 patients per year in the most recent years (*Web Appendix Figure 4.1.B*).

Likewise, the mortality rate after the start of cART substantially decreased over calendar time to 10.2 (8.5-12.1) per 1,000 person-years in 2012 (*Web Appendix Figure 4.1.C*). This decrease should, however, be interpreted with caution since it is, in part, due to a survival effect. Similarly, the incidence of AIDS after the start of cART decreased dramatically and was 7.9 (6.3-9.6) per 1,000 person-years in 2012 (*Web Appendix Figure 4.1.D*).

Observed causes of death are presented in *Web Appendix Table 4.3*. Although the proportion of patients who die of AIDS has decreased significantly since the advent of cART, it still remains substantial, which is likely to be largely driven by the high number of patients who still present late for care. Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figure 4.1*).

***Figure 4.1:*** *Relative changes in causes of death in HIV-1 infected patients in different periods since the first introduction of cART in the Netherlands.*




***Legend:*** *NADM=Non-AIDS-defining malignancy.*

We examined factors associated with death in patients from the start of cART using Cox regression analysis. After correction for all of the variables listed in *Web Appendix Table 4.1*, the odds ratios for the individual categories of the covariates are presented in *Web Appendix Table 4.4*. In general, the time to death was shorter for men than for women. Patients survived for a shorter duration after starting cART if they were born in the Netherlands, were older, had been HIV-1 positive for longer before they started cART or had a CD4-cell count less than 200 cells/mm$^3$ at the start of cART, were underweight or had tested positive for chronic hepatitis B or C infection.

The incidence of the first occurrence of any and individual AIDS-defining events after the start of cART is presented in *Web Appendix Table 4.5*. In these analyses, we concentrate on the first occurrence of any AIDS-defining event after the start of cART. Risk factors for AIDS-defining events are shown in *Web Appendix Table 4.4*. The results of this analysis show that patients were more likely to experience their first AIDS-defining event after the start of cART if they had become HIV-1 positive due to blood contact or injecting drug use, were underweight, had been diagnosed with HIV-1 less than one year before the start of cART, or had a CD4 count less than 200 CD4 cells/mm$^3$.

## International collaborations

**Collaboration of Observational HIV Epidemiological Research Europe (COHERE):**
Few studies consider the incidence of individual AIDS-defining illnesses (ADIs) at higher CD4 counts relevant on a population level for monitoring and resource allocation. Amanda Mocroft et al. investigated this topic on behalf of the COHERE study in EuroCOORD.
Individuals from the COHERE aged 14 years or more, with one or more CD4 counts of 200 cells/mm$^3$ or more between 1998 and 2010 were included.
A total of 12,135 ADIs occurred at a CD4 count of 200 cells/mm$^3$ or more amongst 207,539 persons with 1,154,803 person-years of follow-up (PYFU). Incidence rates declined from 20.5 per 1,000 PYFU (95% confidence interval [CI], 20.0–21.1 per 1,000 PYFU) with current CD4 200–349 cells/mm$^3$ to 4.1 per 1,000 PYFU (95% CI, 3.6–4.6 per 1,000 PYFU) with current CD4 counts of 1,000 cells/mm$^3$ or more.
The incidence of ADIs was higher in individuals with a current CD4 count of 500 to 749 cells/mm$^3$ compared to those with a CD4 count of 750–999 cells/mm$^3$, but did not decrease further at higher CD4 counts. Results were similar in patients virologically suppressed on cART, suggesting that immune reconstitution is not complete until the CD4 increases to more than 750 cells/mm$^3$ [147].

Another study from COHERE found that mortality patterns in most HIV-infected individuals with high CD4 counts on cART are similar to those in the general population. Adults were eligible if they initiated cART between 1998 and 2008 and had one prior CD4 measurement within 6 months. Standardized mortality ratios (SMRs) and excess mortality rates compared with the general population were estimated using Poisson regression. Periods of follow-up were classified according to the current CD4 count.

Of the 80,642 individuals, 70% were men, 16% were injecting drug users (IDUs), the median age was 37 years, the median CD4 count was 225/mm$^3$ at cART initiation and median follow-up was 3.5 years. The overall mortality rate was 1.2/100 person-years (PY; men: 1.3, women: 0.9), 4.2 times as high as that in the general population (SMR for men: 3.8, for women: 7.4). Amongst 35,316 individuals with a CD4 count ≥500 cells/mm$^3$, the mortality rate was 0.37/100 PY (SMR 1.5); mortality rates were similar to those of the general population in non-IDU men [SMR 0.9, 95% confidence interval (95% CI) 0.7-1.3] and, after 3 years, in women (SMR 1.1, 95% CI 0.7-1.7). Mortality rates in IDUs remained elevated, although a trend to decrease with longer durations with high CD4 count was seen. A prior AIDS diagnosis was associated with higher mortality.
The persistent role of a prior AIDS diagnosis underlines the importance of early diagnosis of HIV infection [148].

## Non-AIDS-defining events

We report on the incidence of diabetes mellitus, cardiovascular diseases, renal insufficiency, and non-AIDS malignancies in HIV-1-infected patients on cART, as recorded by HIV treating physicians in the Netherlands.

We present the number of patients experiencing diabetes mellitus, cardiovascular diseases, renal insufficiency, and non-AIDS malignancies for the first time and the incidence per 1,000 person-years of observation in *Web Appendix Table 4.6* and the incidence per calendar year in *Figure 4.2*. We present results of the adjusted logistic regression analyses in *Web Appendix Table 4.7*.

*Figure 4.2: The incidence of diabetes mellitus (A), cardiovascular disease (B), renal insufficiency (C), and non-AIDS-defining malignancies (D) on cART per 1,000 person-years of follow-up.*


## Diabetes mellitus and cardiovascular disease

The incidences of diabetes mellitus and cardiovascular disease remained stable over time (*Figure 4.2; Web Appendix Table 4.6*).

Overall, 480 of the 20,761 patients were diagnosed with diabetes from 2002 onwards. Demographic and clinical factors associated with increased risk of new-onset diabetes were male gender, being of non-Dutch origin, older age, having a BMI greater than 25 kg/m$^2$, BMI less than 18.5 kg/m$^2$, hypertension, transmission of HIV heterosexually, through blood contact or injecting drug use, and AIDS diagnosis prior to cART initiation. (*Web Appendix Table 4.7a*).

Factors associated with cardiovascular disease (n=537 from 2002 onwards) were male gender, being older than 45 years, being of Dutch origin, having a prior AIDS diagnosis, and hypertension.

The effect of cumulative exposure to cART regimens on the onset of diabetes mellitus was investigated in the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) prospective observational cohort study of over 33,000 HIV-infected patients, in which SHM contributes significantly (with approximately 20% of those patients). The strongest relationship with diabetes was exposure to stavudine, although exposure to zidovudine and didanosine was also associated with an increased risk [149].

Another study from D:A:D shows that the risk of a myocardial infarction is more than doubled amongst HIV-infected patients with diabetes. Insulin resistance amongst treated HIV-infected patients is multifactorial; in addition to the common contributors to insulin resistance (e.g., obesity, genetic influences, and physical inactivity), antiretroviral drugs and lipodystrophy, which may be a consequence of treatment, particularly with thymidine analogues, are involved [26].

Two other studies using data from D:A:D found that indinavir, lopinavir-ritonavir, didanosine and abacavir were associated with a significantly increased risk of myocardial infarction [25]. The increased relative risk of myocardial infarction with protease-inhibitor use was partially attenuated by controlling for dyslipidaemia, diabetes and hypertension, suggesting that the effects of antiretroviral therapies on traditional cardiac risk factors might contribute in part to the increased rate of myocardial infarction [27].

## International collaborations

**Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study:**
The aim of a recently published study from the D:A:D: study was to investigate whether there is any association between exposure to atazanavir (ATV), either when boosted or not boosted by ritonavir, and myocardial infarction (MI) or stroke.
Poisson regression was used to investigate the association between cumulative exposure to ATV and MI or stroke risk after adjusting for known demographic and clinical confounders, as well as cumulative and recent exposure to specific antiretroviral drugs. Follow-up was started on enrolment in the study and ended at a new MI or stroke event, death, 6 months after the last clinic visit, or 1 February 2011, whichever occurred first.
The incidence of MI varied from 0.28 (95% CI 0.26-0.30) per 100 PYFU in those with no exposure to ATV to 0.20 (0.12-0.32) per 100 PYFU in those with more than 3 years exposure. There was no evidence of an association between cumulative exposure to ATV and MI risk, either in univariate (relative rate/year 0.96 [95% CI 0.88-1.04]) or multivariable (0.95 [0.87-1.05]) analyses. The incidence of stroke was 0.17 (0.16-0.19) per 100 PYFU in those with no exposure to ATV and 0.17 (0.10-0.27) per 100 PYFU in those with more than 3 years exposure. As with the MI endpoint, there was no evidence of an association with ATV exposure in either univariate (1.02 [0.98-1.05]) or multivariable (0.95 [0.87-1.05]) analyses.
These results argue against a class-wide association between exposure to HIV protease inhibitors and the risk of cardiovascular or cerebrovascular events [150].

## Chronic kidney disease

The incidence of chronic kidney disease (CKD), investigated from the first measured creatinine level in patients without previous confirmed renal insufficiency, remained stable over time (*Figure 4.2; Web Appendix Table 4.6*). From 2007 onwards, 715 cases of CKD were identified. The prevalence for CKD in 2007 was 26 per 1,000 person- years in women and 48 per 1,000 person-years in men. The overall incidence from 2008 onwards declined from 8 to 6.8 per 1,000 person-years in men and from 10 to 6.7 per 1,000 person-years in women (test for trend, p=0.003 for males, p=0.24 for females).

From 2007 onwards, 43 patients on cART started dialysis, and 18 patients received a kidney transplant. Six patients died within 6 months after the onset of CKD.

Earlier in the HIV epidemic, CKD in HIV-infected individuals was dominated by HIV-associated nephropathy (HIVAN), predominantly observed in people of sub-Saharan African origin. A recent study with data from SHM investigating the role of ethnicity in the onset of chronic CKD found that in 16,900 patients with available creatinine measurements, the crude risk of the development of CKD amongst patients from sub-Saharan Africa was lower compared to in patients of European origin (hazard ratio 0.44, 95% CI 0.29-0.66, incidence 3.1

versus 6.9 events/1,000 person-years). After adjustment for age, gender, mode of HIV transmission, nadir CD4 count, hypertension, dyslipidaemia, diabetes mellitus, smoking, previous cardiovascular events and use of nephrotoxic medication, the risk of incident CKD was no longer significantly different between patients from sub-Saharan Africa compared to patients of European origin (adjusted hazard ratio (aHR) 0.79, 95% CI 0.49-1.26). Variables that remained independently associated with the development of CKD were increasing age, female gender, HIV transmission through intravenous drug use or blood products, lower nadir CD4 count, hepatitis B surface antigen positivity, diabetes mellitus, smoking and use of nephrotoxic non-antiretroviral medication and atazanavir. Concurrent use of tenofovir was associated with a lower risk of incident CKD (aHR 0.78, 95% CI 0.63-0.97).

The fact that sub-Saharan African origin was not found to be a risk factor for the incidence of CKD in HIV-infected patients in the Netherlands suggests a shift in etiology of CKD from HIVAN towards other causes. The seemingly protective effect of concurrent tenofovir use probably reflects selection bias towards patients tolerant of the drug [Schoffelen et al, unpublished data].

## International collaborations

**Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study:**
Lene Ryom from the University of Copenhagen and fellow investigators with the D:A:D study group looked at kidney impairment amongst HIV patients with normal renal function who started antiretroviral therapy containing tenofovir.
D:A:D is a large observational study of more than 30 cohorts of people with HIV in Europe, Australia, and the U.S.A. It has provided some the first evidence of various complications of HIV/AIDS and its treatment.
This analysis included more than 22,000 participants who were mostly white men with normal kidney function at baseline, defined as an estimated glomerular filtration (eGFR) rate of more than 90 mL/min. Participants were followed for at least 3 months, and the researchers noted how many had an eGFR less than 70 (a potential intervention threshold) or a confirmed eGFR less than 60, indicating moderate CKD.
During a median follow-up period of 4.5 years, 468 participants (2.1%) ha an eGFR less than 70 (incidence rate [IR] 4.78 per 1,000 person-years), whilst CKD developed in 131 (0.6%) (IR 1.33 per 1,000 person-years). Having an eGFR of 60 to 70 was more likely to lead to discontinuation of tenofovir, but not other antiretrovirals. Cumulative duration of tenofovir and ritonavir-boosted atazanavir use were independent predictors of an eGFR less than 70, but this was not significant for CKD. Lopinavir/ritonavir use was the only significant risk factor for both an eGFR less than 70 and CKD (HR 1.11 and 1.22 per year, respectively). These associations diminished after antiretroviral discontinuation.
Tenofovir, atazanavir/ritonavir, and lopinavir/ritonavir use were independent predictors of chronic renal impairment in HIV-positive persons without pre-existing renal impairment. Increased tenofovir discontinuation rates with decreasing eGFR may have prevented further deteriorations [151].

In another D:A:D study, the incidence of advanced CKD, end-stage renal disease (ESRD) or renal death was low, and predictors included traditional renal risk factors, HIV-related factors and pre-existing renal impairment. The prognosis after advanced CKD or ESRD was poor [152].

## Non-AIDS-defining malignancies

After correction for changes in age, the incidence of non-AIDS-defining malignancies has remained stable over the last 10 years. Overall, 805 of the 20,761 patients on cART in SHM have been recorded as having a non-AIDS malignancy from 2002 onwards. Demographic and clinical factors associated with an increased risk of non-AIDS-defining malignancies were older age, being of Dutch origin, and homosexual transmission of HIV. Also, having hepatitis B co-infection, CD4 counts less than 200 cells/mm$^3$ and an AIDS diagnosis prior to cART initiation were significantly associated with the occurrence of a first non-AIDS-defining malignancy (*Web Appendix Table 4.7c*).

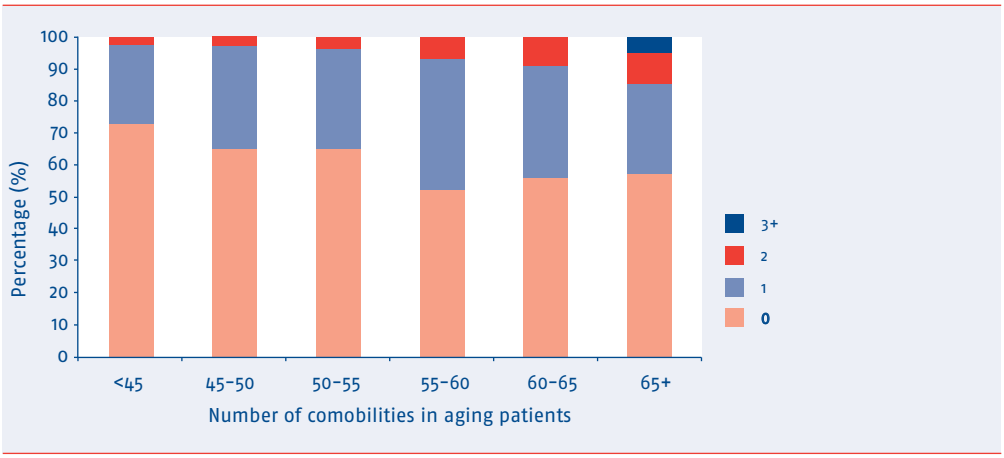
## Co-morbidity in relation to age

In general, older patients with HIV infection have a substantial burden of co-morbidities [153], and this burden may be greater [154] and develop at a younger age than in subjects without HIV [155]. Aging in individuals with HIV-1 infection, besides being associated with the co-morbid conditions previously mentioned, may also be associated with neurocognitive and neuropsychiatric disturbances [156-160] and sexual dysfunction [161].

*Figure 4.3* shows the percentage of HIV-infected patients on cART diagnosed with one or more co-morbidities according to age (at the time of diagnosis of an event or in the case that no events had occurred). The following co-morbidities were taken into account: stroke, myocardial infarction, diabetes mellitus, hypertension, chronic kidney disease, and non-AIDS-defining malignancies. As expected, the proportion of HIV-1 infected patients on cART with one, and especially multiple, co-morbidities increases as patients become older.

The prevalence of these co-morbidities as well as others, particularly in comparison to in individuals not infected with HIV, is examined in more detail within the AGEhIV Cohort Study in which SHM collaborates. The data shown in *Figure 4.3* cannot be directly compared with the data from the AGEhIV Cohort Study, which addressed a wider range of conditions than SHM has access to in monitoring the whole of the Netherlands.

***Figure 4.3:*** *The percentage of one or more co-morbidities (stroke, myocardial infarction, diabetes mellitus, hypertension, CKD and non-AIDS-defining malignancies) in HIV-1-infected patients on cART in the Netherlands according to age*.*




**Age at diagnosis of an event, or current age (as of 1 June 2013) if no comorbidities were diagnosed.*

## Other collaborations

**The AGEhIV Cohort Study:**
Co-morbidity in HIV-infected persons compared to HIV-uninfected individuals.

The AGEhIV Cohort Study, a study in which the HIV outpatient clinic of the Amsterdam Medical Centre (AMC), the Public Health Service Amsterdam (GGD), and SHM closely collaborate, captures a broader spectrum of co-morbid conditions, including at an earlier disease stage, than is currently captured by SHM for the whole of the Netherlands. Importantly, the study also includes an HIV-uninfected control population, which allows a careful assessment of the potential contribution of HIV and associated factors to the risk of co-morbidity. This is relevant in view of reports suggesting that the incidence of serious non-AIDS-defining diseases, such as renal and liver disease, disabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies, is higher amongst infected subjects compared to those who are uninfected.
As such, the study provides important complementary information to the other findings reported in this chapter.

The prevalence of a range of co-morbidities in HIV-uninfected (n=514) and HIV-infected (535) study participants is shown in *Figure 4.4*. These early analyses demonstrate a clear and significantly higher prevalence of CVD within the HIV-infected participants across the spectrum of cardiovascular, cerebrovascular, and peripheral vascular disease and hypertension, as well as of chronic kidney disease. Hypertension (28.2% vs 42.6%, p<0.0001), myocardial infarction (1.6% vs 3.9%, p=0.019), and chronic renal insufficiency (1.9% vs 4.3%, p=0.03) were significantly more prevalent in HIV-infected patients. No statistically significant difference could be demonstrated in the prevalence of diabetes mellitus, chronic obstructive pulmonary disease, osteoporosis, non-traumatic fractures and non-AIDS-defining malignancies, although, numerically, each of these conditions is consistently higher amongst the HIV-infected group.

The proportion of individuals 65 years and older with three or more co-morbidities was clearly higher amongst the HIV-positive group (*Figure 4.5*). Further analyses found increasing age, a family history of co-morbidity, increased waist-hip ratio, smoking, prior exposure to high-dose ritonavir, years spent with CD4 counts less than 200 cells/mm$^3$ and the plasma level of soluble CD14 (a marker of innate immune activation) each to be independently associated with the presence of a higher number of ageing-associated co-morbidities.

*Figure 4.4: Prevalence of each of the different comorbidities at time of enrollment in the two study groups in the AGEhIV study.*

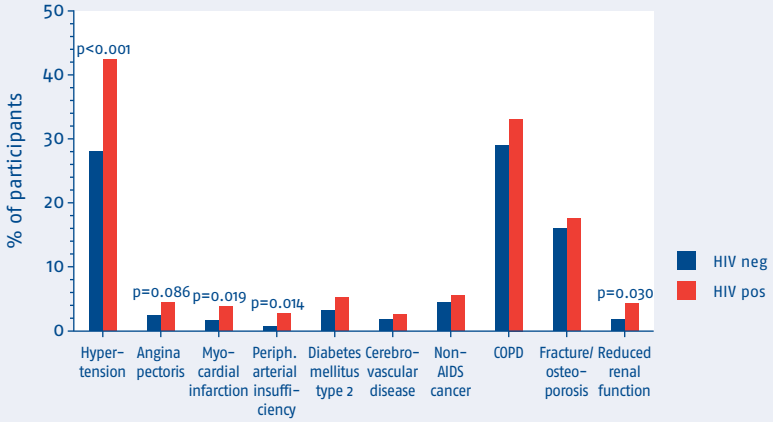
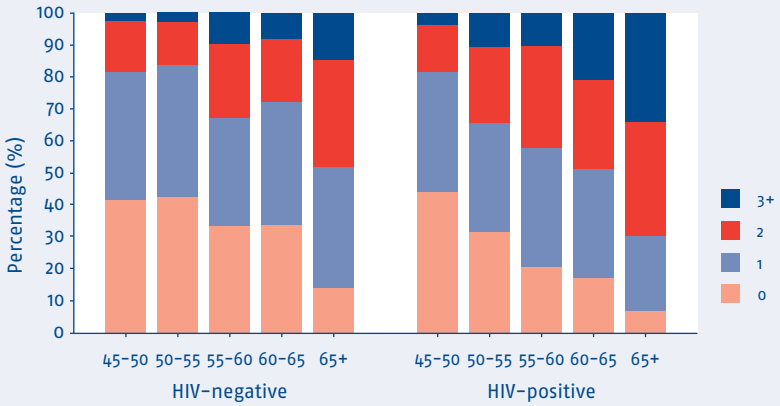



*Figure 4.5: Number of comorbidities at time of enrollment in the two study groups in the AGEhIV Cohort Study.*



## Summary and Conclusions

### Mortality and AIDS

The rates of AIDS and HIV-related death have decreased dramatically since cART became available in the Netherlands in 1996 and continue to be low, consistent with studies from Spain [162], Denmark [163], the U.S.A. [164] and several other European countries [165]. Mortality rates, nonetheless, on average remain higher than in the general population, although they approach rates comparable to those in the general population in certain subsets of patients on treatment with a CD4 count more than 500 cells/mm$^3$. Although a review of the causes of death indicates that there has been a relative decline in the proportion of patients dying of AIDS and a relative increase in non-AIDS causes, the proportion of those dying of AIDS remains substantial. This is likely a reflection of a high proportion of patients continuing to present late for care having already had advanced immunodeficiency, AIDS or both.

### Non-AIDS comorbidity

The likelihood of patients having one, and especially two or more, co-morbid conditions (diabetes mellitus, myocardial infarction, stroke, hypertension, chronic kidney disease, and non-AIDS-defining malignancies) increased as patients became older, compatible with what is expected based on general population studies in the Netherlands [166-172].

### Diabetes and cardiovascular disease

The incidence of diabetes mellitus and cardiovascular disease was found to have remained relatively stable in the cohort. Risk factors were mainly those traditionally known to be associated with these diseases, including age, smoking, hypertension and obesity, similar to what has been reported in other studies [149, 173-175]. Several of these risk factors, notably smoking, have been reported to be more prevalent amongst people living with HIV [143].

The risk of diabetes mellitus amongst people living with HIV has previously been shown to be associated with the use of indinavir, stavudine and didanosine [173]; these drugs either directly affect insulin sensitivity or indirectly affect it by association with peripheral lipoatrophy and central obesity (lipodystrophy) [25-27, 149]. Various antiretrovirals, including the HIV protease inhibitors indinavir and lopinavir, but not atazanavir, and the NRTI abacavir have been associated with an increased risk of myocardial infarction [25]. The move away from such drugs towards those that thus far have not been associated with similar risks, together with increased attention to managing traditional risk factors, may explain the stable incidence of diabetes mellitus and cardiovascular disease we are observing amongst HIV-infected individuals in care in the Netherlands.

### Chronic kidney disease

Older patients and those with traditional risk factors such as diabetes mellitus and hypertension were found to be at increased risk for CKD, as were patients with a previous diagnosis of AIDS or more advanced immunodeficiency. Other studies have reported

hepatitis B and C virus co-infection [176, 177], and the use of tenofovir, atazanavir/ritonavir, and lopinavir/ritonavir to be additional independent predictors of chronic renal impairment [151].

### Non–AIDS-defining malignancies

The incidence of non-AIDS-defining malignancies in the Netherlands has remained stable over time since the introduction of cART. At the same time, the absolute number and proportion of deaths due to non–AIDS-defining malignancies has increased over time. The most common malignancies are lung, liver, kidney, anal, head and neck, and skin cancer, as well as Hodgkin's lymphoma. Several cohorts that included a high proportion of men have reported an increased incidence of non-AIDS cancers [178-180]. Our analyses show that patients were more likely to be diagnosed with non-AIDS malignancies if they were older, born in the Netherlands, had a CD4 count less than 200 cells/mm$^3$ or a previous AIDS diagnosis, similar to what has been reported previously from our cohort [181]. An increase in incidence in non-AIDS-defining malignancies with age has been reported by the Swiss HIV Cohort Study [182], and the D:A:D study has reported an increase in deaths from non-AIDS-defining malignancies [183]. The effect of immunodeficiency may be stronger for infection-related malignancies [181].

### Co-morbidity in HIV-infected compared to in HIV-uninfected individuals

First analyses from the AGEhIV Cohort Study demonstrate a significantly higher prevalence of CVD across the spectrum of cardiovascular, cerebrovascular, and peripheral vascular disease and hypertension, as well as of CKD, in HIV-infected participants compared to those who were uninfected. The prevalence of other co-morbidities such as diabetes mellitus, stroke, chronic obstructive pulmonary disease, osteoporosis or non-traumatic fractures and non-AIDS-defining malignancies for each was numerically also consistently higher amongst those with HIV, although these differences did not reach statistical significance (see boxed section 'Other collaborations' in this chapter).

## Recommendations

Although the proportion of patients dying of AIDS in the Netherlands has markedly declined throughout the cART era, it remains unacceptably high. The best hope to achieve a further reduction is to improve the identification of infected individuals at earlier stages of infection, with immediate linkage to care to allow more timely initiation of treatment. It is possible that this may also have a beneficial impact on the incidence of those co-morbidities, such as non-AIDS malignancies, for which advanced immunodeficiency is a contributing risk factor. In addition, screening for pre-cancerous stages of anal cancer and identification and appropriate treatment of viral hepatitis co-infections may also contribute to lowering the incidence. Studies such as the AGEhIV Cohort Study are needed to provide further insight into the independent contribution of HIV and HIV-associated factors such as (innate and adaptive) immune and coagulation activation and inflammation, thereby guiding the development of interventions targeted at identified relevant mechanisms [134, 184]. In addition,

prolonged follow-up of participants in such studies will demonstrate the extent to which co-morbidity may occur at a significantly younger age in HIV-infected individuals compared to those who are uninfected, thereby further guiding policy for prevention and management.

It is important to realise that the risk of many, if not every one, of the co-morbidities that are frequently identified in people living with HIV is determined by multiple factors. Apart from immunodeficiency, well known traditional unmodifiable risk factors, such as age and genetic predisposition, and modifiable lifestyle-related factors, as well as known and yet unknown effects of antiretroviral treatment and co-infections, are key additional contributors for consideration. Development of antiretrovirals with improved safety profiles for long-term use should continue to remain a priority, given the association of some of the current generation of drugs with CKD, cardiovascular outcomes, bone loss, and possibly cancer [185].

Aging, of course, strongly contributes to the risk of the development of co-morbidity, ranging from cardiovascular and chronic kidney disease to diabetes mellitus and non-AIDS malignancies. Given the steadily rising proportion of individuals in the older age categories in our cohort, it will be imperative to continue and, where possible, improve and expand the monitoring of co-morbidity burden.

Awareness on the part of both physicians and patients of the role of modifiable, lifestyle-related risk factors like smoking, particularly in those who are older or otherwise at high a priori risk of certain co-morbidities, and their appropriate management offer considerable hope for ensuring a lower co-morbidity burden and healthy aging for persons living with HIV. This, of course, particularly applies to conditions such as cardiovascular disease and diabetes mellitus, but is also relevant to conditions such as chronic kidney disease, bone loss and cancer.

# 5. Viral Hepatitis

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## Background

Infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) generally are uncommon in the Netherlands. It is estimated that 0.1 to 0.4% of the total Dutch population has evidence of ever having been exposed to HCV and 0.2 to 0.4% to HBV [186]. In contrast, HCV and HBV infections are much more prevalent in HIV-infected individuals as a result of shared routes of transmission [187].

Individuals with chronic HCV or HBV infection are at risk for the development of liver fibrosis, which in time may lead to cirrhosis and ultimately can result in end-stage liver disease and hepatocellular carcinoma (HCC) [188, 189]. Progression to severe liver disease takes, on average, 20 to 25 years in HCV- or HBV-mono-infected patients [190, 191]. However, in the presence of untreated HIV infection, progression related to HCV and HBV infection is more rapid [192, 193]. These long-term complications have in recent years led to increased mortality rates in HCV and HBV mono-infected persons, as well as in HIV co-infected individuals [194].

In the era when treatment for HIV infection was either unavailable or insufficiently effective to result in sustained suppression of viral replication, patients progressed to AIDS and death before the effects of co-infection with HCV or HBV were able to clinically manifest themselves in terms of severe chronic liver disease. Now that the incidence of AIDS and its associated mortality rate have markedly declined with the widespread use of combination antiretroviral therapy (cART), liver disease has become increasingly apparent as a frequent cause of morbidity and mortality in persons living with HIV [195].

In view of these developments, the Stichting HIV Monitoring (SHM) has greatly increased its efforts to monitor the epidemiology and clinical consequences of HCV and HBV co-infection amongst patients in care at treatment centres in the Netherlands. This chapter summarizes the current information regarding the demographic and clinical characteristics and progression to severe chronic liver disease and mortality, as well as responses to treatment, in this population with HIV and either HCV or HBV co-infection, or both.

A working group on hepatitis, which was set up jointly between SHM and the Nederlandse Vereniging van HIV behandelaren (NVHB, Dutch Association of HIV-treating Physicians), has developed a standardized protocol for the collection of data related to liver disease and hepatitis for inclusion in the SHM database. The extended data collection according to this protocol was implemented in July 2012. Detailed data spanned the whole spectrum of both HBV and HCV infection ranging from serodiagnostics and treatment responses (including

adverse effects) to complications such as severity of liver fibrosis (based on liver elastography [also known as fibroscan], pathology, radiology and endoscopy reports). These additional data allow increasingly reliable reporting of the prevalence and incidence of severe liver disease.

To date, these data have been retrospectively collected for patients co-infected with HCV. However, the collection of similar data for patients with chronic active HBV co-infection is ongoing and as yet incomplete, with the exception of data on HCC. For this reason, the current report on severe chronic liver disease, with the exception of HCC, mainly concerns HCV-co-infected patients. Data for further specification of severe liver disease in patients with HBV co-infection are expected to be available by the end of 2013 and will be included in future SHM monitoring reports.

## HCV

### Demographic and clinical characteristics

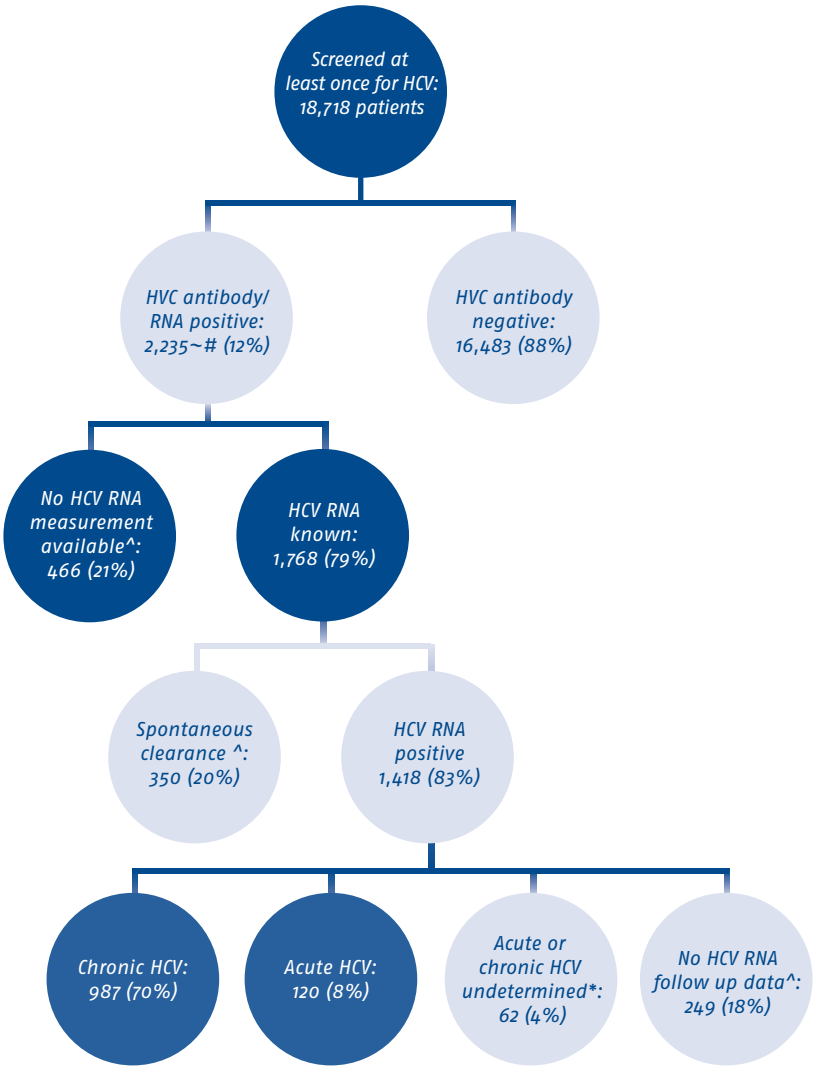
In total, 2,235 (12%) of the 18,718 HIV-1-infected adult patients (≥18 years) ever screened for HCV co-infection had a positive result on an HCV antibody test, confirming a much higher prevalence of HCV in the HIV-infected population compared to estimates for the general population in the Netherlands (*Figure 5.1*). In 466 out of 2,235 (21%) patients, HCV RNA data could not be documented. Of the patients with available HCV RNA, 350 out of the 1,768 (20%) either had a documented positive result of an HCV antibody test, with a subsequent negative result on HCV RNA testing (n=301), or did not fulfil the criteria for having acute HCV infection (n=50), but those 50 patients had a positive HCV RNA test result that reverted to negative within 6 months, which indicated that they had spontaneously cleared an HCV infection.

Of 1,768 patients, 1,418 (83%) had tested positive for HCV RNA. Amongst this group of patients, 987 remained positive for HCV RNA more than 6 months after the first positive test result and thus were considered to be chronically infected with HCV. Of the 1,418 patients who tested positive for HCV RNA, 120 were diagnosed with acute HCV infection; these patients had an anti-HCV IgG seroconversion or an HCV RNA conversion within 12 months.

A negative test result for HCV IgG was documented in 62 patients more than 12 months before a first positive HCV IgG or HCV RNA result, making it undeterminable whether these patients had acute or chronic HCV infection. For the remaining 249 patients who had positive results for HCV RNA, unfortunately, no HCV RNA follow-up data are currently available, so it was impossible to determine whether the HCV infection was acute or chronic. It was therefore decided to exclude these two groups of patients from further analyses. Attempts will be undertaken to obtain additional data from these patients to be able to better classify them for future analyses.

**For these reasons, the analyses described in the remainder of this chapter are limited to patients who could be definitively classified as having either chronic (n=987) or acute (n=120) HCV infection.**

*Figure 5.1: Flowchart of HIV-infected patients tested at least once for HCV.*




~ *Including 172 patients who were HCV RNA positive but no known HCV antibody data.*

\# *Including documented seroconversion (n=182).*

^ *Excluded from further analyses.*

* *Known negative HCV antibody/RNA test greater than 12 months before known positive test; excluded from further analyses.*

The large majority of patients with chronic HCV infection were male (814/987, 82%) and all patients with an acute HCV infection were male. The majority of patients with a chronic or an acute HCV infection originated from the Netherlands (chronic: 641/987 [65%], acute: 98/120 [82%] (*Table 5.1*). Forty-nine percent of the patients ever registered and infected with HIV through (former) injecting drug use ([ex-]IDU) had chronic HCV (341/689). Four percent of the men who have sex with men (MSM) had chronic HCV infection (431/11,134) and 1% had acute HCV infection (114/11,134).

HCV genotypes were determined in 879 of the 987 (89%) patients with a chronic HCV infection. Of those, most patients (62%) were infected with HCV genotype 1, 5% with genotype 2, 16% with genotype 3, and 16% with genotype 4.

In 104 out of the 120 (87%) patients with an acute HCV infection, an HCV genotype was available. Patients with an acute HCV infection were more often infected with genotype 1 (76%) and genotype 2 (13%) compared to those with chronic HCV infection.

*Table 5.1: Demographic characteristics of HCV-co-infected patients registered in the SHM database, 1998-2013.*

| | Total | Chronic HCV | Acute HCV |
|---|---|---|---|
| Total number of patients screened for HCV | 18,718 | 987 | 120 |
| Male gender, n (%) | 15,207 | 814 (82) | 120(100) |
| Age at HIV diagnosis, years (median IQR) | 36 (29-44) | 34 (29-40) | 36 (30-43) |
| Region, n (%) | | | |
| Netherlands | 10,734 | 641 (65) | 98 (82) |
| Europe | 1,766 | 171 (17) | 13 (11) |
| Sub-Saharan Africa | 2,737 | 43(4) | 1(0.8) |
| Caribbean/Latin America | 2,162 | 58(6) | 3 (3) |
| Southeast Asia | 618 | 25(3) | 3 (0.8) |
| Other | 701 | 49 (5) | 2(2) |
| HIV transmission route, n (%) | | | |
| Homosexual | 11,134 | 431 (44) | 114 (95) |
| Heterosexual | 5,683 | 101 (10) | 3 (3) |
| (Former) injecting drug use | 689 | 341 (35) | 1 (0.8) |
| Other | 1,212 | 114 (12) | 2(2) |
| cART, n (%) | 16,233 | 937 (95) | 112 (93) |
| HCV genotype, n (%*) | | | |
| Total determined | | 879 | 104 |
| Genotype 1 | | 548 (62) | 76(76) |
| Genotype 2 | | 40 (5) | 14 (13) |
| Genotype 3 | | 136 (16) | 2 (2) |
| Genotype 4 | | 144 (16) | 11 (11) |
| Genotype other | | 11 (1) | 1 (1) |
| Not determined | | 108 | 16 |
| Deaths, n (%) | 1,698 | 169 (17) | 2 (2) |

*Legend: HCV = hepatitis C virus; n = the total number and (%) the percentage of the total per column; cART = combined antiretroviral therapy*

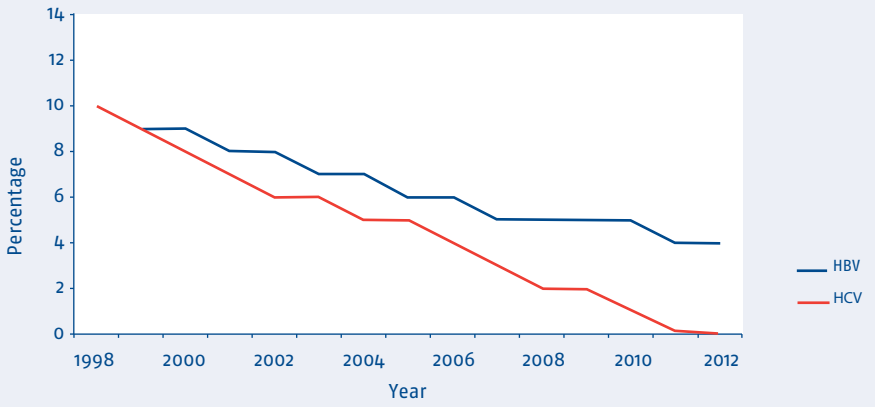
** Percentage from total number of patients with an available HCV genotype*

## Changes over time

### Testing for HCV over time

Screening for HCV infection amongst HIV-infected patients in care increased over calendar time. In 1998, 10% of the HIV-infected patients in care had not been screened for the presence of HCV infection, but with time a strong and steady decrease in the proportion with unknown HCV status has been observed. In 2010, only 1% of the patients in care had not been screened for HCV co-infection, and this total declined further to 0.02% in 2012 (*Figure 5.2*).

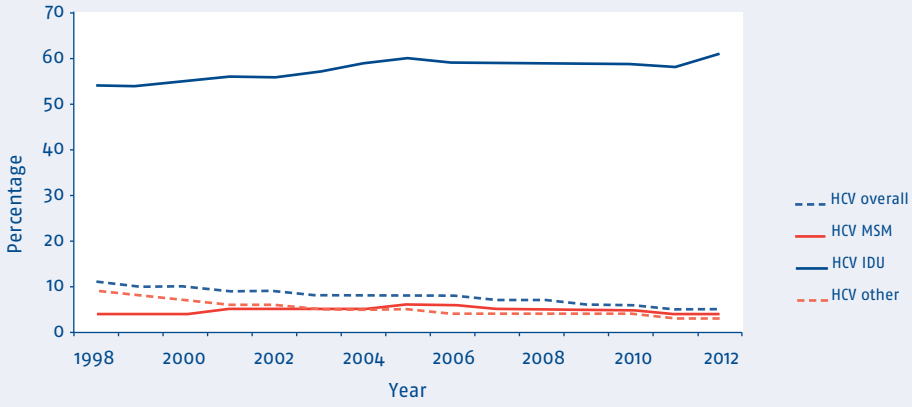
*Figure 5.2: Percentage of patients in care with an unknown status of HBV or HCV infection per calendar year.*




### Prevalence of chronic HCV infection over time

The overall prevalence of chronic HCV infection amongst patients in care decreased from 11% in 1998 to 5% in 2012, but was not equally distributed among HIV transmission categories. The highest prevalence was found amongst patients infected with HIV by (former) IDU, and this number has remained relatively stable between 54% and 61% (*Figure 5.3*). The prevalence of chronic HCV infection amongst MSM was 4% in 1998; it increased to 6% between 2005 and 2006, and dropped again to 4% in 2012.

*Figure 5.3: Prevalence of chronic active HCV co-infected patients per calendar year.*



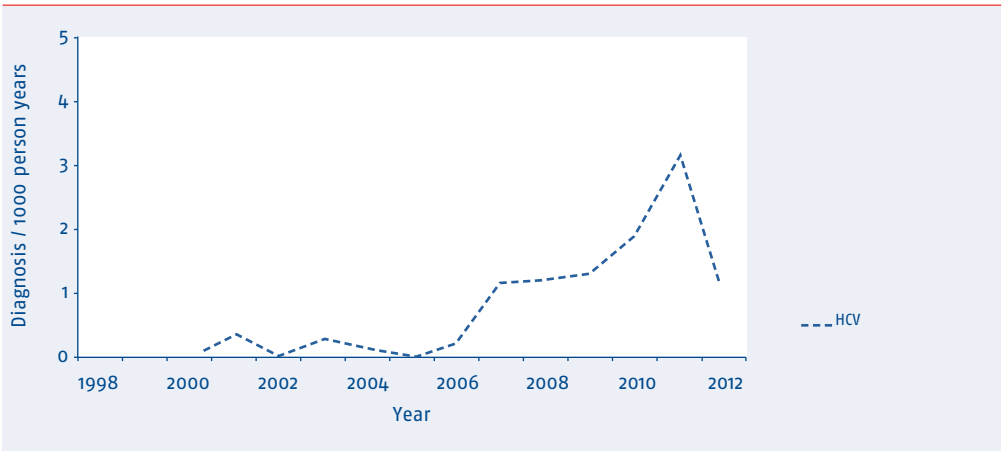
### Incidence of acute HCV infection over time

*Figure 5.4* shows the incidence of acute HCV infection over time. The overall rate of acute HCV infection in HIV-infected patients was 0.90 per 1,000 person-years (PY) of follow-up (95% confidence interval [CI] 0.75-1.08). This incidence increased from 0 diagnoses per 1,000 PY in 1998 to 3.1 diagnoses per 1,000 PY in 2011.

The incidence of acute HCV infection differed importantly between HIV transmission categories. For (former) IDU, the overall incidence was low (0.4 /1,000 PY, 95% CI 0.01-2.22), probably explained by the already large background prevalence of infection in this group and, therefore, the relatively small number of patients still remaining at risk for newly acquired HCV infection.

Amongst MSM, however, a steady increase in incidence of acute HCV infection was observed over time, from 0.47 diagnoses per 1,000 PY in 2003 to 4.5 diagnoses per 1,000 PY in 2011.

***Figure 5.4:*** *Incidence of acute HCV infection per calendar year.*



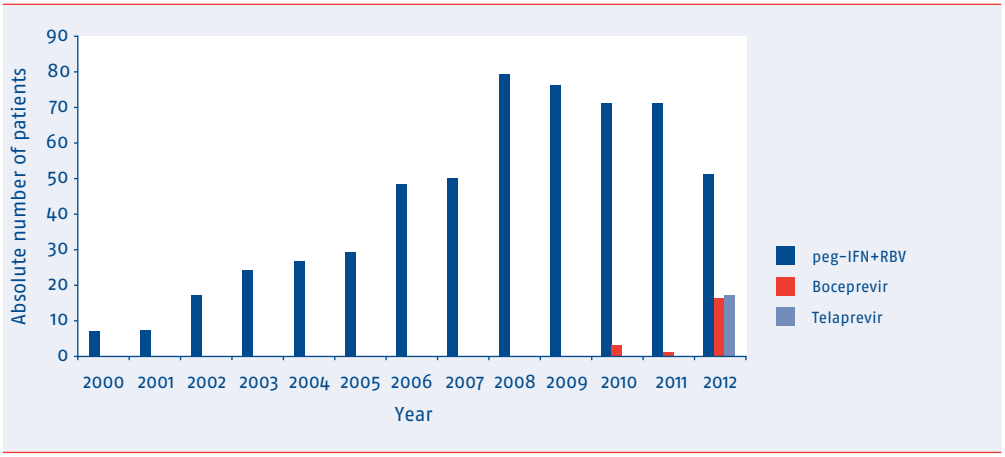
### Treatment for HCV infection

The primary aim of treatment for HCV is to achieve a sustained virological response (SVR) [196]. Until recently, treatment consisted of a combination of originally unpegylated interferon alfa (IFN-alfa) and subsequently pegylated interferon alfa (peg-IFN alfa) with ribavirin (RBV). The usual duration of treatment is 24 or 48 weeks, depending on HCV genotype. In April 2012, the HCV protease inhibitors boceprevir and telaprevir, two direct-acting antiviral agents (DAA) with activity predominantly against HCV genotype 1, became available in the Netherlands [197]. Triple therapy including one of these two agents, together with peg-IFN alfa and RBV, has since become the treatment of choice for chronic HCV genotype 1 infection, whereas a combination of peg-IFN alfa and RBV currently remains the standard treatment for chronic HCV infection with genotypes other than 1, as well as for acute infection with any genotype.

Overall, a total of 567 out of the 1,107 (51%) patients with known chronic or acute HCV infection have been prescribed a combination of peg-IFN alfa and RBV without additional antiviral therapy. In the SHM database, an additional 41 patients are known to have received peg-IFN alfa and RBV with either boceprevir or telaprevir.

*Figure 5.5* shows the absolute number of patients having started HCV treatment per calendar year. The number of patients starting peg-IFN alfa and RBV treatment increased from 7 in 2000 to 76 in 2009 and 51 in 2012. Three patients started a regimen including boceprevir in 2010, 1 patient in 2011 and 16 patients in 2012. Telaprevir was prescribed for 17 patients in 2012 and for 4 patients in 2013.

***Figure 5.5:*** *Number of co-infected patients starting HCV treatment per calendar year.*



### HCV treatment outcome

Given that the number of patients treated with boceprevir or telaprevir is small (n=41) and treatment has not yet been completed in a substantial proportion, this group of patients will not be described further in this year's report. The same applies to the 56 out of 567 patients whose treatment with peg-IFN alfa and RBV is currently ongoing and, therefore, whose outcome cannot yet be definitively assessed. We have thus limited our analyses of treatment outcome to the 511 patients for whom the outcome of treatment with peg-IFN alfa and RBV is currently known.

Of these 511 patients, 346 completed the full course of therapy (i.e., 24 to 48 weeks) with peg-IFN alfa and RBV, whereas 165 patients prematurely discontinued treatment before week 24 because of side effects or lack of response.

Out of 511 patients, 165 (25%) discontinued peg-IFN alfa and RBV treatment within 24 weeks, with 61 of 165 (36%) discontinuing within the first 4 weeks and 65 of 165 (40%) within 14 weeks. An additional 39 of 165 (24%) of the patients prematurely discontinued treatment between weeks 14 and 24.

The most commonly reported reasons for discontinuation were treatment-associated toxicities (n=100/165, 61%) such as depression, extreme fatigue, leucopoenia, neutropenia, thrombocytopenia and anaemia, and 79 out of 165 (48%) patients were non-responders at week 12, as reported by their treating physician in the clinical chart.

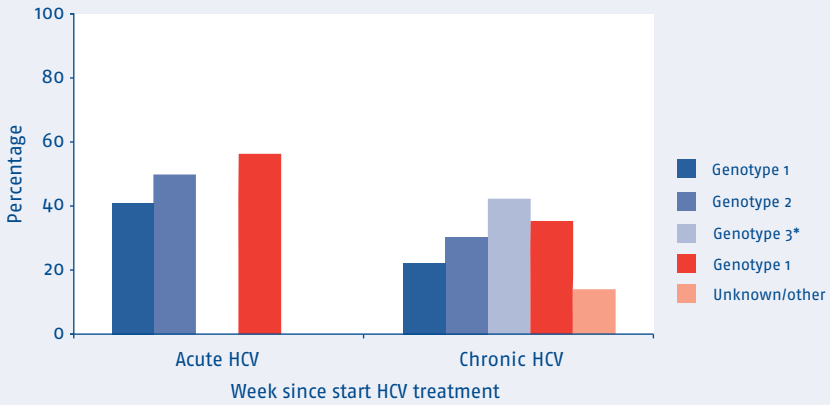
Out of the 511 patients with a known HCV treatment outcome, 90 were treated for acute HCV infection and 421 for chronic HCV infection. These represent 90 out of 120 (75%) of the patients with documented acute HCV infection currently registered in the SHM database, and 421 out of 987 (43%) of those with documented chronic HCV infection in the current SHM database.

### Outcome of treatment for acute HCV infection

The median duration of treatment in the 90 patients who completed treatment with peg-IFN alfa and RBV for acute infection was 24 weeks (interquartile range [IQR]: 21-26).

SVR rates are shown in *Figure 5.6*, stratified by HCV genotype. SVR rates were as high as 56% in patients with HCV genotype 4 and 41% to 50% for genotypes 1 and 2, but of note, the number of treated patients infected with genotypes 2 and 4 was small, limiting any conclusions about treatment response by genotype. None of the patients with genotype 3 received treatment.

*Figure 5.6: SVR achieved by HCV treatment in acute and chronic HCV infected patients, stratified by HCV genotype.*




** None of the treated patients with an acute HCV infection was infected with genotype 3.*

### Outcome of treatment for chronic HCV infection

The median duration of treatment in the 421 patients treated with peg-IFN alfa and RBV for chronic infection was 26 weeks (IQR: 13-48). *Figure 5.6* shows the SVR rate stratified by HCV genotype. Forty-two percent of the patients with genotype 3 achieved an SVR, but this proportion was much lower for the other genotypes, that is, 22% for genotype 1, 30% for genotype 2, 35% for genotype 4 and 14% for patients with an unknown or other genotype.

## HBV

Forty-eight percent of the 19,417 HIV-infected patients ever registered in the SHM database and ever screened for hepatitis B core antibody (anti-HBc) tested positive and thus have been exposed to HBV.

In total, 16,807 (87%) HIV-infected patients were tested for both anti-HBc and antibody to hepatitis B surface antigen (anti-HBs). Of those, 4,100 (24%) patients were anti-HBc-negative and anti-HBs-positive, indicating that they had been successfully vaccinated against HBV. These figures were 28% for MSM, 20% for heterosexuals, and much lower (7%) for (former) IDU.

Therefore, overall, approximately 28% of the HIV-infected patients had not been exposed to HBV or were not (or not successfully) vaccinated and remained at risk for HBV (100% - 48% exposed - 24% vaccinated = 28%). Among MSM, 21% remained at risk for HBV (100% - 51% exposed - 28% vaccinated = 21%).

Patients in these categories may be offered HBV vaccination. Some patients might already be protected from acquiring HBV by the use of tenofovir as part of their cART regimen, which has been suggested by recent findings from one of the Dutch treatments centres [198].

Chronic active HBV co-infection was found in 1,739 of the 19,217 (8%) HIV-infected patients ever screened for HBV, which, similar to HCV co-infection, is considerably higher than the rate of HBV infection in the general Dutch population. Patients co-infected with HBV were predominantly male (1,474/1,739, 85%), also similar to those co-infected with HCV (*Table 5.2*). However, compared to patients co-infected with HCV, those co-infected with HBV were more often born in sub-Saharan Africa and more often acquired HIV by heterosexual contact. HBV co-infection was less common than HCV co-infection amongst (former) IDU.

***Table 5.2:** Demographic characteristics of HIV-infected patients with an active chronic HBV infection registered in the SHM database.*

| | Total | HBsAg positive |
|---|---|---|
| Total number of patients screened for HBV | 19,217 | 1,739 |
| Male gender, n (%) | 15,500 (81) | 1,474 (85) |
| Age at HIV diagnosis, years (median IQR) | 36 (29-44) | 34 (29-42) |
| Region, n (%) | | |
| Netherlands | 10,976 (57) | 950 (55) |
| Europe | 1,791 (9) | 156 (9) |
| Sub-Saharan Africa | 2,901 (15) | 334 (19) |
| Caribbean/Latin America | 2,204 (11) | 180 (10) |
| Southeast Asia | 643 (3) | 59 (3) |
| Other | 702 (4) | 60 (3) |
| HIV transmission group, n (%) | | |
| Homosexual | 11,282 (59) | 1,015 (58) |
| Heterosexual | 5,985 (31) | 498 (29) |
| Injecting drug use | 692 (4) | 96 (6) |
| Other | 1,258 (7) | 130 (7) |
| cART, n (%) | 16,664 (87) | 1,598 (92) |
| Deaths, n (%) | 1,852 (10) | 253 (15) |

***Legend:** HBV = hepatitis B virus; cART = combination antiretroviral therapy; n = the total and (%) the percentage of the total per column*

### Testing for HBV infection over time

Screening for HBV infection amongst HIV-infected patients in care improved over calendar time. In 1998, 10% of the patients were not screened for the presence of HBV infection. Although a strong decrease was observed subsequently for the proportion of HIV-infected patients with an unknown HBV status, 4% of all patients in care in 2012 still had an unknown HBV status, according to the data available to us (*Figure 5.1*).

One explanation might be that patients who reported that they had been successfully vaccinated in a programme elsewhere may not have been offered repeated testing in their HIV treatment centre.

### Prevalence

The overall prevalence of chronic active HBV infection amongst patients in care decreased from 11% in 1998 to 8% in 2012. The highest prevalence was found amongst patients infected with HIV by homosexual contact. In 1998, 12% of the MSM had chronic active HBV infection, with a decrease to 8% in 2012 (*Figure 5.7*). This decreasing prevalence of chronic HBV infection might be the result of an increasing proportion of patients being vaccinated against HBV (*Figure 5.8*).

***Figure 5.7:*** *Prevalence of chronic active HBV co-infected patients per calendar year.*

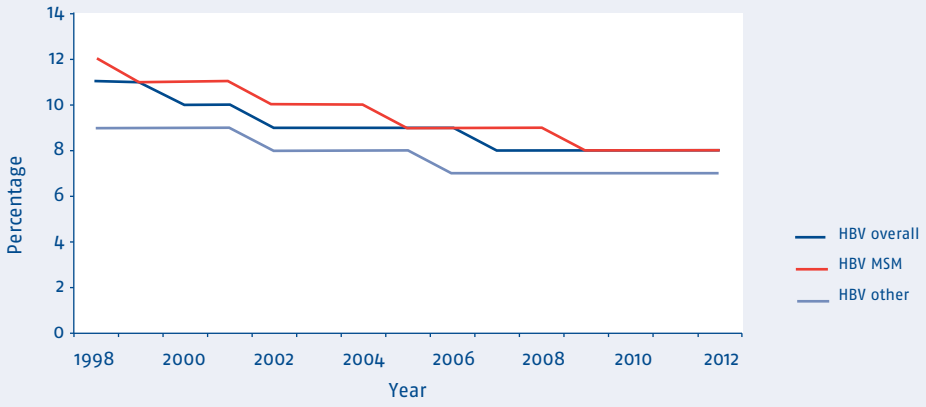
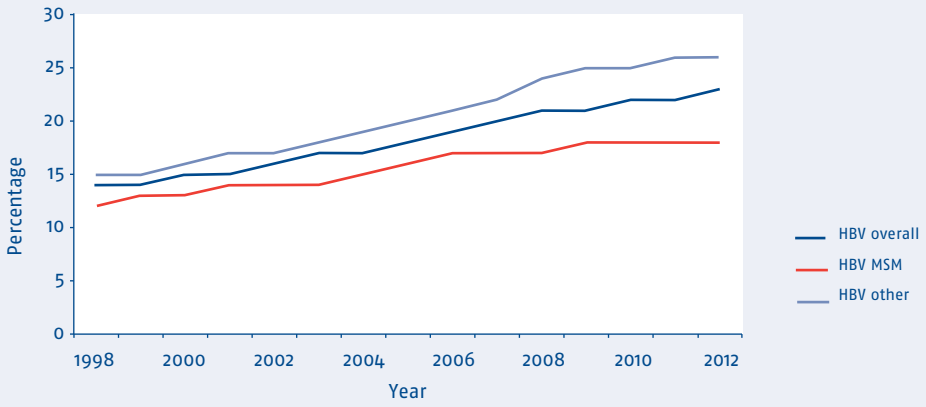


*Figure 5.8: Prevalence of patients vaccinated for HBV per calendar year.*




## Treatment for chronic active HBV infection

Since chronic HBV infection is defined by the presence of the HBV surface antigen (HBsAg+), therapy is aimed at lowering the level of HBs antigen in order to result in HBsAg negativity in a subgroup of patients. When HBsAg negativity persists and antibodies against HBs develop (anti-HBs), this is called HBs seroconversion. HBs seroconversion is the penultimate goal of HBV therapy. In those patients who are also e-antigen positive (HBeAg+), a similar seroconversion can take place from HBeAg positivity to HBeAg negativity, with subsequent development of anti-HBe antibodies. This so-called e-seroconversion is an important secondary treatment parameter, since studies have shown it results in a clinically important lowering of the HBV DNA. Lastly, HBV DNA is the parameter most directly influenced by therapy with nucleos(t)ide analogues. Therefore, HBV DNA undetectability is the best surrogate marker for response, but even persistent lowering of HBV-DNA levels to <2,000 IU per millilitre has been shown to delay progression of liver fibrosis to cirrhosis, and in some patients it has even led to fibrosis regression. Several antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and tenofovir, are also active against HBV.

Of the 1,739 patients with HIV in the SHM database co-infected with chronic HBV, 1,590 (91%) ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for patients not receiving anti-HBV treatment included dying before being able to start treatment (n=23), entering care very recently (n=17), not receiving cART (n=14), or being lost to follow up (n=70). Further information is not available for the remaining 25 patients.

Most patients (n=988/1,590, 62%) initially received lamivudine as monotherapy against HBV. Of these 988 patients, 355 (36%) switched to a regimen containing tenofovir-lamivudine after a median of 1.6 years (IQR: 0.5-3.6), and 274 (28%) to a tenofovir-emtricitabine-containing regimen after a median of 1 year (IQR: 0.3-2.6) prior exposure to lamivudine monotherapy for HBV. For 602 of 1,590 patients (38%), their initial cART regimen included tenofovir and one additional agent with activity against HBV; in 128 of the 602 (21%) patients, the additional agent was lamivudine, and in 474 out of the 602 (79%), it was emtricitabine.

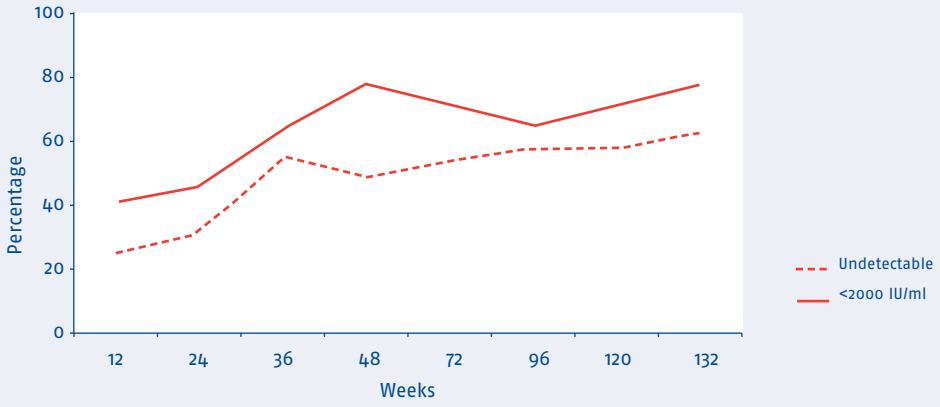
It has been shown that a persistently inactive HBV carrier state with an HBV-DNA of <2,000 IU per millilitre confers a favourable long-term outcome, with low risk of cirrhosis and HCC in the majority of HBV-mono-infected patients. Whether this also holds true for HBV-HIV co-infected patients being successfully treated for both infections has not yet been definitively demonstrated. We therefore decided to analyse available data not only using a threshold of <20 IU per millilitre as an indicator of levels being undetectable, but also a threshold of <2,000 IU per millilitre.

*Figure 5.9* shows the percentage of patients with an undetectable HBV DNA level (<20 IU/ml) and those with HBV DNA levels below 2,000 IU per millilitre. Twelve weeks after the start of HBV treatment, 25% of the patients had an undetectable HBV DNA level, and 41% an HBV DNA level below 2,000 IU per millilitre. The percentage of patients with an undetectable HBV DNA level (<20 IU/ml) increased to 63% 2.5 years after the start of treatment. At that time, 78% of the patients had an HBV DNA level <2,000 IU per millilitre.

Amongst the 1,590 patients whose antiretroviral regimen ever included one or more agents with activity against HBV, 475 of the 1,586 (30%) patients with a documented test result for HBeAg before the start of treatment were positive. Of these 475 patients, 303 (64%) were retested, with 137 (45%) patients converting from HBeAg positivity to negativity and HBe antibodies developing in 83.

Of 1,590 patients for whom repeat HBsAg and anti-HBs antibody test results were available following the start of treatment, HBsAg clearance during HBV treatment could be measured in 908 (57%) and HBs seroconversion in 993 (62%). HBsAg clearance was achieved in 223 of the 908 (24%) patients and conversion to anti-HBs positivity (from anti-HBs negativity) in 106 of 993 (11%).

*Figure 5.9: Percentage of patients with undetectable HBV DNA levels or HBV DNA levels <2000 IU/ml since the start of HBV treatment.*




## Morbidity and mortality

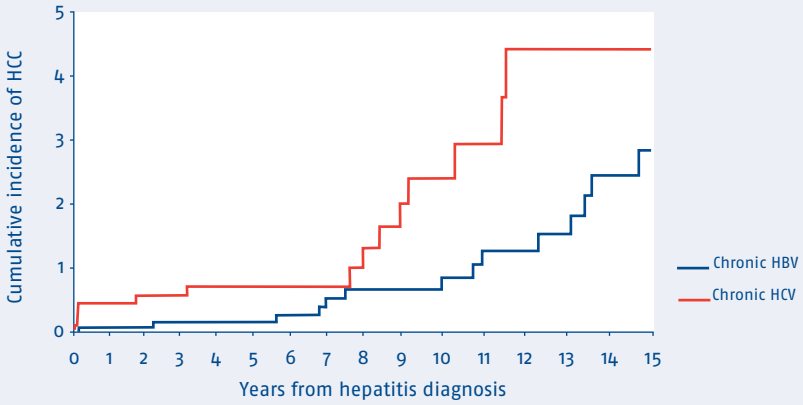
### Morbidity

Additional data on pathology reports from liver biopsy, fibroscan, or both were available for 792 out of the 987 patients with chronic HCV infection. On review of these additional data with use of our previous definition of severe chronic liver disease, that diagnosis (presumptive and definitive combined) was determined in 300 of the 792 (30%) of patients. Amongst these 300 chronic HCV co-infected patients, 64 had definitive chronic liver disease, with most having clinical evidence of splenomegaly (n=48 of 64) and ascites (n=12 of 64).

Among the patients with an acute HCV infection, additional data on liver disease were available for 62 out of the 120 patients. Nineteen patients with an acute HCV infection were reported to have evidence of severe liver disease (including one case in which the patient had been exposed to didanosine [ddI] and may have had non-cirrhotic portal hypertension).

HCC was diagnosed in 15 out of 987 (1.5%) patients with chronic HCV co-infection, of whom 11 were born in the Netherlands. HCC was found in 18 (1%) patients with a chronic HBV co-infection, 10 of whom were born in the Netherlands, 4 in sub-Saharan Africa, and one each in the Caribbean, Asia, the United States and Australia. The cumulative incidence of HCC did not differ between patients with chronic HCV or HBV infection (p=0.79) (*Figure 5.10*). Ten years after a known diagnosis of viral hepatitis, HCC had developed in 1.0% (95% CI 0.3-2%) of patients with chronic HCV and in 1.0% (95% CI 0.5-2%) of those with chronic active HBV co-infection.

*Figure 5.10: Cumulative incidence of hepatocellular carcinoma (HCC) amongst co-infected patients with HIV and HCV or HBV. Kaplan Meier estimate was used to estimate the time to HCC. Follow-up time was from the date of HIV diagnosis to the date of last contact diagnosis of HCC, or 1 January 2013.*




## Mortality

The overall rate of death from any cause was 17% for the 987 patients with chronic HCV co-infection and 15% for the 1,739 patients with chronic active HBV co-infection. Four percent of the HCV co-infected patients and 2% of the HBV co-infected patients died of a liver-related cause (*Table 5.3*). Seventeen out of the 169 (10%) patients with chronic HCV infection died of an AIDS-related cause, and 18 out of the 169 (11%) died of a malignancy that was not associated with AIDS or hepatitis. Amongst patients with a chronic HBV infection, 48 out of 253 (19%) died of an AIDS-related cause and 26 out of 253 (10%) of a non-AIDS- or non-hepatitis-related malignancy.

*Table 5.3: Morbidity and mortality in HCV and HBV co-infected patients registered with the SHM.*

| | Chronic HCV infection | Acute HCV infection | Active chronic HBV infection |
|---|---|---|---|
| Total | 987 | 120 | 1,739 |
| Severe (chronic) liver disease#, n (%) | 300 (30) | 19 (16) | Data currently insufficient for analysis |
| HCC, n (%) | 15 (1.5) | 0 (0) | 15 (1) |
| Deaths from any cause*, n (%) | 169 (17) | 2 (1.7) | 253 (15) |
| Liver-related deaths, n (%) | 37 (4) | 0 (0) | 35(2) |

*Legend: HCV = hepatitis C virus; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; n = the total and (%) the percentage of the total per column*

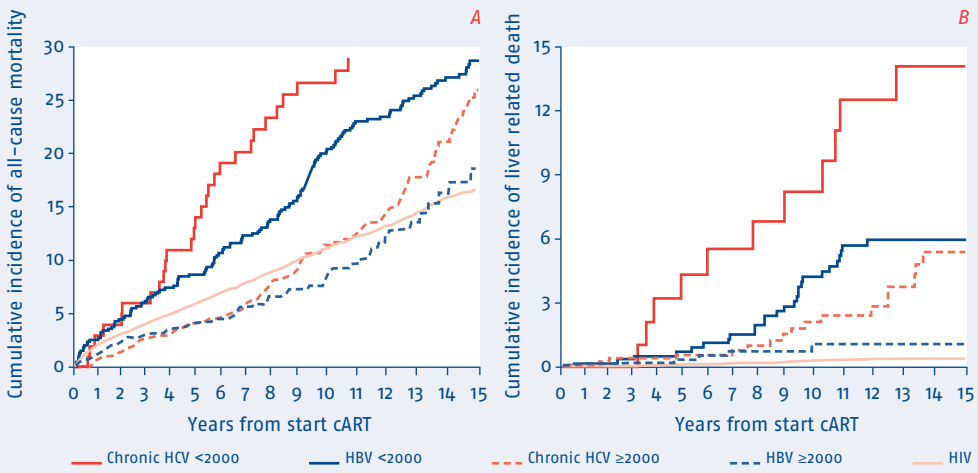
*# Including presumptive and definitive severe liver disease*

** Including liver-related death*

### All-cause mortality

The cumulative incidence of death from any cause was higher among patients who were diagnosed with chronic HCV or chronic HBV before 2000 compared to those who were diagnosed in later calendar years (*Figure 5.11*).

***Figure 5.11:*** *Cumulative incidence of all-cause mortality (A) and liver-related death (B), stratified by calendar year period of HCV or HBV diagnosis. A Kaplan Meier estimate was used to estimate the time to death. Follow-up time was from the date of HIV diagnosis to the date of last contact, death, or 1 January 2013.*




When the risk of death from any cause was adjusted for differences in demographic and clinical characteristics (age at HIV diagnosis, gender, region of origin, HIV transmission risk group, calendar year of cART initiation, CD4 count and HIV RNA level at time of cART initiation, alcohol use and smoking, time since HIV diagnosis and calendar year of HIV diagnosis), there was no significant difference in the risk of death between HIV mono-infected patients and patients with a chronic HCV co-infection diagnosed before 2000. However, for patients with a chronic HCV co-infection diagnosed after 2000, the overall risk of death remained higher compared to that in HIV mono-infected patients.

For patients with a chronic HBV co-infection diagnosed before 2000, the overall risk of death was higher compared to that in HIV-mono-infected patients (*Table 5.4*). This difference, however, no longer remained significant for patients with chronic HBV infection diagnosed from 2000 onwards.

*Table 5.4: Adjusted hazard ratios of time from start of cART to all-cause mortality and liver-related death amongst HIV-infected patients with hepatitis co-infection compared to patients infected with HIV only. To evaluate the impact of HBV and HCV co-infection on risk of death, time on cART to death was estimated by a Cox proportional hazard model. Follow-up time was from the date of cART initiation until date of last contact, most recent follow-up visit, death or 1 January 2013.*

| | Risk of death from any cause | p-value | Risk of liver-related death | p-value |
|---|---|---|---|---|
| | Hazard ratio (95% CI) | | Hazard ratio (95% CI) | |
| HIV | 1 | 0.01 | 1 | <0.0001 |
| HIV/chronic HCV, <2000 | 1.02 (0.70-1.48) | | 7.83 (3.31–18.49) | |
| HIV/chronic HCV, ≥2000 | 1.48 (1.14-1.91) | | 6.17 (2.85-13.39) | |
| Acute HCV | 0.85 (0.12-6.05) | | - | |
| HIV/chronic HBV, <2000 | 1.26 (1.05-1.51) | | 8.01 (4.45-14.39) | |
| HIV/chronic HBV, ≥2000 | 1.18 (0.88-1.59) | | 3.07 (0.89-10.52) | |

*Legend: cART = combination antiretroviral therapy; CI = confidence interval; HCV = hepatitis C virus; HBV = hepatitis B 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, duration of HIV infection, and calendar year of HIV diagnosis.*

### Liver-related death

In total, 72 patients co-infected with hepatitis died of a liver-related cause (*Table 5.4*).
Ten years after cART initiation, 9% (95% CI 6-20%) of the chronically HCV co-infected patients who were diagnosed with HCV before 2000 had a liver-related cause of death. This proportion was lower amongst patients with an HCV diagnosis after 2000 (3%, 95% CI 2-6%). Seven percent of the HBV co-infected patients diagnosed before 2000 (95% CI 4-10) and 1% (95% CI 0-2%) with a diagnosis after 2000 had a liver-related cause of death (*Figure 5.11*).

After adjustment for demographic and clinical characteristics, chronic HCV co-infected patients diagnosed both before and after 2000, as well as chronic HBV co-infected patients diagnosed before 2000, remained more likely to have a liver-related cause of death compared to HIV mono-infected patients, but this was not the case for patients with chronic HBV co-infection diagnosed after 2000 (p<0.0001) (*Table 5.4*).

## International collaborations

**COHERE (Collaboration of Observational HIV Epidemiological Research in Europe):**
The hepatitis working group of COHERE has evaluated the impact of HCV treatment on CD4 counts and the risk of dying. This analysis included data from the SHM. The short- and long-term effects of anti-HCV treatment on mortality were evaluated in this large European collaboration. During the first twelve weeks of anti-HCV treatment, CD4 counts decreased significantly and became stable from week 24 onwards. This decrease in CD4 counts is probably caused by (peg-)IFN alfa-related leucopenia. Despite the lowering effect on CD4 counts, this was not associated with increased mortality and the impact on HCV tended to remain a benefit [199].

**EuroSida:**
EuroSida determined the rate of HCV treatment uptake among co-infected patients and also estimated the effect of treatment on all-cause and liver-related mortality. The incidence of treatment for HCV among co-infected patients increased from 1998 until 2007 and was common in those with higher CD4 cell counts and lower HIV-RNA, consistent with HCV treatment guidelines. The effects of HCV treatment on mortality resembled those of the above mentioned study from COHERE [200].

In another study, EuroSida evaluated the association between HCV co-infection and the development of chronic kidney disease. Compared with patients with HIV mono-infection, HIV-infected patients with chronic HCV co-infection, rather than clearing HCV infection, were at increased risk for the development of chronic kidney disease. This suggests an impact from active HCV infection on the pathogenesis of chronic kidney disease [177].

## Conclusion

Screening for HCV and HBV co-infection in the HIV-infected population has improved over time, although there is still room for improvement. In 1998, 10% of the HIV-infected patients in care were not screened for co-infection with HBV or HCV. This proportion decreased to 0.02% in 2012 for HCV and 4% for HBV.

Five percent of the HIV-infected patients registered in the SHM database were chronically infected with HCV, and acute HCV infection was reported in 1% of patients. Eight percent of the patients ever in care had chronic active HBV infection. The prevalence of HBV decreased over time, probably as a result of an increased proportion of patients vaccinated for HBV. Nonetheless, an estimated 28% of HIV-infected patients overall, and 22% of MSM either had not been exposed to HBV or had not been successfully vaccinated and may remain at risk of acquiring HBV. Efforts to increase successful vaccination rates amongst this subgroup of patients should be considered.

Patients co-infected with HCV or HBV are at increased risk of progression to chronic liver disease [188, 189]. Six percent of the HCV co-infected patients had evidence of severe chronic liver disease. In both HCV and HBV co-infected patients, we observed an increase in the proportion of patients with hepatocellular carcinoma in relation to the duration of hepatitis infection. Overall, patients with chronic HCV or HBV co-infection remain at increased risk of having a liver-related cause of death, although this likelihood has clearly been reduced for patients with chronic HBV diagnosed after 2000, possibly as a result of increasingly effective treatment through the use of tenofovir-containing cART.

Continued and optimized screening for HCV and HBV co-infections and their management in individuals with HIV is needed to further limit the impact of co-infection on liver-related morbidity and mortality.

Although there has been a remarkable improvement in the uptake of HCV treatment, with the proportion of patients receiving treatment increasing from 1.2% in 2000 to 62% in 2012, approximately half of the patients remain untreated.

Of note, a considerable proportion of patients discontinued treatment prematurely because of insufficient response or side effects, or both. Amongst those treated with a combination of peg-IFN alfa and RBV, only 39% overall could be considered cured.

Thus, a substantial number of patients with HIV co-infected with HCV in care either remain untreated or have not yet been successfully treated for HCV. This group of patients remains in need of future HCV treatment to prevent progression of liver fibrosis and complications of severe chronic liver disease, including hepatocellular carcinoma. From the beginning of 2012 onwards, boceprevir and telaprevir, two recently licensed direct-acting antiviral agents that are active only against HCV genotype 1 infection, have become available in the Netherlands [201]. The results of recent studies with boceprevir and telaprevir in patients co-infected with HIV and HCV presented at different conferences have shown improved SVR rates compared to the standard treatment with peg-IFN alfa and RBV [202-204]. The use of these agents currently remains limited in the Netherlands, and apart from the high cost of these treatments, they are associated with clinically significant toxicities and potentially important drug-drug interactions with cART [205] *(www.hep-druginteractions.org)*. Of note, a large number of additional direct-acting oral antivirals against HCV with activity against multiple genotypes, rather than just against genotype 1, are in advanced stages of clinical development [201]. It is expected that the use of such agents in the not-too-distant future may even allow the use of interferon-free all-oral combination regimens for the treatment of HCV infection in HIV-infected patients.

## Recommendations

Continued efforts must be made to ensure that all patients with HIV are adequately assessed for the presence of HBV and HCV co-infection. In addition, HBV vaccination for the

substantial proportion of HIV-infected patients who may be at particular increased risk of becoming infected with HBV remains an important goal. Further evaluation of the many novel direct-acting antivirals against HCV in patients with concomitant HIV infection is important. This should lead to markedly improved treatment options, including for the populations that are more difficult to treat, such as those with no or partial response to, as well as with relapse after, currently available treatments, those with chronic liver disease including cirrhosis, and injecting drug users. Over the longer term, these improved treatments will contribute to reducing the burden of severe chronic liver disease, hepatocellular carcinoma and liver-related mortality amongst persons living with HIV. Continued monitoring of the population co-infected with HIV and hepatitis in the Netherlands will thus be key not only for monitoring the epidemiology of these infections and the response to existing and novel treatments, but also for assessing the impact of treatment on reducing the burden of morbidity and mortality from chronic liver disease.

## Definitions:

**Chronic HCV infection:**

Patients who remain HCV RNA positive more than 6 months after their first known HCV RNA positive test result.

**Acute HCV infection:**

1. Positive anti-HCV IgG and a documented negative anti-HCV IgG within the previous 12 months.
2. Detectable HCV RNA in the presence of either a documented negative HCV-RNA or a documented anti-HCV IgG seroconversion within the previous 12 months [111, 206].

**Spontaneously cleared HCV infection:**

1. Patients with a documented HCV antibody positive test result with a subsequent negative HCV RNA test result.
2. Patients who fulfilled the criteria above for acute HCV who subsequently have a negative HCV RNA test without having received HCV treatment.
3. Or those who do not fulfil the definition of acute HCV infection but with a positive HCV RNA test result who became negative within 6 months without treatment.

**Chronic HBV infection:**
Two or more consecutive positive test results for HBsAg over a consecutive period of at least 6 months.

**SVR:**
Sustained virological response defined as a negative HCV RNA test result 24 weeks after treatment discontinuation in patients treated for prior documented acute or chronic HCV infection.

**Severe (chronic) liver disease:**
1. Defined presumptively by clinically documented evidence of:
   - Bleeding from gastric or oesophageal varices, hepatic encephalopathy or hepatorenal syndrome, and/or
   - 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
2. Defined definitively if:
   - Combined with a pathology or fibroscan report documenting severe liver fibrosis or cirrhosis (metavir score F3-F4 or fibroscan stiffness ≥8kPa).

# 6. Distinct populations

## HIV-1 infected children in the Netherlands

Anouk Kesselring, Colette Smit, Annemarie van Rossum

### Background

Health care for HIV-infected children living in the Netherlands is now provided mostly by four paediatric HIV treatment centres, but some of the older children are receiving care in one of the general HIV treatment centres. As with adult patients, diagnosis, treatment and follow-up of these children are monitored by Stichting HIV Monitoring (SHM). Overall, demographic and clinical data were collected by SHM for 489 HIV-1 infected children aged 0 through 17 years at the time of HIV diagnosis. As of June 2013, 312 HIV-infected children had received care in one of the four paediatric HIV treatment centres. For 292 of those children, demographic and clinical data were available. Out of 489 children with available demographic and clinical data, 197 did not receive care in one of the four dedicated paediatric HIV treatment centres, but were cared for as adolescents/ adults in one of the adult HIV treatment centres. The majority of these children were infected by sexual contact and had a median age at diagnosis of 17 years (IQR 16-18).

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-infected children worldwide [207-210]. Early initiation of cART in HIV-infected children has been proven to be beneficial for their survival [211-215]. Results from birth cohort studies of vertically infected children suggest that 70% to 80% of untreated children survive to only 5 years of age. The World Health Organization (WHO), at the time these data were analyzed, advised starting cART in all children less than 2 years of age, regardless of their CD4 T-cell count or clinical status [216]. In the Netherlands, CD4-cell counts are leading in deciding whether to start treatment in children more than 2 years of age. Very recently, WHO guidelines have changed, and they currently recommend that all children less than 5 years of age commence cART, regardless of their CD4 count [217].

The effect of age at initiation of ART on clinical outcome is difficult to assess, given that disease progression is slow in children receiving ART. Alternative approaches include the use of virological or immunological endpoints, but in young children the considerable age-related variation in HIV RNA load and CD4-cell count complicates such assessments. To avoid this problem, CD4-cell count can be adjusted for age.

Here we describe demographic and treatment characteristics and long-term immunological and virological responses in the 292 HIV-1-infected children cared for in the four dedicated paediatric treatment centres in the Netherlands. In addition, we investigate whether age at initiation amongst HIV-infected children is associated with immunological outcome by use of Z-scores for CD4-cell counts (CD4 Z-scores), which standardizes the counts in relation to age.

## Demographics

Demographic and clinical data were available for 292 out of 312 HIV-1 infected children (*Table 6.1*). Median follow-up time since diagnosis was 10 years (IQR 6-14).

The median age at diagnosis for vertically infected children was 2 years (IQR 0.5-6). Although 42% of these children were born in the Netherlands, for only 4% (9 out of 248) did both parents originate from the Netherlands, and for 63% (157 out of 248) of the children, at least one parent originated from sub-Saharan Africa. The route of transmission for 44 children who were non-vertically infected with HIV included sexual contact (n=16), blood contact (n=11), and other (n=3). The mode of transmission was unknown for 14 of these 44 children. The median age at the time of diagnosis was 11 years (IQR 7-15). The majority of the non-vertically infected children (75%) were born in sub-Saharan Africa.

*Table 6.1: Demographic and HIV characteristics of 292 HIV-1 infected children in care in one of the four paediatric HIV centres in the Netherlands.*

| Characteristic | Vertically acquired HIV-1 infection n (%) | Non-vertically acquired HIV-1 infection n (%) | Route of transmission unknown n (%) |
|---|---|---|---|
| Total | 248 (85) | 27 (9.2) | 17 (5.8) |
| Gender | | | |
| Male | 122 (49) | 7 (26) | 12 (71) |
| Female | 126 (51) | 20 (74) | 5 (29) |
| Country of origin | | | |
| The Netherlands | 105 (42) | 4 (15) | 2 (12) |
| Sub-Saharan Africa | 112 (45) | 20 (77) | 13 (77) |
| Other | 31 (13) | 2 (8) | 2 (12) |
| Country of origin mother | | | |
| The Netherlands | 21 (9) | 2 (7) | 2 (12) |
| Sub-Saharan Africa | 152 (61) | 17 (63) | 10 (59) |
| Other | 75 (8) | 8 (30) | 5 (29) |
| Age at diagnosis | 2 (0.5-6) | 14 (11-16) | 8 (4-11) |
| Year of HIV diagnosis | | | |
| <1998 | 57 (23) | 6 (22) | 3 (18) |
| 1998-2004 | 84 (34) | 12 (44) | 6 (35) |
| ≥2004 | 107 (43) | 9 (33) | 8 (47) |
| CDC category at HIV diagnosis* | | | |
| B | 30 (12) | 4 (15) | 2 (12) |
| C | 35 (14) | 3 (11) | 2 (12) |
| Current age in years (median, IQR) | 13 (9-18) | 26 (21-28) | 17 (14-21) |
| cART treated | 229 (92) | 23 (85) | 16 (94) |
| Therapy-naïve at cART initiation | 193 (84) | 23 (87) | 16 (94) |
| CD4 at cART initiation | 605 (290-1155) | 350 (160-440) | 368 (150-572) |
| VL (log cps/ml) at cART initiation | 3.8 (3.0-4.8) | 3.4 (2.7-4.2) | 3.6 (2.8-4.8) |
| cART regimen | | | |
| NNRTI + ≥2 NRTI's | 65 (28) | 7 (30) | 5 (31) |
| PI + ≥2 NRTI's | 160 (70) | 16 (69) | 8 (50) |
| NNRTI +PI + 2 NRTI's | 3 (1) | - | 1 (6) |
| 3 NRTI's | 1 (1) | - | 2 (12) |

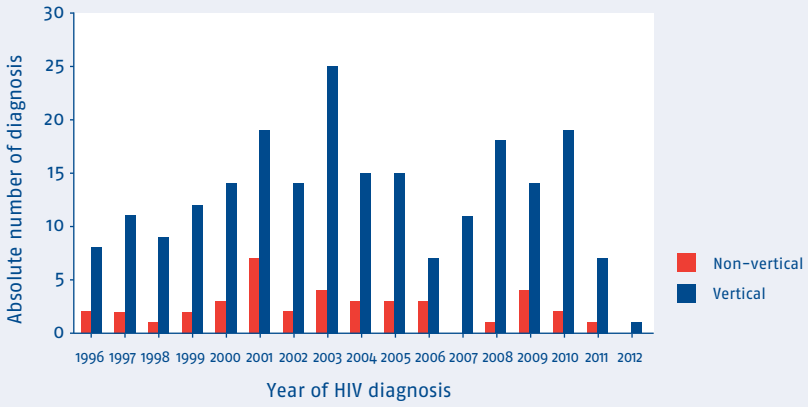
*Legend: * Categories as defined by the Centers for Disease Control and Prevention; cART=combination antiviral therapy; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.*

*Data are number (%) of children or median (interquartile range).*

## Registered HIV-1 diagnoses

*Figure 6.1* shows the number of registered diagnoses amongst children according to the year of diagnosis, whilst *Figure 6.2* shows the annual number of children infected with HIV through vertical transmission according to their region of origin. Most HIV-1 infected children (85%) in care in the Netherlands were vertically infected (*Table 6.1*), and absolute numbers varied over time from 25 in 2003 to 1 in 2012. The number of HIV-infected children that were not infected by mother-to-child transmission (MTCT) varied between 1 and 7 per calendar year.

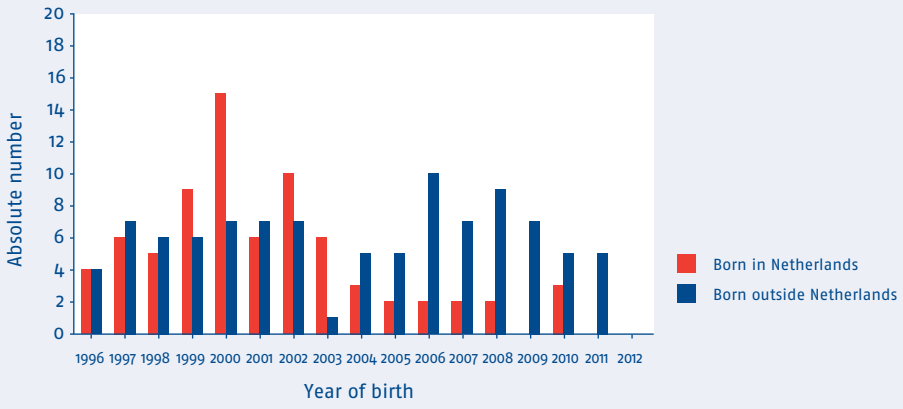
*Figure 6.1: Vertically and non-vertically HIV-1-infected children according to their year of diagnosis.*




## Vertical transmission of HIV in the Netherlands

The number of children born in the Netherlands and infected through MTCT has declined since 2004 (*Figure 6.2*). This decline is most likely due to compulsory HIV screening amongst pregnant women introduced in 2004 [218, 219]. Eight children born with HIV in the Netherlands have been reported to the SHM since the introduction of this screening. Two of them were born in 2004 to women who became pregnant before 1 January 2004. Four children were born to mothers who tested positive after giving birth; the mothers of two children tested negative during screening and became infected during the pregnancy. One child was born to a mother who was known to be infected with HIV, but who was not receiving treatment during her pregnancy for an unknown reason. The remaining child was born to a mother without a known screening or known HIV status during pregnancy. In 2012 one new vertically infected child was identified, but this child was born in sub-Saharan Africa.

*Figure 6.2: Number of vertically HIV-infected children according to their year of birth, stratified by region of origin.*




## Treatment

The majority of HIV-infected children in the Netherlands are now receiving cART (*Table 6.1*). Most children (69%) were treated with a first-line regimen including a protease inhibitor (PI) and 2 or more nucleoside reverse transcriptase inhibitors (NRTI's); 29% of the children received a non-nucleoside reverse transcriptase (NNRT)-based first-line regimen with 2 or more NRTI's. The median time on first-line regimens was 16 months (IQR: 5-32). Not taking into account weight-related dose changes, 204 children discontinued their first-line treatment regimen. The most important reasons for changing first-line cART regimens included simplification (24%), toxicity (19%) and virological failure (12%). Poor adherence accounted for 5% of changes. Other reasons included pharmacological reasons (12%), patient decision (2%), new available drugs (1.5%) and other reasons (19.9%). The cause was unknown for 4.6% of switches. No significant difference in the occurrence of virological failure and adherence was found amongst children of different ages. Children aged 5 to 17 years more often changed or discontinued their regimen because of simplification (29% vs 20% and 11%, p=0.06), and toxicity (24% vs 16% and 7%, p=0.03) compared to children 2 to 5 years of age, and those less than 2 years old.

## International collaborations

**Paediatric European Network for Treatment of AIDS (PENTA):**
In PENTA [220], the effect of planned treatment interruptions (PTIs) of antiretroviral therapy (ART) on adherence were investigated. HIV-infected children were randomised to CD4-guided PTIs (n=53) or continuous therapy (CT, n=56). Caretakers and, if appropriate, children completed questionnaires on adherence to ART and acceptability of PTIs. There was no difference in reported adherence on ART between CT and PTI groups; non-adherence (reporting missed doses over the last 3 days or marking <100% adherence since the last clinical visit on a visual analogue scale) was 18% (20/111) and 14% (12/83) on caretaker questionnaires in the CT and PTI groups, respectively (odds ratios, OR [95% CI] = 1.04 (0.20, 5.41), x(2) (1) = 0.003, p=0.96). Caretakers in Europe/U.S.A. reported non-adherence more often (31/121, 26%) than in Thailand (1/73, 1%; OR [95% CI] = 54.65 (3.68, 810.55), x(2) (1) = 8.45, p=0.004). The majority of families indicated they were happy to have further PTIs (caretakers: 23/36, 64%; children: 8/13, 62%); however, many reported that more clinic visits during PTI were a problem (caretakers: 15/36, 42%; children: 6/12, 50%).

## cART initiation

The WHO (2010 guidelines) recommends starting cART in all children less than 2 years of age, irrespective of CD4 counts or clinical condition [216]. Amongst the 233 vertically infected children in the SHM database (including children in care prior to publication of the 2010 guidelines), 129 were less than 2 years of age at the time of HIV diagnosis, and 71% of these children received cART before the age of 2 years. In children between 2 and 5 years of age, cART initiation was recommended in those with CD4 counts ≤750 cells/mm$^3$ or a CD4 percentage below 20 [216]. Amongst the children in whom cART was initiated between 2 and 5 years of age, the median CD4 count was 680 cells/mm$^3$ (IQR 400-1030) (*Table 6.2*). For children aged 5 years or older, cART was recommended when CD4 counts reached a threshold of 350 cells/mm$^3$ or a CD4 percentage below 15 [216]. In children aged 5 years or older, the median CD4 count at the start of cART was 350 cells/mm$^3$ (IQR 160-517).

When we took the 2010 WHO recommendations for starting cART in children into account, those aged less than 2 years and those 5 years or more at the start of cART initiated therapy in time to achieve a good response. A substantial proportion of children (34 out of 55, 62%) aged between 2 and 5 years at the start of cART initiated treatment with less than 750 CD4 cells/mm$^3$; however, the majority of these children started cART prior to 2007 (71%), before the 2010 guidelines were issued. According to the guidelines applicable in 2007, cART initiation was timely. Other reports have also shown that early treatment in asymptomatic children is not widespread clinical practice in many centres [221], which has been in line with the earlier guidelines [222].

*Table 6.2: Characteristics of 229 vertically infected and 34* non-vertically infected children in the Netherlands on combination antiretroviral therapy (cART).*

| Characteristic | Vertically infected children | | | Non-vertically infected children* |
|---|---|---|---|---|
| Age at cART initiation | 0-2 years | 2-5 years | 5-18 years | 5-18 years |
| n | 97 | 51 | 81 | 34 |
| Age ** | 0.5 (0.3-0.9) | 3.1 (2.5-3.7) | 8 (6-10) | 16 (12-17) |
| Time between HIV diagnosis and cART initiation (months)** | 0.9 (0.4-2.4) | 9.8 (2.5-22) | 16 (2-60) | 9 (1.5-38) |
| CDC category at cART initiation*** | | | | |
| B | 22 (23) | 9(18) | 19 (23) | 7 (21) |
| C | 28 (29) | 7 (14) | 8 (10) | 8 (24) |
| CD4 count at start of cART (cells/mm$^3$)** | 1,310 (700-2,015) | 680 (400-1,030) | 360 (175-530) | 345 (135-435) |
| CD4+ Z-score at cART initiation ** | -1.0 (-1.6 to -0.5) | -1.0 (-1 to - 0.5) | -0.9 (-1.2 to -0.6) | -0.7 (-1.2 to -0.6) |
| HIV VL at cART initiation ** (log cps/ml) | 4.4 (3.5-5.3) | 3.7 (3.0-4.7) | 3.3 (2.7-4.3) | 3.3 (2.7-4.2) |

* *Includes children with unknown route of transmission, on cART, more than 5 years of age (n=11). Five children on cART less than 5 years of age with unknown route of transmission are not included in this table. Three of these five children originated from sub-Saharan Africa, 1 from Asia and 1 from the Netherlands.*

** *median (IQR; Interquartile range)*

*** *n (%)*

## Immunological response

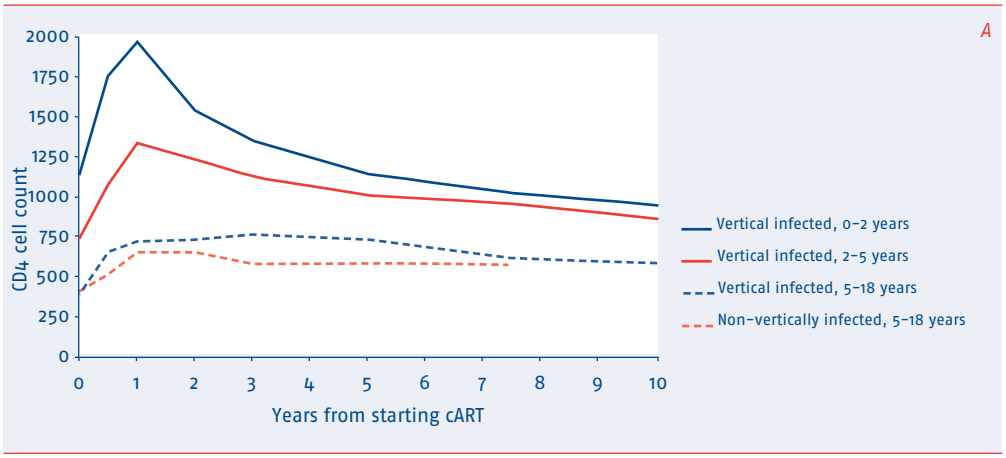
The clinical benefit of cART is strongly related to the level to which CD4 cells recover [88]. To investigate long-term CD4-cell count changes, we stratified the children on cART according to their age at the time of cART initiation (1. vertically infected, 0-1 year; 2. vertically infected, 2-4 years; 3. vertically infected, ≥5 years; 4. non-vertically infected or unknown mode of HIV transmission and ≥5 years), as CD4-cell counts in children aged less than 5 years are higher compared to older children and adults, and CD4 counts decrease with increasing age [223]. *Table 6.2* shows the significant differences in CD4 counts between younger and older HIV-1-infected children at the time of cART initiation.

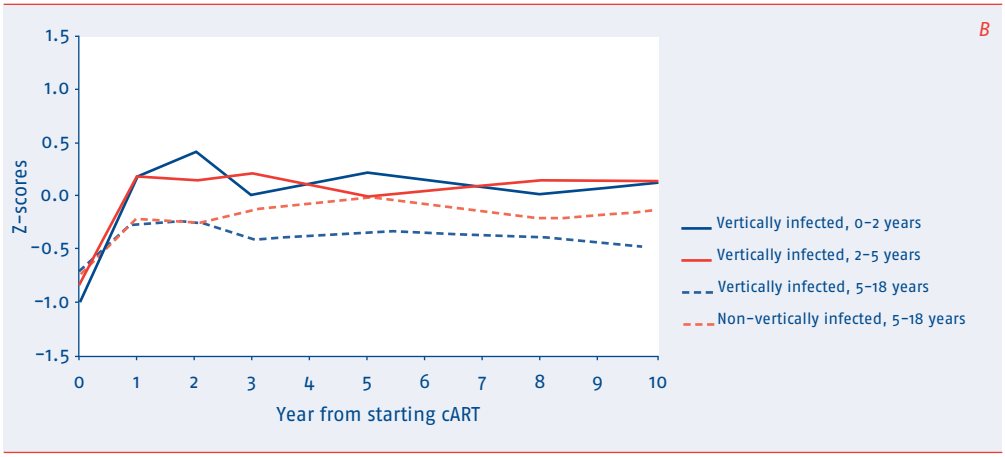
*Figure 6.3* shows the longitudinally modelled changes in CD4 counts during 10 years after cART initiation amongst HIV-infected children, stratified by age at cART initiation. CD4 counts of 265 patients were included in the first year, 242 from the second year, 220 from the third year, 185 from the fifth year and 147 from the eighth year onwards. Amongst all three age groups of vertically infected children, CD4 counts significantly increased in the first 6 months after cART initiation. Although not statistically significant, CD4 counts also increased during the first 6 months amongst the non-vertically infected children. Amongst vertically infected

children aged 0-1 year, CD4 counts remained stable during the second year on cART, and then the counts steadily decreased during the next 5 years on cART before they became stable. This decrease is age-related [223].

A slow decrease in CD4 counts was also observed amongst vertically infected children aged 2 to 5 years, which also reflects the age-related decrease [223]. In this group, CD4 counts became stable and remained constant during the second half of the first decade on cART.

*Figure 6.3: A) Changes in absolute CD4 counts (cells/mm³) amongst HIV-infected children, stratified by age at cART initiation. Immunologic trajectories were assessed in a random effects model, and time is in years since start of cART. B) Changes in Z-scores for CD4 T-cell counts amongst HIV-infected children, stratified by age at cART initiation.*



After an increase in CD4 counts during the first year on cART, the counts became relatively stable over time for the next 5 to 10 years amongst vertically and non-vertically infected children aged 5 years or older. Although CD4 counts steadily decreased during the first 5 years on cART amongst children aged 0-1 year and 2-4 years at the time of cART initiation, these children over the longer term showed higher CD4 counts compared to children who started cART when they were ≥5 years of age.

CD4 Z-scores, which represent the standard deviation from reference values for HIV-negative children, were calculated for CD4-cell counts to correct for age-related differences. All absolute CD4 T-cell counts were transformed into Z-scores by subtracting the age-related reference value for the age at the time of the CD4 measurement [224] and dividing this by the age-related standard deviation. A Z-score of zero represents the age-appropriate median. A CD4 Z-score of minus 1 indicates that a child's CD4-cell count is 1 standard deviation below the age-specific median of the HIV-negative population.

The youngest children (under 2 years of age at cART initiation) had the highest absolute CD4-cell counts at cART initiation ($p<0.001$), but age-adjusted CD4 Z-scores did not differ significantly between groups (*Table 6.2*). In the first 2 years after cART initiation, CD4 Z-scores significantly increased in all children ($p<0.001$). The increase was significantly lower in patients aged 5 to 18 years, both vertically and non-vertically infected, ($p<0.001$) compared to vertically infected children less than 2 years of age (*Figure 6.3B*). This is suggestive of a beneficial early treatment effect, as children less than 2 years old were treated promptly after the diagnosis of HIV.

## Virological response to cART

At the time of cART initiation, young children less than 2 years of age had significantly higher HIV RNA levels compared to older children ($p=0.0020$) (*Table 6.2*). Twelve months after starting cART, 81% of the children had a successful virological response. A successful virological response was defined as two consecutive HIV RNA levels below 500 copies/ml, as the lower limit of detection of follow-up tests of HIV viral load decreased from less than 1,000 copies/ml to less than 40 copies/ml from 1996 onwards, and a large number of tests had a lower detection limit of 500 copies/ml [225].

The poorest virological responses were observed amongst those less than 2 years of age (72%) and those aged 2-4 years (80%); the best responses were amongst vertically infected children aged ≥5 years (93%) and those non-vertically infected (88%) (*Figure 6.4*). These differences were confirmed by the Cox proportional hazard model (*Table 6.3*). *Figure 6.5* shows the longitudinally modelled long-term virological response to cART over a period of 10 years. In all groups HIV RNA levels significantly decreased during the first 6 months on cART ($p<0.0001$), with a slower decrease amongst children less than 2 years of age ($p<0.0001$). However, 2 years after the start of cART, virological response to cART no longer differed between the groups. This slower decrease in HIV RNA levels in young children compared to

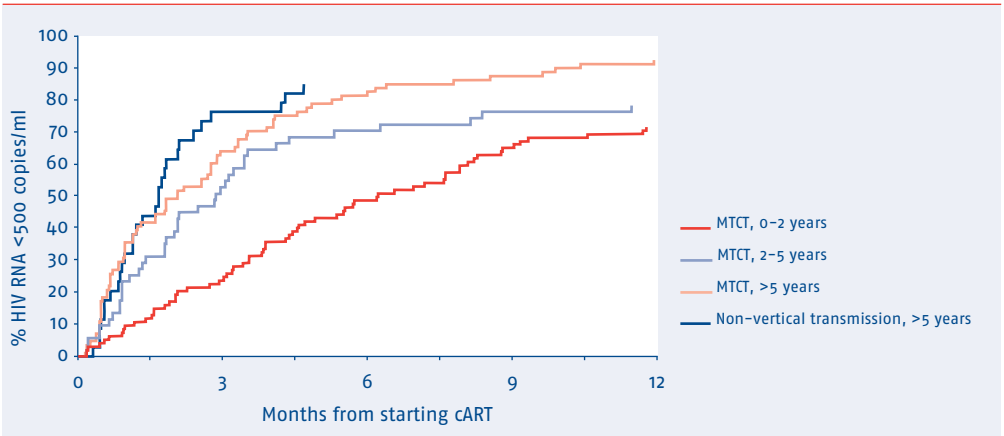
older children and adults has also been shown by others [226]. The lower initial virological response to cART might be explained by difficulties in the regular dosing adjustments needed for young children [227]. However, cART regimens for young HIV-infected children have improved substantially over time [228]. Stratification by calendar year of cART initiation (<2000, ≥2000) showed a significantly more rapid decline in viral load during the first year on cART amongst those who started cART from 2000 onwards (p=0.0004).

*Table 6.3: Results from an adjusted Cox proportional hazard model of the time from the start of combination antiretroviral therapy (cART) to the first of 2 consecutive plasma HIV RNA concentrations of <500 copies/ml in vertically infected children aged 0–2 years at the time of starting cART; in those aged 2–5 years; those aged >5 years; and in those with other routes of transmission and aged ≥5 years at the start of cART.*

| | Hazard ratio* | 95% Confidence interval | p-value |
|---|---|---|---|
| According to age at time of cART initiation | | | |
| Vertically infected, 0–1 years | 1 | | <0.0001 |
| Vertically infected, 2–4 years | 1.47 | (0.99–2.17) | |
| Vertically infected, ≥5 years | 2.30 | (1.57–3.36) | |
| Other mode of transmission ≥5 years | 2.45 | (1.52–3.95) | |

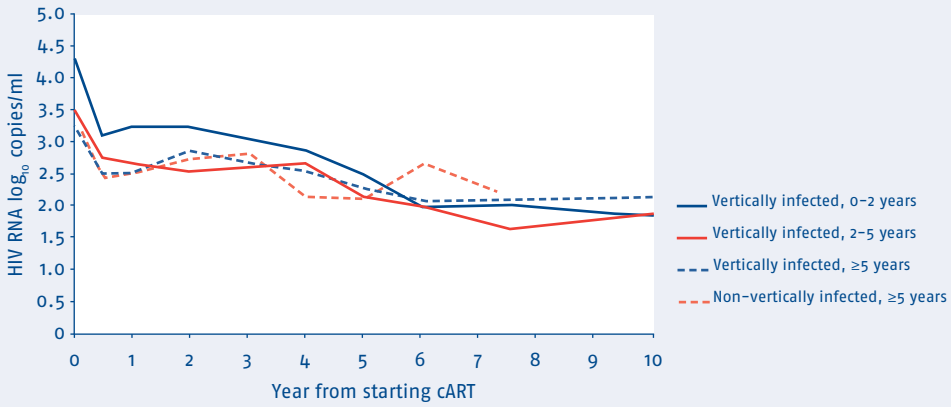
** Adjusted for gender, calendar year of HIV diagnosis, region of origin, time between HIV diagnosis and cART initiation, baseline log RNA levels and baseline CD4-cell counts.*

*Figure 6.4: Kaplan-Meier estimates of the percentages of HIV-infected children with initial suppression (<500 copies/ml) during the first year after starting combination antiretroviral therapy (cART), by age at cART initiation and HIV transmission mode.*




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

*Figure 6.5: Changes in HIV RNA levels amongst HIV-infected children, stratified by age at combination antiretroviral therapy (cART) initiation. Virological responses were assessed in a random effects model; time is in years since start of cART.*




## Mortality

During follow-up in the paediatric HIV treatment centres from 2006 to 2012, two (1%) deaths occurred in the 292 children. The median time between date of HIV diagnosis and date of death was 2.3 years (IQR 1.5-3.1). Two boys died, one at 11 and the other at 12 years of age; both children were born outside the Netherlands. One of those boys was non-vertically infected and was diagnosed with HIV when he was 10 years old; the cause of death was multiorgan failure, and the child never received cART. The other boy was vertically infected with HIV and diagnosed when he was 9 years of age; he died of an HIV-related event whilst being treated with cART.

## Transfer to adult HIV care

As of 1 June 2013, 201 out of the 292 HIV-infected children were still in care in one of the Dutch paediatric HIV treatment centres. Of 292 registered patients ever in care in a paediatric treatment centre, 2 children died, 15 children moved abroad, 1 child's parents objected to inclusion and 2 patients became lost to follow-up. Seventy-two children transferred to adult care. The median age at transfer was 19 years (IQR 18-20 years). The median time in care after transfer was 2.5 years (IQR 0.9-6.5 years). Three patients became lost to follow-up after transfer, 2 moved abroad and 1 child's parents objected to inclusion. The other 66 are currently alive and in care. Sixty-three of those patients (88%) are currently on a cART regimen, of which 21 (33%) at the last known time point had a detectable viral load; their current median CD4 count is 530 cells/mm$^3$ (IQR 407-711).

## Summary and conclusions

The majority of HIV-infected children ever in care in the Netherlands have received cART. During the first 6 months of treatment, a significant decline in HIV viral load was seen in children of all ages. HIV viral load tended to decrease during the first 10 years after cART initiation. At cART initiation, vertically infected children less than 2 years of age had a higher HIV viral load in comparison to the other age groups. Although we observed a poorer initial virological response in these children, the long-term virological response was comparable to that in older children. Also, the early response to cART improved over calendar time, most probably as a result of the introduction of improved regimens [225, 228, 229]. Protease inhibitors nelfinavir and (boosted) indinavir were used in the early years of cART [230], but are now no longer prescribed, and they have been replaced by (boosted) lopinavir and efavirenz, which is the most frequently used NNRTI, in line with current guidelines [228, 231].

The younger children less than 5 years of age have significantly higher CD4 counts at cART initiation compared to the older children, which reflects age-related differences in children's CD4-cell counts, regardless of HIV. Age-adjusted CD4 Z-scores at cART initiation did not differ between groups. CD4 counts and CD4 Z-scores significantly increased in the first 6 months after cART initiation in children of all age groups. After an initial increase and stabilization, CD4 counts of children aged less than 5 years steadily decreased during the next years before stabilizing, which reflects an expected age-related decrease [223]; their CD4 Z-scores remained stable. After an increase in CD4 counts during the first year on cART, CD4 counts became relatively stable for the next 5 to 10 years amongst vertically and non-vertically infected children aged 5 years or older; their CD4 Z-scores remained stable, as well. After 3 to 10 years, children less than 2 years of age showed higher CD4 counts, as well as CD4 Z-scores compared to children who started cART when they were ≥5 years of age. This suggests a beneficial early treatment effect, as children less than 2 years are treated promptly after diagnosis of HIV.

We observed low mortality rates in HIV-infected children in care in the Netherlands. A large proportion of the children have survived into adulthood and are now in care in one of the adult HIV treatment centres. The majority of these patients are on cART, but the high rate of children with detectable HIV viral loads is of concern.

The substantial decline in vertically HIV-infected infants born in the Netherlands from 2004 onwards can be explained by the successful introduction of an HIV screening programme in the first trimester of pregnancy [228]. However, mother-to-child transmission cannot be completely excluded by this measure. Screening for HIV only in the first trimester does not completely rule out maternal infection, as it can occur during the second or third trimester. In addition, when testing is performed shortly after primary infection of the mother, test results may still be negative. However, because the prevalence of HIV amongst pregnant women in the Netherlands is between only 0.04 and 0.08% [219], a nationwide second pregnancy screening is not likely to be very effective. It may be beneficial to perform a second screening later in pregnancy amongst women from specific risk groups.

## Recommendations

The provision of care for HIV-infected children living in the Netherlands in four specially designated paediatric HIV treatment centres has resulted in generally favourable outcomes and should be continued. The number of children born in the Netherlands and infected through mother-to-child transmission has declined over time, most likely because of the introduction of HIV screening amongst pregnant women, introduced in 2004. Still, a limited number of vertical transmissions have occurred since the start of the national screening. Most HIV-infected children in care are receiving cART. Overall, virological response to cART in children has improved over time, which is probably a reflection of the availability of novel cART regimens in more recent years. Although the early virological treatment response in vertically infected children less than 2 years of age at the time of cART initiation was relatively poor compared to older children, their long-term immunologic response was more favourable than that of older children, which suggests a beneficial response to early treatment. We observed low mortality rates in HIV-infected children in care in the Netherlands. A large proportion of the children have survived into adulthood and are now receiving care in one of the adult HIV treatment centres. Although most are receiving cART, one third of these patients currently do not have undetectable HIV viral loads. All children who have survived into adulthood are currently alive. HIV-infected children will face lifelong treatment with cART. For them, it will be a challenge to maintain lifelong adherence to cART and achieve lifelong virological suppression. Early identification and treatment of children infected with HIV will benefit their long-term treatment outcomes.

# Pregnancies in HIV-1 infected women in the Netherlands

Anouk Kesselring, Colette Smit, Liesbeth van Leeuwen

## Introduction

Transmission of HIV from an infected mother to her child is the most common route of transmission amongst children aged 0 to 15 years worldwide [2]. Mother-to-child-transmission (MTCT) can take place in utero, during labour and delivery, and post-natally during breastfeeding. Without intervention, the risk of MTCT varies between 15% and 20% [232]. Since the introduction of combination antiretroviral therapy (cART) in pregnant women, the risk of MTCT has been dramatically reduced to less than 1% [233, 234].

Knowledge of a woman's HIV status during pregnancy is necessary for timely initiation of cART and, thus, for reduction of the risk of MTCT. In January 2004, voluntary HIV-antibody testing of pregnant women with the possibility of opting-out was introduced in the Netherlands [235]. Since then, 268 women who were unaware of their HIV infection have been diagnosed during their pregnancy and reported to the SHM. By June 2012, a total of 1,788 pregnancies in 1,131 women were registered amongst the total 4,016 HIV-infected women monitored by the SHM. Overall, 54% of the pregnant women were diagnosed with HIV before the onset of pregnancy.

## Demographics

### Maternal characteristics

Characteristics of HIV-infected women with a registered pregnancy are presented in *Table 6.4*. Of the 1,131 women with a documented pregnancy, 177 (16%) originated from the Netherlands and 954 (84%) from elsewhere. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=669, 59%) or in the Caribbean/Latin American region (n=165, 15%). Women of Dutch origin were more often aware of their HIV infection before they became pregnant compared to women of non-Dutch origin, 72% and 51% respectively, p<0.0001. Women of Dutch origin were significantly older at the time of their first registered pregnancy with a median age of 30 years (IQR 26-35), compared to a median age of 28 years for women of non-Dutch origin (IQR 24-33, p<0.0001). Heterosexual contact was the most common route of HIV transmission (94%) in both groups of women. However, women of Dutch origin were more often infected with HIV by another route compared to women of non-Dutch origin (p=0.0002). Injecting drug use was reported as the route of transmission in nine women of Dutch origin (5%), with none of these transmissions having occurred after 2001.

Twenty mothers were documented to have died during follow-up, with a median time between onset of the first registered pregnancy and death of 4.4 years (IQR 1.8-9.0). Two mothers died within 1 month after parturition, one as the result of an obstetric complication and the other for unknown reasons.

In total, 187 women became lost-to-follow-up, which was more often the case in women of non-Dutch origin (18%) compared to women of Dutch origin (7%).

### Pregnancy-related characteristics

Overall, 1,131 women accounted for 1,788 registered pregnancies. Sixty-two percent of the women had one registered pregnancy, 25% two pregnancies, and 14% of the women had three or more registered pregnancies (*Table 6.4*).

Of the pregnancies, 1,788 gave rise to 1,337 newborns (75%), and 395 (22%) ended in miscarriage or abortion. Fifty-eight percent of the newborns were delivered vaginally; 69% of the women of Dutch origin delivered vaginally compared to 56% of the women of non-Dutch origin (p=0.004).

A total of 516 newborns were delivered by caesarean section. Elective caesarean delivery is known to reduce the risk of MTCT if the maternal viral load is detectable, but such a delivery is less beneficial if viral-load suppression is achieved following successful treatment with cART [236, 237]. The proportion of elective caesarean deliveries in first pregnancies decreased over time from 36% in 2000 to 11% in 2011 (p=0.0005). In accordance with the decrease in elective caesarean sections, the proportion of women with an undetectable viral load at the time of delivery increased over time, from 56% in 2000 to 75% in 2011 (p=0.0002). Although we observed a difference in the proportion of caesarean deliveries between women of Dutch origin and those of non-Dutch origin, the proportion of women with a detectable HIV RNA load at the time of delivery did not differ significantly between these groups (*Table 6.4*).

*Table 6.4: Characteristics of HIV-infected pregnant women registered and monitored by Stichting HIV Monitoring from January 1998 to 1 June 2012.*

| | Total N=1,131 N (%) | Dutch origin N=177 (16%) N (%) | Non-Dutch origin N=954 (84%) N (%) |
|---|---|---|---|
| **Maternal characteristics** | | | |
| HIV diagnosis before pregnancy | 613 (54) | 128 (72) | 485 (51) |
| Age at start of first pregnancy occurring in HIV infection, years (median [IQR*]) | 29 (24-33) | 30 (26-35) | 28 (24-33) |
| HIV Transmission route | | | |
| Heterosexual | 1,060 (94) | 155 (88) | 905 (95) |
| Other | 71 (6) | 22 (12) | 49 (5) |
| Ever CDC class C event | 218 (19) | 33 (19) | 185 (19) |
| Deaths | 20 (2) | 6 (3) | 14 (1) |
| Lost to follow-up | 187 (17) | 12 (7) | 175 (18) |
| **Pregnancy-related characteristics** | | | |
| Total number | 1,788 | 278 (16) | 1,510 (84) |
| Maximum number of pregnancies after HIV diagnosis | | | |
| 1 | 695 (61) | 106 (60) | 589 (62) |
| 2 | 280 (25) | 50 (28) | 230 (24) |
| 3 | 113 (10) | 14 (8) | 99 (10) |
| ≥4 | 43 (4) | 7 (4) | 36 (4) |
| Mode of delivery | | | |
| Vaginal | 782 (44) | 149 (53) | 633 (42) |
| Caesarean | 516 (29) | 63 (23) | 453 (30) |
| Unknown | 490 (28) | 66 (24) | 424 (28) |
| Pregnancy outcome | 37 (2) | 7 (3) | 30 (2) |
| Partus | 1,337 (75) | 217 (78) | 1,120 (74) |
| Abortion | 395 (22) | 54 (27) | 341 () |
| Unknown | 14 (1) | 0 | 14 (1) |
| Pregnancy duration | | | |
| ≥37 weeks | 1,079 (81) | 182 (84) | 879 (80) |
| 32-37 weeks | 154 (12) | 23 (11) | 131 (12) |
| <32 weeks | 65 (5) | 8 (4) | 57 (5) |
| Missing | 39 (3) | 4 (2) | 35 (3) |
| Birth weight (gram, IQR) | 3,090 (2,695-3,420) | 3,160 (2,750-3,445) | 3,080 (2,670-3,410) |
| Perinatal deaths | 47 (4) | 5 (2) | 42 (4) |
| CD4-cell counts (cells/mm$^3$) at the onset of first pregnancy (median, IQR) | 400 (250-550) | 520 (360-725) | 380 (240-523) |

| | Total N=1,131 N (%) | Dutch origin N=177 (16%) N (%) | Non-Dutch origin N=954 (84%) N (%) |
|---|---|---|---|
| Start cART | | | |
| Before pregnancy | 995 (56) | 159 (57) | 836 (55) |
| During pregnancy | 677 (38) | 96 (35) | 581 (38) |
| No cART during pregnancy* | 116 (6) | 23 (8) | 93 (6) |
| HIV RNA plasma levels before delivery in first pregnancy (n=1,131) | | | |
| HIV RNA available | 959 (85) | 153 (87) | 806 (84) |
| Undetectable | 698 (72) | 118 (77) | 580 (72) |
| Detectable | 261 (27) | 35 (23) | 226 (28) |
| Unknown | 172 (15) | 24 (13) | 148 (14) |

***Legend:*** *IQR=Interquartile range; cART=combination antiretroviral therapy*

The duration of 81% of the pregnancies was at least 37 weeks. The median weight of newborns was 3,090 grams (IQR 2,695-3,420). A total of 219 newborns (16%) were born preterm, after a pregnancy duration of 32 to 37 weeks for 154 newborns (12%, median weight 2,315 [IQR 1,920-2,645]) and of less than 32 weeks for 65 newborns (5%, median weight 815 [IQR 258-1,210]). Perinatal death occurred in 3.5% (47) of the births; of those deaths, 72% occurred after a pregnancy duration of less than 32 weeks. No significant differences in pregnancy duration, birth weight and perinatal death were found between women of Dutch and non-Dutch origin.

The earliest median CD4 count measured during pregnancy was significantly higher in women of Dutch origin ($p<0.0001$), which is likely explained by a higher proportion of these women having already been diagnosed and treated for HIV prior to the onset of pregnancy. This explanation is consistent with the median first CD4 count being significantly lower in women who were first diagnosed with HIV during pregnancy (370 cells/mm$^3$, IQR 220-534) than that in women who became pregnant whilst already known to be HIV-infected (420 cells/mm$^3$, IQR 291-553, $p=0.0001$).

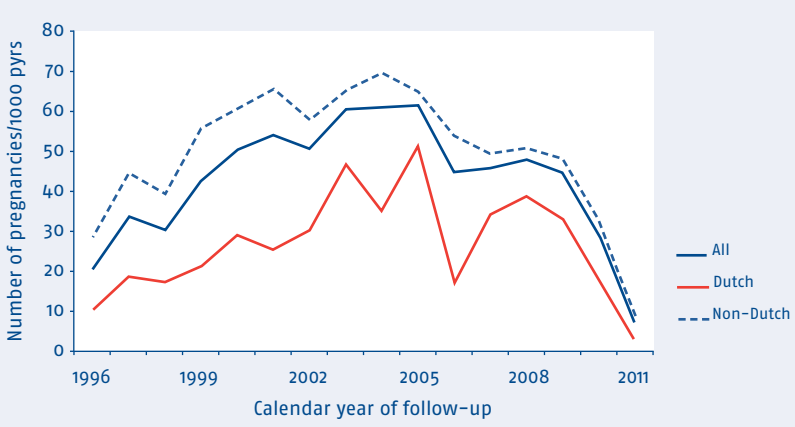
The majority of the women used cART during their pregnancy; 56% initiated cART before the onset of the pregnancy, and 38% started while pregnant. As a result of cART treatment, the maternal viral load was undetectable at the time of delivery in 72% of the pregnancies.

## Trends in pregnancy rate amongst HIV-infected women

Overall, the rate of pregnancy amongst HIV-infected women aged 16 to 45 years was 43 pregnancies per 1,000 person-years (95% CI 41-46) (*Figure 6.6*). The highest pregnancy rates were found amongst women of non-Dutch origin. Earlier studies have also shown differences in pregnancy rates amongst women of different geographical origin [238]. An HIV-infected woman's decision to become pregnant has been found to be socially and culturally related [239].

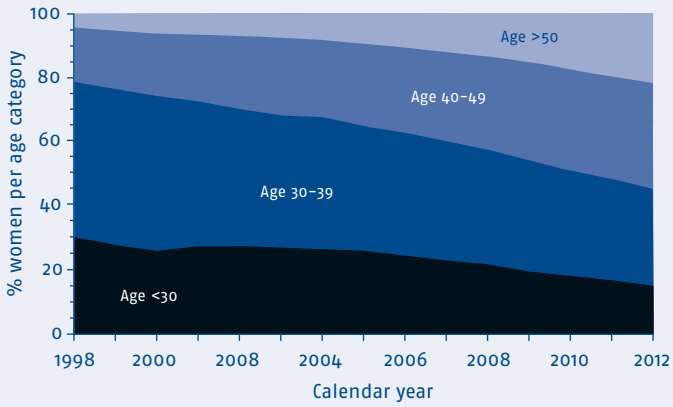
The annual incidence of pregnancies amongst HIV-infected women steadily increased from 30 per 1,000 person-years in 1998 to 61 per 1,000 person-years in 2004 and 2005. However, the incidence became considerably lower from 2006 onwards; it decreased to 45 per 1,000 person-years in 2006, remained stable until 2009 and decreased further in 2010 to 29 per 1,000 person-years. A similar decrease in birth rate has been reported in the general (non-HIV infected) population since the onset of the economic crisis in the Netherlands [240]. The lower number of pregnancies recorded in 2011 (8 per 1,000 person-years) might be a result of a backlog in the registration of pregnancies due to the visit-based collection of data regarding pregnancy.

***Figure 6.6:*** *Incidence of pregnancies per 1,000 person-years amongst HIV-infected women, overall and according to region of origin.*
*The incidence of pregnancy in HIV-infected women in the Netherlands per calendar year of follow-up was calculated per 1,000 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 last visit, death, the point at which the patient was lost to follow-up or 1 January 2011.*



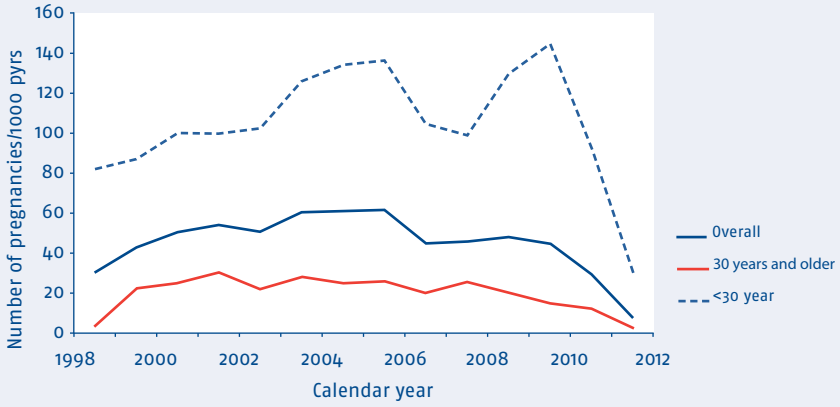

In women of both Dutch and non-Dutch origin, pregnancy rates became lower after 2005, probably as a result of increasing age of those in follow-up. The median age of HIV-infected women in follow-up increased from 34 years (IQR 29-39) in 1998 to 40 (33-48) in 2011 (*Figure 6.7*). This increase is mainly a consequence of the improved life expectancy of HIV-infected patients after the introduction of cART. As a result of this increasing age, a smaller proportion of women of childbearing age are now in clinical care; 54% of the women are currently 40 years or older.

*Figure 6.7: The age distribution of HIV-infected women in follow-up as of 1 June of each calendar year is shown. The proportion of women in older age categories has increased over calendar-time. In 1998, 30% of the women in follow-up were younger than 30 years of age, whereas 4% were 50 years or older. In 2011, these proportions were 17% and 20%, respectively.*




Pregnancy rates were significantly higher among women aged less than 30 years (97 pregnancies/1,000 person-years of follow-up, 95% CI 91-104) compared to women aged 30 years or more (19 pregnancies/1,000 person-years, 95% CI 17-21) (*Figure 6.8*). The majority of women who became pregnant before they were 30 years old were newly diagnosed with HIV during their pregnancy (57%) compared to 31% of the older women. HIV screening during pregnancy was likely to detect infection in these women. From 2004 onwards, all pregnant women have been screened according to an opting-out strategy. However, before 2004, a selective screening policy was used, which aimed to screen women with an increased risk of HIV infection, such as those originating from a high endemic region or having been an injecting drug user [218].

*Figure 6.8: Incidence of pregnancies per 1,000 person-years of follow-up, overall and according to time-updated age of follow-up (<30 years, ≥30 years).*




## Response to cART in pregnant women

Between 1 January 1998 and 1 June 2012, 1,036 women with a registered pregnancy started cART. Women were categorised into two groups according to whether cART was initiated before or during pregnancy. In 416 (40%) of the women, cART was initiated before they became pregnant, and in 620 (60%), it was initiated during their pregnancy (*Table 6.5*).

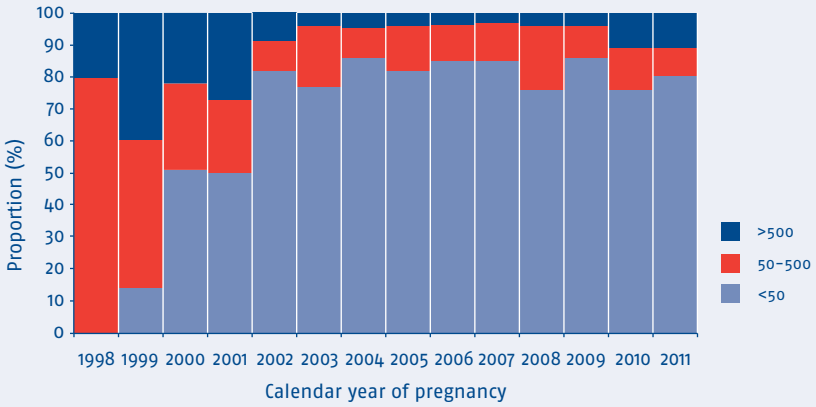
As expected, CD4 counts were significantly lower in women who started cART before pregnancy compared to those who started during their pregnancy (p<0.0001) because a proportion of women is only treated to prevent MTCT. Also, median HIV RNA levels were significantly lower in women who started cART during their pregnancy compared to women who started cART before they became pregnant (p<0.0001).

Of women on cART with an available HIV RNA measurement within 2 months prior to delivery (n=849), 81 (9.5%) had detectable HIV RNA levels (>500 cps/ml) at the time of delivery. These 81 women delivered 58 live babies, 38 of which were delivered by caesarean section. *Figure 6.9* shows the percentage of women over time with an undetectable load at the time of delivery; HIV RNA levels were categorised as <50 copies/ml, 50-500 copies/ml and >500 copies/ml. Overall, 626 (74%) of the women had an HIV RNA level <50 copies/ml at the time of delivery, and 142 (14%) had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with an HIV RNA level <50 copies/ml increased from 14% in 1999 to 86% in 2004 (p<0.0001). Between 2005 and 2011, the proportion of women with an HIV RNA level <50 copies/ml varied between 76% and 86%. At the time of delivery, women who started cART before they became pregnant had an HIV RNA level below 50 copies/ml (79%) relatively more often than women who started cART during their pregnancy (72%, p=0.003).

*Table 6.5: Characteristics of 1,036 HIV-infected pregnant women aged between 16 and 45 years who initiated combination antiretroviral therapy (cART) between 1 January 1998 and 1 June 2012.*

| | cART initiation | |
|---|---|---|
| | **Before pregnancy** | **During pregnancy** |
| Total n=1,036 | 416 | 620 |
| Median age at start of cART, years (IQR) | 29 (25-32) | 28 (24-32) |
| Region of origin, n (%) | | |
| Netherlands | 72 (17) | 85 (14) |
| Other | 344 (83) | 535 (86) |
| Calendar year of cART initiation, n (%) | | |
| ≥2000 | 131 (31) | 54 (9) |
| 2001-2007 | 235 (56) | 400 (65) |
| ≥2007 | 50 (12) | 166 (27) |
| **At start of cART** | | |
| CD4-cell counts (cells/mm$^3$), median (IQR) | 230 (136-350) | 396 (241-540) |
| HIV RNA levels (log$_{10}$ copies/ml), median (IQR) | 3.9 (2.7-4.9) | 2.7 (1.9-3.8) |
| **At parturition** | | |
| CD4 counts (cells/mm$^3$), median (IQR) | 437 (295-570) | 462 (304-650) |
| HIV RNA levels (log$_{10}$ copies/ml), median (IQR) | 1.7 (1.6-1.7) | 1.7 (1.7-1.9) |
| Detectable HIV RNA levels, n (%) | 36 (11.5) | 45 (8.4) |

*Figure 6.9: Distribution of women with HIV RNA levels <50 copies/ml, 50-500 copies/ml and >500 copies/ml at delivery over time.*



### Time to initial virological success

Time from cART initiation to the first of two consecutive plasma HIV RNA concentrations of <50 copies/ml (or 500 copies/ml, depending on the detection limit of the HIV RNA assay used) in pregnant women was compared in women who started cART before they became pregnant to those who started cART during pregnancy; the women were further categorised according to the calendar time of cART initiation (≤2000, 2001-2006, ≥2007).

By 6 months after the start of cART, 84% of the women had experienced a virological response (two consecutive HIV RNA levels <50 or 500 copies/ml). The strongest response was observed amongst women who started cART during their pregnancy after 2007 (93%; 95% CI 89-97%) and women who started cART during their pregnancy between 2000 and 2006 (90%; 95% CI 86-94%), with poorer responses among those who started cART before pregnancy (*Figure 6.10*, p<0.0001). Hazard ratios for the time to initial virological success were significantly higher for the women who started cART from 2001 onwards compared to those who initiated cART in 2000 or before (*Table 6.6*).

***Figure 6.10:*** *Time to initial viral suppression of HIV RNA to 50 (or 500) copies/ml after the start of cART amongst HIV-infected pregnant women. Pregnant women were divided into those who initiated combination antiretroviral therapy (cART) before pregnancy and those who initiated cART during pregnancy and by calendar time of initiation. The Kaplan–Meier method was used to estimate the time between the start of cART and virological suppression.*

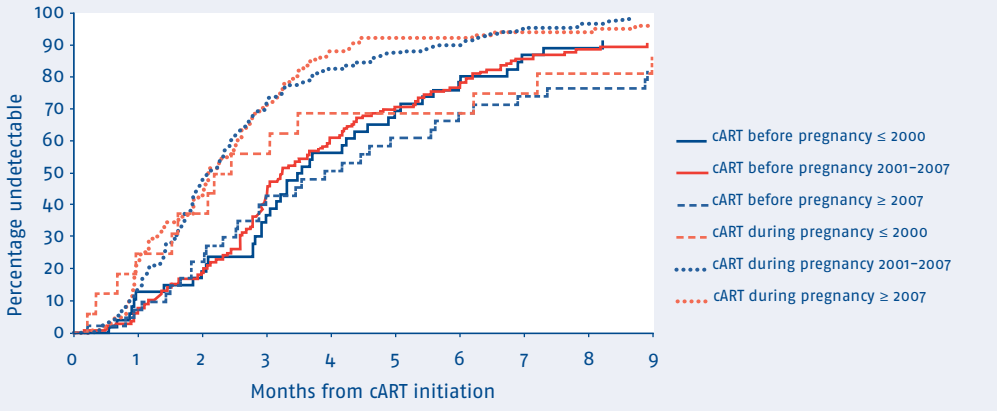


*Table 6.6: Risk estimates for the hazard of treatment success. Time from start of combination antiretroviral therapy (cART) until initial viral suppression of HIV RNA to 50 (or 500) copies/ml was analysed with a Cox regression model.*

| cART initiation | Hazard ratio* 95% Confidence interval | p-value |
|---|---|---|
| Before pregnancy ≤2000 | 1 | <0.0001 |
| Before pregnancy 2001–2007 | 1.36 (1.04–1.78) | |
| Before pregnancy ≥2007 | 1.77 (1.21–2.60) | |
| During pregnancy ≤2000 | 0.78 (0.53–1.15) | |
| During pregnancy 2001–2007 | 1.46 (1.13–1.88) | |
| During pregnancy ≥2007 | 2.28 (1.71–3.05) | |

** Adjusted for region of origin, CD4 counts and HIV RNA levels at time of cART initiation.*

### Time to virological failure after initial virological suppression

*Figure 6.11* shows the time to virological failure after initial suppression amongst pregnant women. Overall, the Kaplan–Meier estimate for the time to virological failure within 6 months after initial suppression was 18% (95% CI 16-21%). It must be noted that a considerable number of women can stop cART after pregnancy because of good immunity, however, these women are also considered as virological failures.

The highest failure rates were observed amongst pregnant women who started cART in pregnancy, 22% (95% CI 13-37%) for those who started cART in 2000 or before, 26% (21-31%) for 2001-2007 and 27% (20-37%) for women who started from 2007 onwards. In women who started cART before they became pregnant and before 2000, 12% failed after virological suppression (95% CI 7-19%), and the lowest failure rate was observed among pregnant women who started cART after 2007 before they became pregnant (5%; 95% CI 1-17%; p<0.0001). These findings are confirmed by the hazard ratios for the time to virological failure (*Table 6.7*). The goal of ART is to achieve maximal and sustained suppression of HIV RNA levels during pregnancy. Treatment guidelines for 2013 by the United States Department of Health and Human Services recommend starting cART as soon as 12 weeks' gestation or even in the first trimester, depending on CD4 count, HIV RNA levels and maternal condition [9].

When we repeated the analyses by taking into account time since parturition, we found that amongst 204 women who initiated cART prior to pregnancy and had undetectable HIV RNA levels, 6% (95% CI 4-11%) reached a detectable HIV RNA level within 6 months after parturition. This percentage was much higher amongst women who had initiated cART during pregnancy; 40% (95% CI 34-47) of 200 women reached a detectable HIV RNA level within 6 months after parturition, which suggests that, apart from issues of postpartum adherence, at least some of these women discontinued cART after parturition because their CD4 counts were above recommended CD4 cut-off values for cART initiation. New guidelines, however, recommend starting cART regardless of CD4 counts [241], though this is not commonly practised in the Netherlands.

Of women who were on cART during pregnancy (n=1,036), cART regimens were discontinued in 227 (22%) women and changed in 734 (71%) women after parturition. Most common reasons for these changes were end of pregnancy (23%), simplification of the regimen (13%), patient's choice (13%) and toxicity (23%).

In women in whom cART was initiated prior to pregnancy, median time to changing cART regimen was 0.6 months after pregnancy (IQR 0.1-2.1). Median time was 0.3 months for women who had initiated cART during pregnancy (IQR 0.1-1.8). Median CD4 counts prior to this change did not differ significantly between these two groups (470, IQR 320-680 vs 440, IQR 300-650, p=0.13).

Overall, 2 women died within 1 year after parturition. Both women were in their early 30s; one from sub-Saharan Africa died in 2004, and the other from Latin America/Caribbean died in 2003. Both women started cART during pregnancy and died within 1 month after parturition.

***Figure 6.11:*** *Time to virological failure (HIV RNA >500 copies/ml) after initial suppression amongst HIV-infected pregnant women. Pregnant women were divided into groups by initiation of combination antiretroviral therapy (cART) either before pregnancy or during pregnancy and by calendar time of cART initiation. Kaplan–Meier method was used to estimate the time between start of cART and virological suppression.*

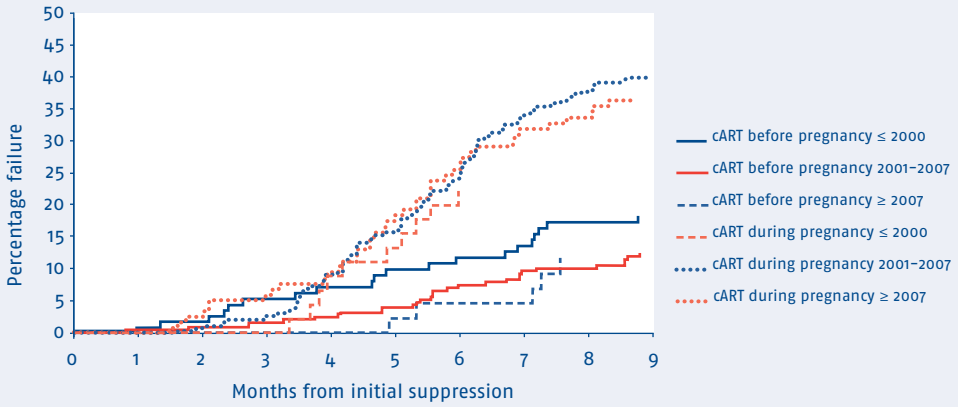


*Table 6.7: Risk estimates for the hazard of virological failure after initial suppression. Time from date of virological suppression until viral failure (HIV RNA> 500 copies/ml) was analysed in a Cox regression model.*

| | Hazard ratio* 95% Confidence interval | p-value |
|---|---|---|
| cART initiation | | |
| Before pregnancy <2000 | 1 | <0.0001 |
| Before pregnancy 2001–2007 | 0.72 (0.50–1.04) | |
| Before pregnancy ≥2007 | 0.72 (0.37–1.42) | |
| During pregnancy <2000 | 1.29 (0.82–2.02) | |
| During pregnancy 2000–2007 | 1.70 (1.24–2.33) | |
| During pregnancy ≥2007 | 1.58 (1.05–2.37) | |

** Adjusted for region of origin, CD4 counts and HIV RNA levels at time of cART initiation.*

## Summary and Conclusions

Pregnancy rates in HIV-infected women in the Netherlands have declined over time, likely as a result of increasing age in women in follow-up. In more than 60% of pregnant women, cART was initiated during pregnancy. Viral load, the most important factor in preventing MTCT, was generally low around the time of delivery. However, approximately 10% of women had a detectable HIV RNA level at the time of delivery.

The proportion of women with non-suppressed HIV RNA levels at time of delivery in our population was lower than in other reports [242]. In our population, time to virological suppression improved over calendar time. In recent calendar years, time between start of cART and viral suppression has become shorter compared to time during the early years of cART. Factors associated with a detectable viral load at delivery are lower CD4 counts and higher HIV RNA levels at the start of pregnancy [243, 244]. Improvement in virological response may be a result of more effective and safer cART regimens that have become available over time.

We observed a marked difference between virological failure after pregnancy between women who initiated cART prior to pregnancy (6%) and women who initiated cART during pregnancy (40%). This difference is probably due, in part, to the fact that CD4 counts of women initiating cART during pregnancy were above recommended CD4 cut-off values for cART initiation and some of these women discontinued cART after pregnancy. Such women in the current analysis would, in fact, be inappropriately categorized as "virologically failing" their regimen. Overall, 22% of women discontinued cART after parturition. CD4 counts were significantly higher in women who started cART during their pregnancy compared to those who started before their pregnancy. New guidelines recommend starting cART, regardless of CD4 count levels [9]. Several studies have demonstrated that adherence to ART may worsen in the postpartum period [241, 245-248]. Clinicians caring for women postpartum who are receiving ART should specifically address adherence, including an evaluation of specific facilitators and barriers to adherence.

We found a stronger response to treatment amongst women who started cART during their pregnancy than amongst those who were already on cART before they conceived. The strong response to treatment during pregnancy may be due to improved adherence during pregnancy as a result of increased clinical and social support or increased motivation to adhere to therapy [246].

## Recommendations

Although the proportion of HIV-infected pregnant women with appropriately suppressed viraemia at the time of delivery has markedly increased over time, room for improvement remains. As a result of the change in DHSS treatment guidelines of HIV and pregnancy, cART will be given earlier in pregnancy. This may lead to a greater level of viral suppression during labour. Robust evidence is lacking to support the concept that the start of cART at 12 weeks leads to a greater proportion of patients without viraemia during labour than patients who start at 20 weeks of pregnancy. Exposure to cART in the first trimester is associated with more prematurity, and it is unknown if longer exposure to cART is harmful to the foetus. Women may suffer from severe nausea at 12 weeks of pregnancy which may lead to less adherence and treatment failure. These factors must be considered when cART is initiated. Women infected with HIV who become pregnant require a high level of clinical support not only during their pregnancy, but also after delivery. Continued monitoring of HIV-infected women after pregnancy is necessary for prevention of decreased motivation in adherence to cART and for early detection of virological failure.

# 7. Quality of Care

Esther Engelhard, Kees Brinkman, Colette Smit, Ard van Sighem, Peter Reiss, Suzanne Geerlings

Stichting HIV Monitoring (SHM), in addition to increasing the understanding of the HIV epidemic and the course of infection of patients in care, aims to contribute to the improvement of the quality of HIV care. In principle, HIV treatment is accessible to all infected individuals residing in the Netherlands. For the past decade, the care of HIV-infected patients has been centralised in a number of hospitals meeting certain criteria to serve as legally acknowledged HIV treatment centres. These centres are required to collaborate with SHM in the continuous collection of data for the purpose of monitoring of HIV treatment and treatment outcomes in the Netherlands.

In 2012, a formal certification process for HIV treatment centres was launched. During this process, in a collaboration between the Dutch Association of HIV-treating Physicians (NVHB) and 'Harmonisatie kwaliteitsbeoordeling in de zorgsector' (HKZ), the standards for HIV treatment centres were more clearly formulated and further specified. SHM has been involved in the discussions of which data may serve as the most appropriate measures of quality of care, as well as how it may assist in making such data available for monitoring quality of care.

In addition, SHM is participating in the Q-HIV study, assessing the quality of care in HIV treatment centres in the Netherlands. The aim of this study, financially supported by the Aids Fonds, is to investigate the factors related to patients, care providers, and hospitals that are associated with quality of care. Clinical outcomes will be assessed, and, additionally, the evaluation of quality of care in this study will directly involve patients by use of Patient Reported Outcome Measures (such as health-related quality of life and patient satisfaction).

Monitoring is considered an essential component of HIV care [249-251] and facilitates the evaluation of quality of care. Monitoring data can also be used to assess the course of the HIV-care continuum, which is often illustrated as the cascade of care showing the proportions of patients at different stages in the continuum (see *Figure 7.1* and *Figure 7.2*).

*Figure 7.1: As of June 2013, 93% of all patients diagnosed with HIV and linked to care were retained in care. 81% of the patients were taking combination antiretroviral therapy (cART) and 73% of the patients linked to care had an undetectable viral load (<100 copies/ml).*

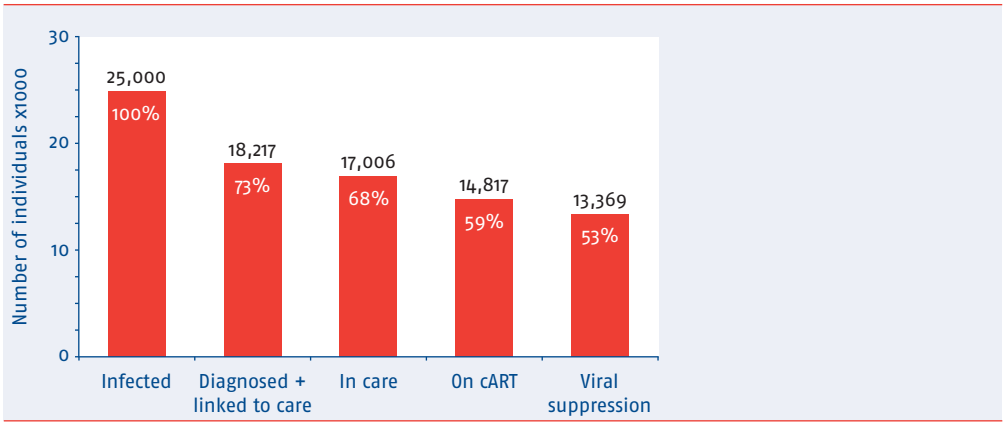
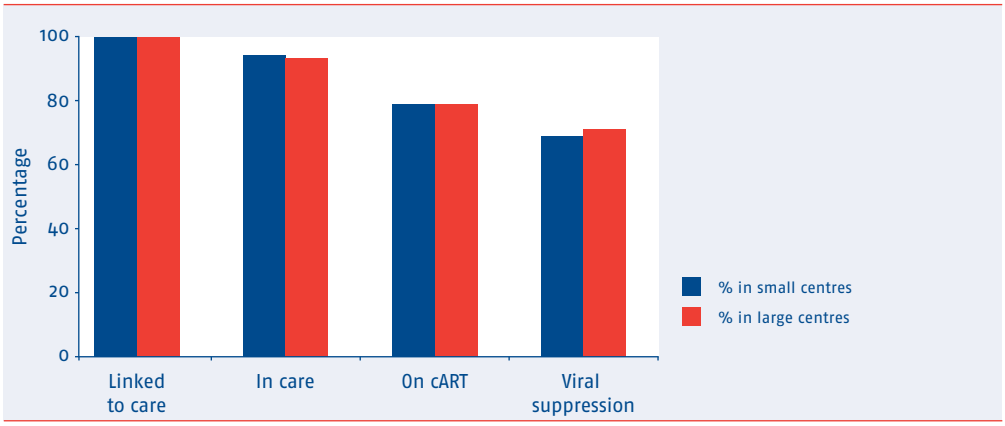



*Figure 7.2: Initial results from the Q-HIV study. For this analysis the cascade of care was assessed for all patients registered by SHM between 2002 and 2013 and stratified by treatment centre size. The proportions of patients retained in care, on combination antiretroviral therapy (cART) and with an undetectable viral load were found not to differ by treatment centre size.*




In the Netherlands, general health care access and the provision of care by legally acknowledged HIV treatment centres may contribute not only to the observed high proportions of patients retained in care receiving combination antiretroviral therapy (cART) but also to the lack of difference between centres with varying HIV-clinic size. These data compare favourably with previously published cascade of care data from other parts of the world [3].

# Special reports

## 8. The Amsterdam Cohort Studies on HIV infection – Annual Report 2012

Ineke Stolte, Maria Prins for the ACS

### Introduction

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS were started shortly after the first cases of AIDS were diagnosed in the Netherlands. Since October 1984, men who have sex with men (MSM) have been enrolled in a prospective cohort study. A second cohort involving drug users (DU) was initiated in 1985. In 2012, the cohorts reached 28 years of follow-up. The initial aim of the ACS was to investigate the prevalence and incidence of, and risk factors for, HIV-1 infection and AIDS, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. During the past 28 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; more in-depth studies were performed later 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) among the participants in the ACS.

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

As of 31 December 2012, 2,511 men who have sex with men (MSM) and 1,661 (injecting) drug users (DU) were included in the Amsterdam Cohort Studies (ACS). Every 3 to 6 months, participants complete a standardised questionnaire designed to obtain information regarding medical history, sexual and drug use behaviour, underlying cognitions, health care use, depression, psychological disorders, and demographics. In addition, they have undergone a medical examination (HIV-positive participants and, in the past, HIV-negative DU, as well), and blood is drawn for diagnostic tests and storage. The ACS have been conducted in accordance with the ethical principles set out in the declaration of Helsinki, and participation in the ACS is voluntary; written informed consent (the most recent version approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the DU cohort) is obtained for every participant.

Of the 2,511 MSM, 614 were HIV-positive at study entry, and 232 seroconverted during follow-up. For the 1,661 DU, 322 were HIV-positive at study entry, and 99 seroconverted during

follow-up. By 31 December 2012, 354 MSM and 510 DU had died, and several other participants were asked to leave the study or left at their own request. In total, MSM visited the Public Health Service of Amsterdam 51,502 times, and DU visited 27,007 times.

## Collaborating institutes and funding

Within the ACS, different institutes collaborate to bring together the data and biological sample collections and to conduct research. 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 (UvA, Departments of Medical Microbiology, Experimental Immunology, Internal Medicine/Division of Infectious Diseases, Tropical Medicine and AIDS, and HIV treatment centre of Emma Children's Hospital), University Medical Center Utrecht (UMCU, Department of Immunology), Stichting HIV Monitoring (SHM), and the Jan van Goyen Medical Center (Department of Internal Medicine). From the start, Sanquin Blood Supply Foundation has been involved in the ACS, and until 2007 research in the ACS was conducted by the Department of Clinical Viro-Immunology of Sanquin Research. Sanquin financially supports the maintenance of the biobank of viable peripheral-blood mononuclear cells at the Department of Experimental Immunology at the AMC. Also, the ACS is involved in a significant amount of collaborative work with other research groups both within and outside the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control of the Netherlands National Institute for Public Health and the Environment.

## The ACS in 2012

### The cohort of men having sex with men

In 2012, 612 MSM were in active follow-up within the ACS. Of the MSM in active follow-up by the end of 2012, 498 were HIV-negative, and 114 were HIV-positive MSM who filled in behavioural questionnaires. The median age of the MSM was 38.8 years (interquartile range [IQR] 34.4-43.8), 9.5% were non-Dutch and 78.6% had attained a high level of education (college degree or higher). The majority of the participants (94.5%) were residents of Amsterdam. Thirty-eight of them were newly recruited, and one died in 2012.

Until 1995, men of all age groups were eligible to participate if they lived in or around Amsterdam and had had at least 2 male sexual partners in the previous 6 months (see Annex 4, Figure 1). In the period 1995–2004, only men 30 years or less with at least 1 male sexual partner in the previous 6 months could enter the study. From 2005, recruitment has been open for MSM of all ages with at least one sexual partner in the preceding 6 months.

In 1999, follow-up of HIV-positive participants was transferred from the PHSA to the Jan van Goyen Medical Center in Amsterdam and 6-monthly behavioural follow-up ceased. However, since 2000, HIV-infected MSM in follow-up at the Jan van Goyen Medical Center have again been asked to complete behavioural ACS questionnaires once a year. In 2012, 150 of the HIV-positive MSM had been in active follow-up at the Jan van Goyen clinic since 1999.

Of these, 41 were HIV seroconverters, and 29 were defined as (1) slow or non-progressor or matched fast progressor in 1996 or (2) were HIV-positive for more than 10 years and had a CD4 count greater than 400 cells/mm$^3$ after 10 years of follow-up without antiretroviral therapy. In total, 57 MSM in active follow-up at the Jan van Goyen clinic completed a behavioural questionnaire.

Behavioural and clinical follow-up of individuals with a recent HIV infection at study entry at the PHSA and of HIV seroconverters in the period after 1999 was newly initiated in October 2003, in accordance with the 'HIV Onderzoek onder Positieven' (HOP) protocol. These participants return for follow-up at the PHSA or at an HIV treatment centre, and all ACS behavioural data are collected on a 6-monthly basis, with clinical data provided through the SHM. Of the 69 HIV-positive MSM in active follow-up in 2012 in accordance with the HOP protocol, 3 were newly included and 45 were HIV seroconverters. A behavioural questionnaire, as required by the HOP, was completed by 57 HIV-positive MSM.

In 2006, HIV-positive steady partners of HIV-negative participants and all steady partners of HIV-positive participants were also invited to participate in the ACS. Thirteen HIV-discordant and 3 HIV-positive concordant couples were included in this partner study, of which 5 couples were still in active follow-up in 2012.

Since November 2008, all MSM followed at the PHSA have been routinely screened for STI.

### The cohort of drug users

In 2012, 285 DU were followed at the PHSA. The median age of the DU was 50.5 years (IQR 44.4-55.2), 16.2% were non-Dutch, and 9.5% had attained a high level of education. 326 (99.7%) were residents of Amsterdam. Of the 285 DU followed in 2012, 18 were HIV-positive at entry, 13 seroconverted for HIV during follow-up in the ACS and 20 DU died. Inclusion criteria are individuals between 18 and 30 years who regularly use hard drugs in Amsterdam and individuals older than 30 years who started injecting hard drugs in the preceding 2 years in Amsterdam. Although the cohort is open and efforts were made to include new participants, only 3 were recruited in 2012, which might be explained by the unpopularity of injecting drugs in Amsterdam.

## Affiliated studies and studies linked to the ACS

### Primo-SHM study

In addition to the cohorts previously described, the ACS also included 238 patients who presented with primary HIV-1 infection at the outpatient clinic of the AMC in the so-called "Primo-SHM study" from May 2003 until March 2010. The Primo-SHM study is a national randomised study on the effects of early temporary (24 or 60 weeks) antiviral therapy as compared to no therapy. Some of these patients were seronegative men in the ACS amongst the MSM who seroconverted during follow-up. Some of them are also still in follow-up in

accordance with the HOP protocol of the ACS at the PHSA. Plasma and peripheral-blood mononuclear-cell samples that are collected within the Primo-SHM study are part of the ACS and stored at the AMC. At present, biological samples are still prospectively collected for Primo-SHM participants visiting the AMC clinic until 1 year after recommencing therapy. ACS researchers make use of these samples for their studies.

### The Dutch-C study

The Dutch-C (Drug Users Treatment for Chronic Hepatitis C) study was started within the DU cohort to evaluate the possibility of HCV testing and treatment combined with methadone programmes. This project aimed to offer HCV screening and treatment to all DU participating in the ACS and to develop guidelines for HCV treatment of active DU outside a clinical setting. Drug users were offered HCV testing and, if chronically infected, medical and psychiatric screening and HCV treatment. Various specialists collaborated to provide optimal HCV care at the PHSA. Almost 60% of DU tested positive for HCV antibodies, and 64% of them were positive for HCV RNA. Of 57 chronically infected DU that started treatment and had sufficient follow-up after a treatment stop in 2010, 37 (65%) achieved a sustained virological response. On account of successful results seen in ACS DU, it was decided in 2007 to extend HCV treatment to DU who were not participants in the ACS, and they were referred from methadone clinics and other addiction clinics in Amsterdam. A total of 88 DU from the ACS and methadone clinics were treated for HCV by the end of 2011. The first active DU chronically infected with HCV genotype 1 started treatment at the PHSA in 2012 with telaprevir combined with peginterferon and ribavirin. We will continue to evaluate HCV treatment uptake and the short- and long-term outcomes amongst ACS participants, using the rich data collection and infrastructure of the ACS.

### AGEhIV Cohort Study

The AGEhIV Cohort Study, a collaboration between the AMC Department of Infectious Diseases, Department of Global Health and Amsterdam Institute of Global Health and Development, the PHSA, and SHM, was started in November 2010. 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 45 years and older and to determine the extent to which co-morbidities, their risk factors and their relation to quality of life differ between HIV-infected and uninfected groups. Participants undergo a comprehensive assessment for co-morbidities and fill in a questionnaire at intake and 2 years afterwards. By the end of 2012, the first data wave was completed and the second data wave started. In total, 597 HIV-1-infected participants were included through the AMC HIV outpatient clinic, and 550 HIV-uninfected individuals belonging to the same HIV exposure groups were included through the STI clinic of the PHSA (n=486) or the Amsterdam Cohort Studies (n=64). All participants are ≥45 years and are as comparable as possible with respect to age, gender, ethnicity and risk behaviour.

### 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 colleagues in the Departments of Obstetrics and Gynaecology and Experimental Immunology at the AMC analyse factors involved in neonatal HIV-1 transmission. The children infected with HIV are included in the Paediatric Amsterdam Cohort on HIV-1 (PEACH, n=60). The HIV-exposed children (30-40 annually) are studied in the context of the European Collaborative Study on Mother-to-Child Transmission of HIV (ECS), an ongoing birth cohort study that recently merged with the Paediatric European Network for Treatment of AIDS (PENTA in EuroCoord). Plasma and peripheral mononuclear-cell samples that were collected within the study until 2008 are part of the ACS and stored at the AMC. Currently, no new samples are being collected. The stored samples are available for ACS research.

### H2M study

The H2M (HIV and HPV in MSM) study is a successful collaboration between the Center for Infectious Disease Control (CIb), PHSA, the Jan van Goyen Medical Center, VUmc and the AMC. The study aims to compare the prevalence, incidence and clearance of high-risk (hr) HPV infections between HIV-negative and HIV-infected MSM. It also aims to investigate whether anal or penile hrHPV infections may be a risk factor for acquiring HIV. In July 2010, the H2M study started recruiting. The participants are recruited from three sites: the ACS (n=520; mostly HIV-negative), the STI clinic of the PHSA Amsterdam (n=120; all HIV-infected), and the Jan van Goyen Medical Center (n=160; all HIV-infected). Participants answer additional questions regarding sexual behaviour, smoking and circumcision and provide self-collected anal and penile-shaft swabs, as well as oral rinse-and-gargle specimens. These are tested for the presence of HPV DNA, and if positive, HPV types are determined. Serum is tested for L1 HPV antibodies. Two years of follow-up per participant was completed in July 2013.

## The HIV epidemic

### HIV incidence

Three MSM and no DU participating in the ACS seroconverted for HIV in 2012. The observed HIV incidence among MSM declined to 0.6 per 100 person-years in 2012.
The observed HIV incidence in DU has continued to decline with less than 1 case per 100 person-years since 1999. *Figures 8.1* and *8.2* show the yearly observed HIV incidence rates for MSM and DU from the start of the ACS through 2012.

*Figure 8.1: Observed HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2012.*

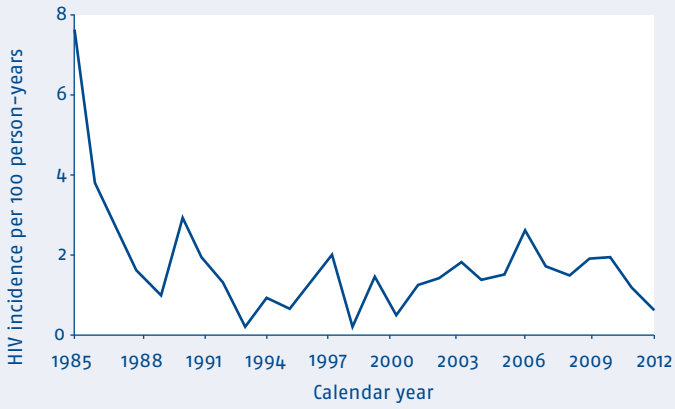
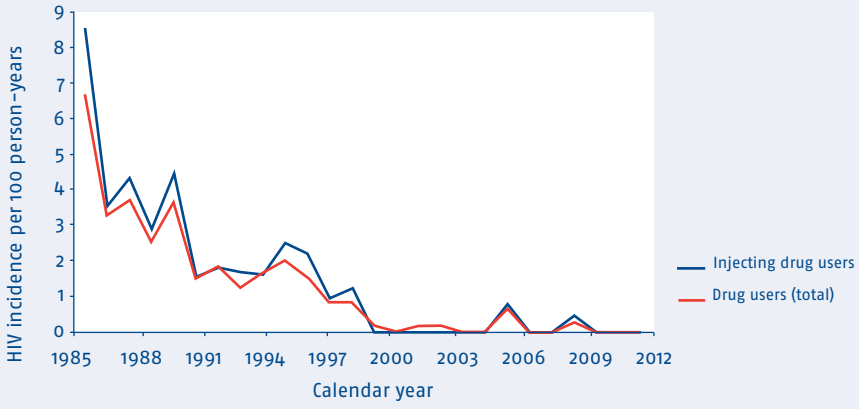



*Figure 8.2: Observed HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among drug users, 1986–2012.*




## Transmission of therapy-resistant HIV strains

Surveillance of transmission of drug-resistant HIV-1 strains was performed for 3 MSM seroconverters. None of the individuals were infected with virus-harbouring resistance-associated mutations; only naturally occurring sequence variation was found. Phylogenetic analysis showed that two individuals harboured subtype B HIV-1 strains and one subtype F1.
In the cohort of DU no seroconversions or seropositive entries appeared.

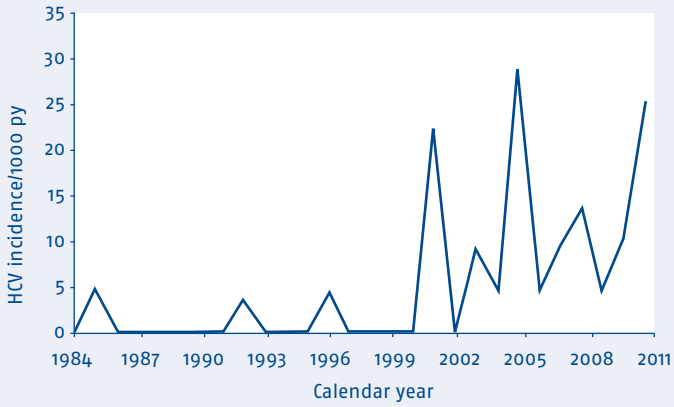
## Highly active antiretroviral therapy (HAART) uptake

Of all 218 HIV-positive MSM visiting the Jan van Goyen Clinic or one of the other HIV treatment centres in the Netherlands according to the ACS protocols in 2012 and for whom treatment data were available, 211 (97%) received some form of antiretroviral therapy. Of 211 MSM for whom viral load results were available and were on therapy in 2012, 191 (91%) had a viral load of less than 50 copies/ml (assays: m2000rt).
Of the 31 HIV-positive DU who visited the PHSA in 2012, 25 (81%) received some combination of antiretroviral therapy. Of the 25 DU, 22 (88%) had an undetectable viral load (less than or equal to 150 copies/ml [assay: m2000rt]) at their latest visit.

## HCV incidence in MSM and DU

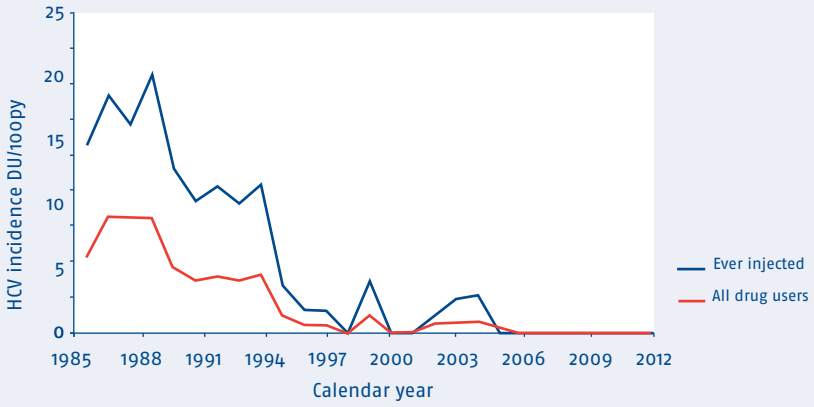
In 2012 the observed HCV incidence was updated for the MSM cohort through 2011. No incident HCV infections were recorded among HIV-uninfected MSM. Among HIV-infected MSM, HCV incidence rates increased significantly after 1999. However, the incidence seems to have levelled off in recent years around 10/1,000 person years. This stabilizing incidence is in line with recent findings from the STI clinic of the PHSA.

*Figure 8.3: HCV observed incidence per calendar year in the Amsterdam Cohort Studies (ACS) among HIV-infected MSM, 1986–2011.*




In 2012 the HCV incidence was also updated for the DU cohort. The The observed HCV incidence in the total group and among injectors has strongly declined over the years to 0/100 person years since 2005 (see *Figure 8.4*).

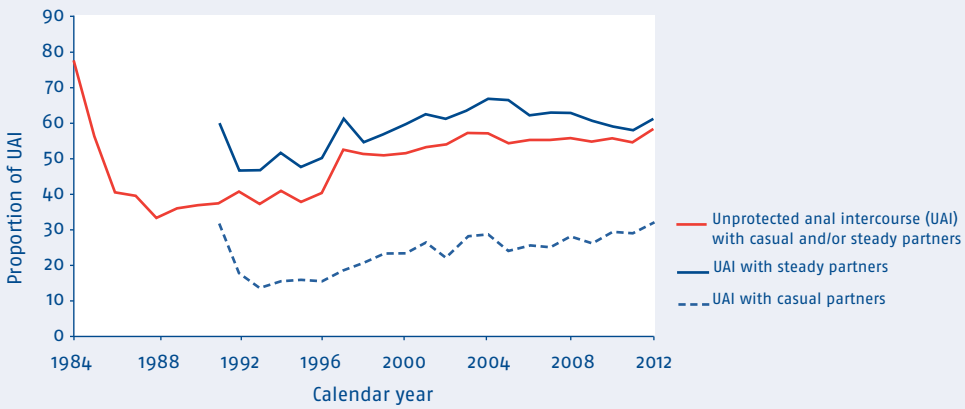
*Figure 8.4: Observed HCV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among drug users, 1986–2012.*




## Risk behaviour of MSM

Information from the 895 questionnaires completed by 498 HIV-negative MSM during cohort visits in 2012 resulted in 485 reports (54%) of unprotected anal intercourse (UAI) in the preceding 6 months. Higher proportions of UAI were reported for steady partners (37%) compared to casual partners (22%). Trends in UAI, especially with casual partners, among HIV-negative MSM participating in the ACS have slowly increased since 1996. (*Figure 8.5*).

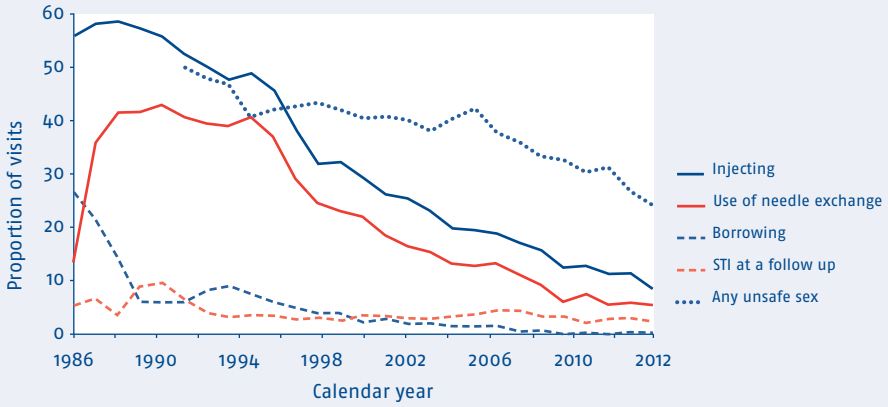
*Figure 8.5: Trends from the Amsterdam Cohort Studies (ACS) in unprotected anal intercourse (UAI) in the past 6 months amongst HIV-negative men having sex with men (MSM) with a casual and/or steady partner, 1984–2012.*



## Risk behaviour of DU

In HIV-negative DU, reports of both injecting and borrowing needles significantly declined over the period 1985-2011. Reports of high-risk sexual behaviour at follow-up visits decreased before 1996, remained relatively stable until 2005 and further decreased to approximately 24% in 2012. Reports of STI have remained relatively stable at approximately 3% in recent years (see *Figure 8.6*).

*Figure 8.6: Proportion of visits per calendar year at which injecting and high-risk sexual behaviour was reported amongst 1,315 drug users (DU) who were HIV-negative on entry to the Amsterdam Cohort Studies (ACS), 1986-2012.*




## STI screening among MSM in ACS

Since October 2008, all MSM in the ACS have been routinely screened for chlamydia and gonorrhoea by polymerase chain reaction (PCR) techniques on samples of urine and pharyngeal and rectal swabs. Cases of syphilis are detected by TPHA (Treponema pallidum haemagglutination assay). In 2012, a total of 545 MSM from the ACS were screened for STI; 130 MSM were screened once, 396 twice and 19 more than twice. The overall prevalence of any STI was 8.8% (87/989). The prevalence of any STI was significantly higher among HIV-infected MSM (23.1%) compared to HIV-uninfected MSM (6.8%).

## ACS research highlights 2012

Infection with HIV-1 may result in severe cognitive and motor impairment, referred to as HIV-1-associated dementia (HAD). Whilst its prevalence has dropped significantly in the era of combination antiretroviral therapy, milder neurocognitive disorders persist with a high prevalence. To identify additional therapeutic targets for treating HIV-associated neurocognitive disorders, several candidate gene polymorphisms have been evaluated, but few have been replicated across multiple studies. We tested seven candidate gene polymorphisms and five recently identified single nucleotide polymorphisms (SNPs) affecting HIV-1 replication

in macrophages for their association with HAD in a case-control study. A significant difference in genotype distribution among all cases and controls irrespective of the year of AIDS diagnosis was found for only an SNP in candidate gene Prep1 ($p = 1.2 \times 10(-5)$). Prep1 has recently been identified as a transcription factor preferentially binding the -2,518 G allele in the promoter of the gene encoding MCP-1, a protein with a well established role in the etiology of HAD [252].

Previously we established that at 3 years post-seroconversion, approximately 30% of HIV-infected individuals have cross-reactive neutralizing activity (CrNA) in their sera. Here we studied the kinetics with which CrNA develops and how these relate to the development of autologous neutralizing activity as well as viral escape and diversification. We found that CrNA can rapidly develop after HIV-1 infection is established, even within the first year after seroconversion, in an elite neutralizer as opposed to five other patients in whom CrNA was first detected at 20 to 35 months post-seroconversion. The kinetics with which CrNA developed paralleled the development of autologous neutralizing activity, as well as gp160 sequence diversity. Viral escape occurred in all individuals, despite the CrNA in their sera, which was reflected by the increasing gp160 sequence diversity that was higher in individuals with CrNA, especially in the elite neutralizer. This implies that CrNA in sera adds extra pressure on the virus to escape this potent immune response. The rapid escape was in line with the absent effect of CrNA on the clinical course of infection [253].

The HIV-1 characteristics associated with transmission are still poorly defined, but a better understanding of which viruses are selected would aid in the development of drugs or vaccines aimed at preventing infection. At the Laboratory of Experimental Virology of the AMC, mothers infected with HIV-1 subtype A or C viruses, including several who infected their children, were studied. The genotypic characteristics of the V1-V5 region of the gp120 envelope proteins of viruses, found not only in transmitting mothers and their infected children, but also in non-transmitting mothers, were investigated. An association with transmission was identified; viruses with a potential N-glycosylation site on position AA339 were preferably transmitted, not only in transmitting mothers, but also in acute sexual transmissions. The function of the potential N-glycosylation site at AA339 in the HIV-1 envelope protein remains to be determined; however, AA339 is situated in the α2-helix region of C3 of the gp120 molecule. Residues within that region of subtype C viruses have a unique mutational pattern, which may be associated with neutralization by antibodies [254].

Trends in HIV incidence among MSM who have recently had post-exposure prophylaxis (PEP) prescribed in Amsterdam were compared with MSM participating in the ACS. We used data from MSM who were prescribed PEP in Amsterdam between 2000 and 2009, who were HIV-negative at the time of PEP prescription, and who had follow-up HIV testing 3 and/or 6 months after PEP prescription (n=395). For comparison, cohort data from MSM participating in the ACS in the same period were used (n=782). Between 2000 and 2009, among MSM who were prescribed PEP, an overall HIV incidence of 6.4 (95% confidence interval [CI] 3.4-11.2)

per 100 person-years was found, compared with an HIV incidence of 1.6 (95% CI 1.3–2.1) per 100 person-years among MSM participating in the ACS (p<0.01). In both cohorts, an increasing trend in HIV incidence over time was observed (incidence rate ratio [IRR per calendar year] 1.3 [95% CI 0.9–1.7] and 1.1 [95% CI 1.0–1.2] among MSM prescribed PEP and MSM of the ACS, respectively). Particularly in more recent years, MSM who were recently prescribed PEP had a higher HIV incidence compared with MSM participating in the ACS, indicating ongoing sexual risk behaviour [255].

The hepatitis C virus (HCV) disease burden among injecting drug users (IDUs) is determined by HCV incidence, the long latency period of HCV, competing mortality causes, presence of co-infection and HCV treatment uptake. We examined the effect of these factors and estimated the burden of HCV disease in Amsterdam. A Markov model was developed, incorporating HCV and human immunodeficiency virus (HIV), and parameterized with data of the IDU population of Amsterdam from the ACS, surveillance studies and literature. HCV infection was simulated from its acute phase to HCV-related liver disease (i.e., decompensated cirrhosis and hepatocellular carcinoma).

We found that the HCV prevalence among IDUs in Amsterdam increased to approximately 80% in the 1980s. From 2011 to 2025, the HCV-related disease prevalence will accordingly rise by 36%. In total, HCV-related liver disease will develop in 945 (95% range 617–1,309) individuals. This burden would have been 33% higher in the absence of HIV. In Amsterdam, 25% of HIV-negative IDUs receive successful HCV treatment, reducing the cumulative disease burden by 14%. Further reduction of 36% can be achieved by improving treatment, resulting in 603 cases (95% range 384–851). The hepatitis C virus burden among IDUs in Amsterdam has been reduced by a high competing mortality rate, particularly caused by HIV infection, and to a smaller extent by hepatitis C virus treatment. Improved hepatitis C virus treatment is expected to contribute to reduce the future hepatitis C virus disease burden [256].

## Steering committee: The politburo

In 2012, the "politburo" met four times. Twenty-five proposals for use of data and/or samples (serum/PBMC) were submitted to the politburo: five from AMC-Experimental Immunology, nine from the AMC-Medical Microbiology, four from the UMCU, six from the PHSA, one from AMC-internal medicine and one from researchers not affiliated with the ACS. Twenty-four requests were approved, some after revision, and one request was denied. Three of the approved proposals were collaborations with groups outside the ACS of whom two were from groups abroad.

# Publications in 2012 that include ACS data


1. Baan E, de Ronde A, Luchters S, Vyankandondera J, Lange JM, Pollakis G, Paxton WA. **HIV Type 1 Mother-to-Child Transmission Facilitated by Distinctive Glycosylation Sites in the gp120 Envelope Glycoprotein.** *AIDS Res Hum Retroviruses. 2012 Jul;28(7):715-724.*

2. Bol SM, Booiman T, van Manen D, Bunnik EM, van Sighem AI, Sieberer M, Boeser-Nunnink B, de Wolf F, Schuitemaker H, Portegies P, Kootstra NA, van 't Wout AB. **Single nucleotide polymorphism in gene encoding transcription factor Prep1 is associated with HIV-1-associated dementia.** *PLoS One. 2012;7(2):e30990.*

3. van den Boom W, Stolte I, Sandfort T, Davidovich U. **Serosorting and sexual risk behaviour according to different casual partnership types among MSM: the study of one-night stands and sex buddies.** *AIDS Care. 2012 Feb;24(2):167-73.*

4. Bunders MJ, van der Loos CM, Klarenbeek PL, van Hamme JL, Boer K, Wilde JC, de Vries N, van Lier RA, Kootstra N, Pals ST, Kuijpers TW. **Memory CD4+CCR5+ T cells are abundantly present in the gut of newborn infants to facilitate mother-to-child transmission of HIV-1.** *Blood. 2012 Nov 22;120(22):4383-90.*

5. Cornelissen M, Pasternak AO, Grijsen ML, Zorgdrager F, Bakker M, Blom P, Prins JM, Jurriaans S, and van der Kuyl AC. **HIV-1 dual infection is associated with faster CD4+Tcell decline in a cohort of men with primary HIV infection.** *Clinical infectious diseases 2012:54, 539-547.*

6. Edo-Matas D, Rachinger A, Setiawan LC, Boeser-Nunnink BD, van 't Wout AB, Lemey P, Schuitemaker H. **The evolution of human immunodeficiency virus type-1 (HIV-1) envelope molecular properties and coreceptor use at all stages of infection in an HIV-1 donor-recipient pair.** *Virology. 2012 Jan 5;422(1):70-80.*

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10. Gijsbers EF, van Nuenen AC, Schuitemaker H, Kootstra NA. **Gag sequence variation in an HIV-1 transmission cluster influences viral replication fitness.** *J Gen Virol. 2012 Nov 7. [Epub ahead of print].*

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12. Grebely J, Prins M, Hellard M, Cox AL, Osburn WO, Lauer G, Page K, Lloyd AR, Dore GJ; on behalf of the International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC(3)). **Hepatitis C virus clearance, reinfection, and persistence, with insights from studies of injecting drug users: towards a vaccine.** *Lancet Infect Dis. 2012 May;12(5):408-414.*

13. Grebely J, Morris MD, Rice TM, Bruneau J, Cox AL, Kim AY, McGovern BH, Shoukry NH, Lauer G, Maher L, Lloyd AR, Hellard M, Prins M, Dore GJ, Page K; on behalf of the InC Study Group. **Cohort Profile: The International Collaboration of Incident HIV and Hepatitis C in Injecting Cohorts (InC3) Study.** *Int J Epidemiol. 2012 Nov 30. [Epub ahead of print].*

14. Grijsen ML, Vrouenraets SM, Wit FW, Stolte IG, Prins M, Lips P, Reiss P, Prins JM. **Low bone mineral density in men who have sex with men regardless of HIV status.** *J Infect Dis. 2012 Nov 12. [Epub ahead of print].*

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## Theses in 2012 that include ACS data

**Zelda Euler** – 20 April 20 2012, "Humoral immunity in HIV-1 infection".

# 9. Curacao

Ard van Sighem, Gonneke Hermanides, Ashley Duits

## Introduction

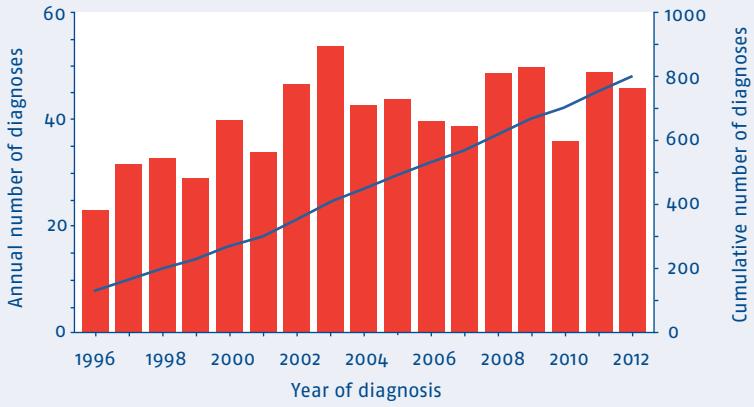
For the better part of a decade, Stichting HIV Monitoring (SHM) has collected demographic and clinical data about HIV-infected individuals in clinical care at the St. Elisabeth Hospital in Willemstad in Curacao. As a result of this registration and monitoring, an extensive database has been established that presents a clear picture of the HIV-infected population, the effectiveness of HIV care, and the current challenges in this small Caribbean setting. This special report endeavours to provide a concise overview of the present state of HIV infection in Curacao.

## HIV-infected population

As of June 2013, of the total of 833 HIV-infected patients ever registered in Curacao, 162 (19%) died after their initial registration. The total follow-up for the entire group of 833 patients was 5,402 person-years since HIV diagnosis. Of the 671 patients who were still alive as of June 2013, 467 (70%) were also still in clinical care and had at least one contact with the treating physician in Curacao since January 2012.

In total, 268 (32%) of the registered patients were diagnosed with HIV in or before 2000; 82 (31%) of those patients died before June 2013 (*Figure 9.1; Web Appendix Table 9.1*). Between 2001 and June 2013, 531 patients were diagnosed and entered care, although in 2013 no newly diagnosed HIV patients were reported as most likely because of a temporary discontinuation in data collection after retirement of the data collector. For the remaining 34 patients, no information regarding the date of their first positive HIV test was available. By far, the majority of patients were infected with HIV-1, whilst two patients were infected with HIV-2, and four patients had antibodies against 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 9.1*).

*Figure 9.1: Annual and cumulative number of HIV diagnoses amongst 833 HIV-infected patients in Curacao registered by Stichting HIV Monitoring as of June 2013. In total, 111 patients were diagnosed prior to 1996, whilst for 34 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 9.1: Characteristics of the HIV-infected population in Curacao registered by Stichting HIV Monitoring as of June 2013.*

| | Alive, N=671 | | Dead, N=162 | | Total, N=833 | |
|---|---|---|---|---|---|---|
| | N/median | %/IQR | N/median | %/IQR | N/median | %/IQR |
| Sex | | | | | | |
| Male | 407 | 61 | 113 | 70 | 520 | 62 |
| Female | 264 | 39 | 49 | 30 | 313 | 38 |
| Transmission | | | | | | |
| MSM | 129 | 19 | 17 | 10 | 146 | 18 |
| Heterosexual | 460 | 69 | 101 | 62 | 561 | 67 |
| Other/unknown | 82 | 12 | 44 | 27 | 126 | 15 |
| Country of birth | | | | | | |
| Antilles | 471 | 70 | 144 | 89 | 615 | 74 |
| Haiti | 80 | 12 | 7 | 4 | 87 | 10 |
| Dominican Republic | 57 | 8 | 6 | 4 | 63 | 8 |
| Other | 63 | 9 | 5 | 3 | 68 | 8 |
| Treated with cART | | | | | | |
| No | 151 | 23 | 57 | 35 | 208 | 25 |
| Yes | 520 | 77 | 105 | 65 | 625 | 75 |

| | Alive, N=671 | | Dead, N=162 | | Total, N=833 | |
|---|---|---|---|---|---|---|
| | N/median | %/IQR | N/median | %/IQR | N/median | %/IQR |
| Diagnosis | | | | | | |
| CD4 (cells/mm$^3$) | 349 | 164–505 | 99 | 41–352 | 329 | 100–491 |
| RNA (log$_{10}$ copies/ml) | 4.4 | 3.8–5.0 | 4.9 | 3.9–5.4 | 4.5 | 3.8–5.0 |
| Age (years) | 38 | 30–47 | 41 | 32–57 | 38 | 30–47 |
| AIDS | 36 | 5 | 31 | 19 | 67 | 8 |
| Time to cART | 1.0 | 0.2–4.0 | 0.8 | 0.2–4.1 | 1.0 | 0.2–4.1 |
| Follow-up (years) | 5.6 | 1.4–11.1 | 2.7 | 0.3–7.2 | 5.0 | 1.3–10.3 |
| Start of cART | | | | | | |
| CD4 (cells/mm$^3$) | 186 | 65–303 | 77 | 13–185 | 166 | 51–287 |
| RNA (log$_{10}$ copies/ml) | 4.9 | 4.3–5.4 | 4.9 | 4.4–5.5 | 4.9 | 4.3–5.4 |
| Age (years) | 42 | 34–49 | 46 | 38–57 | 43 | 34–51 |
| AIDS | 68 | 10 | 52 | 32 | 120 | 14 |
| Follow-up (years) | 4.5 | 1.6–9.0 | 1.8 | 0.2–4.7 | 4.1 | 1.3–8.1 |
| Present (June 2013)[a] | | | | | | |
| CD4 (cells/mm$^3$) | 495 | 332–692 | – | – | 495 | 332–692 |
| RNA <500 copies/ml | 308 | 73[b] | – | – | 308 | 73[b] |
| RNA <100 copies/ml | 281 | 67[b] | | | 281 | 67[b] |
| Age (years) | 49 | 40–56 | – | – | 49 | 40–56 |

*Legend: IQR=interquartile range; MSM=men who have sex with men; cART=combination antiretroviral therapy.*
*a for 467 patients still in clinical care;*
*b percentage of 422 patients with a viral load measurement.*

## Children and adolescents

Amongst HIV-infected patients ever registered in Curacao, 15 patients were younger than 13 years of age ('children') at the time of diagnosis, and 16 were aged 13 to 18 years ('adolescents'). Most of the children, 12 in total, were infected by mother-to-child transmission. Adolescents were mainly infected via either heterosexual contact (11 patients) or homosexual contact (4 patients). In total, 9 children and 1 adolescent died. Of the other 6 children, 1 was still in clinical care, as were 8 adolescents.

There is some confusion regarding the number of children in Curacao infected via mother-to-child transmission, either in utero, during labour and delivery, or postnatally during breastfeeding. According to the Public Health Service in Curacao, 7 children were found to be HIV-positive between 2001 and 2009, but only 3 infected children were registered by SHM during this period.

## Country of infection

For 532 patients, or 64%, of the registered population, the most likely country of infection was known. For 474 (89%) of those patients, the country of infection was the former Netherlands Antilles. This percentage was even higher (96%) amongst the 418 patients who

were also born in the Antilles. Of the 532 patients, 19 reported that they were infected in the Netherlands, 16 in Haiti, and 9 in the Dominican Republic. All but four of the 236 patients with a known HIV-1 subtype were infected with a subtype B virus, which is the most prevalent subtype amongst patients of non-African origin in both the Caribbean and the Netherlands.

## Hepatitis B and C

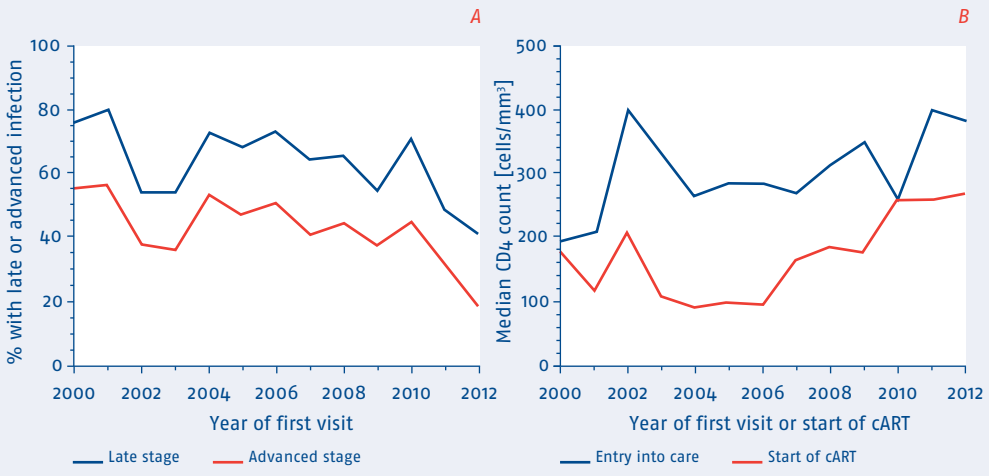
In total, 46 patients, or 8%, of the 613 tested were co-infected with hepatitis B. The prevalence of hepatitis B did not differ by transmission risk group, but it appeared to be somewhat higher amongst men (9%) than women (5%). Co-infection with hepatitis C was found in only 8 patients, or 1% of the 539 who were ever tested for hepatitis C.

## Late presentation and start of treatment

At the time of the first visit to the hospital, 415 (62%) of the 665 patients who could be classified presented with late-stage HIV infection, that is, with a concurrent AIDS diagnosis or with CD4 counts below 350 cells/mm$^3$ (*Figure 9.2A*) [7]. Of these 415 patients, 285 (69%) were already in an advanced stage of their infection with less than 200 cells/mm$^3$. Late presentation probably reflects a combination of late testing and a delay between HIV diagnosis and entry into care.

As a result of late entry into care, median CD4 counts at the start of combination antiretroviral treatment (cART) were low, 166 cells/mm$^3$, which is markedly below the recommended threshold by any guideline to start treatment. Nevertheless, only 14% of the patients had been diagnosed with an AIDS-defining event by the time treatment was started [146]. In recent years, some increase in CD4 cell counts has been seen at the start of cART (*Figure 9.2B*). Between 2009 and 2013, 41% of the patients for whom a CD4 count was available at the start of cART had less than 200 cells/mm$^3$, whilst 39% had counts between 200 and 350 cells/mm$^3$.

*Figure 9.2: (A) From 2000 onwards, 62% of patients entered clinical care with late-stage HIV infection, whilst 42% had advanced HIV infection. Late-stage infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 counts. Advanced-stage infection: CD4 counts below 200 cells/mm³ or having AIDS. (B) From 2000 onwards, median CD4 counts were 307 cells/mm³ (interquartile range [IQR] 113-463) at the time of entry and 180 cells/mm³ (IQR 61-287) at the start of cART. In recent years, both CD4 counts at the time of entry into care and at start of cART increased to 383 and 270 cells/mm³, respectively, in 2012, indicating more timely diagnosis and start of treatment.*



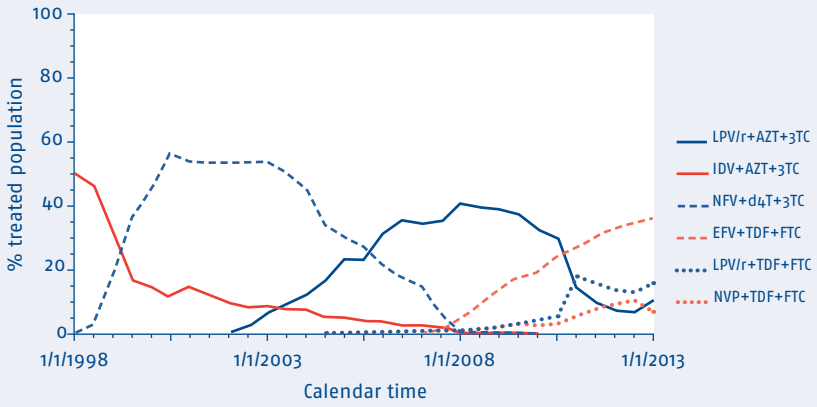

## Patient monitoring

Current guidelines recommend monitoring HIV-infected patients two or three times a year, depending on CD4 count and treatment status [9]. In most recent years, these guidelines have been generally well followed. Between 2007 and 2012, on average, 2.1 immunologic measurements were performed annually per patient. During the same period, the viral load was monitored 2.0 times per year, whilst follow-up visits for each patient averaged 2.5 per year.

## Combination treatment

In total, 625 (75%) patients started cART. Of the 298 who did so between 2007 and 2013, 41% started with a combination of tenofovir/emtricitabine and efavirenz and 39% with a combination of zidovudine/lamivudine and ritonavir-boosted lopinavir. Over time, shifts in the treatment regimens have occurred (*Figure 9.3*). Since 2008, a combination of tenofovir/emtricitabine with either efavirenz, nevirapine, or lopinavir has become more widely used. Of the 412 patients who started cART and were still in clinical care as of June 2013, 39% were receiving efavirenz, 25% lopinavir, and 15% nevirapine, whilst 73% were receiving tenofovir/emtricitabine and 10% zidovudine/lamivudine.

*Figure 9.3: 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 50% in 1998 to almost 0% after 2008. This decrease was counterbalanced by an increase in the proportion of patients treated with NFV+d4T+3TC. Since 2002, a combination of LPV/r+AZT+3TC has been used increasingly until 2010. The use of EFV+TDF+FTC and LPV/r +TDF+FTC increased from 2008 onwards, and at the beginning of 2013, 36% of the patients were receiving EFV+TDF+FTC, 16% LPV/r+TDF+FTC, and 11% LPV/r+AZT+3TC.*



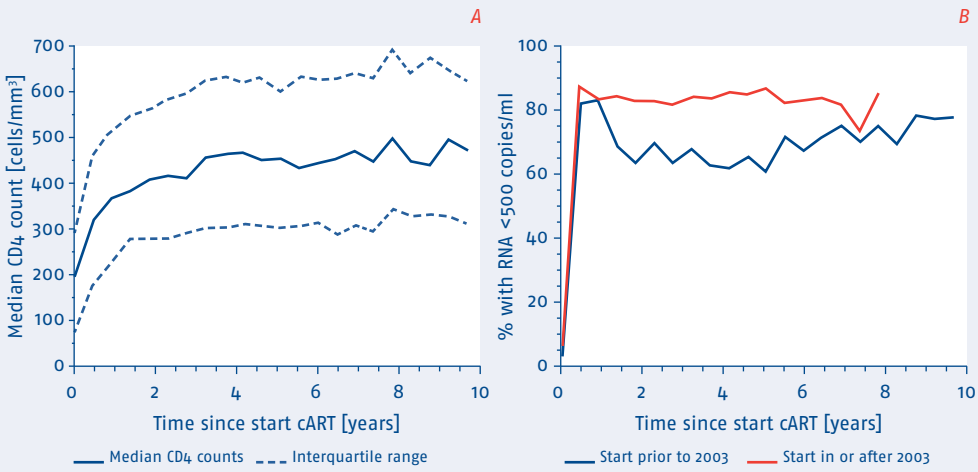

*Legend: LPV/r=ritonavir-boosted lopinavir; AZT=zidovudine; 3TC=lamivudine; NFV=nelfinavir; d4T=stavudine; EFV=efavirenz; TDF=tenofovir; FTC=emtricitabine; NVP=nevirapine; IDV=indinavir.*

## Treatment outcome

For 45% of the 582 antiretroviral therapy-naïve patients who started cART, CD4 counts increased by at least 150 cells/mm$^3$ during the first 6 months of treatment; after 2 years, this proportion increased to 78%. At the same time, 81% of the patients reached a viral load below 500 copies/ml and 73% below 100 copies/ml within 6 months after starting treatment.

In patients who were still in clinical care as of June 2013, CD4 counts reached a plateau between 450 and 500 cells/mm$^3$ after 5 years of cART (*Figure 9.4A*). During the same period, the proportion of patients with a viral load below 500 copies/ml decreased from 84% after 48 weeks to 75% after 5 years of treatment. However, amongst those who started cART in 2003 or later, i.e., when more efficacious treatment combinations came into use in Curacao, the proportion of patients who were able to retain viral suppression remained approximately 80% (*Figure 9.4B*). For 80% of the patients still in clinical care, the most recent viral load was below 500 copies/ml, whilst 74% had a viral load below 100 copies/ml. These proportions were the same irrespective of the period in which cART was started.

*Figure 9.4: CD4 cell counts and viral load in 412 treated patients who were still in care as of June 2013. (A) Median CD4 counts increased from 196 (IQR 74–303) cells/mm³ at the start of combination antiretroviral therapy (cART) to 319 (IQR 176–469) cells/mm³ after 24 weeks and reached a plateau between 450 and 500 cells/mm³ after 5 years. (B) The proportion of patients with HIV RNA <500 copies/ml was 84% 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 5 years for those who started prior to 2003.*




## Virological failure

As viral suppression rates appear to have increased, one may presume that, conversely, rates of virological failure have decreased. Indeed, when virological failure is considered to be HIV RNA above 200 copies/ml despite at least 4 months of continuous treatment, the proportion of patients with failure steadily declined from approximately 36% between 2000 and 2004 to 12% in 2012. Nevertheless, failure rates are still higher than in the Netherlands.

## Mortality and survival

Of the group of 701 patients who were still alive as of 1 January 2005 or were diagnosed with HIV after that date, 82 had died by June 2013. Overall, the survival probability after 7 years of follow-up was 85%. Altogether, 369 patients started cART in or after 2005, and out of this group, 41 died, and 17 of those died within 6 months of starting cART. After 7 years, the survival probability was 81%.

## Drug resistance

With so many patients experiencing virological failure, resistance to one or more antiretroviral drugs in some patients may be expected. For 155 patients, 236 genotypic sequences of the protease and reverse transcriptase (RT) gene could be examined for drug resistance after the start of treatment. In total, 86, or 55%, of those sequenced had high-level resistance to at least one antiretroviral drug, according to the Stanford interpretation algorithm [74].

In total, 199 out of the 236 genotypic sequences were obtained when the 155 patients were supposedly being treated. Altogether, 62% of these 199 sequences showed high-level resistance to at least one antiretroviral drug. Resistance to lamivudine and emtricitabine was observed in 42% of the sequences; resistance to at least one other nucleoside RT inhibitor was found in 20%, to protease inhibitors in 32% and to non-nucleoside RT inhibitors in 24%. On the other hand, 30% of the sequences indicated full susceptibility to all drugs. Most likely, this means that about a third of the patients who experienced virological failure did so because of complete non-adherence to treatment.

## Transmitted drug resistance

Patients becoming infected with a resistant virus, with the consequent preclusion of certain drugs from the antiretroviral arsenal, does not seem to be a major problem at the moment, although no sequences were available for the most recent calendar years. Infection with resistant virus was investigated in 64 patients who had a genotypic sequence within 1 year of diagnosis but before the start of treatment. Resistance-associated mutations were detected in five patients [112]. These mutations gave rise to high-level resistance in only one patient, who was discussed in last year's report [1].

## Conclusion

In recent years, the quality of monitoring and treatment offered to HIV-infected patients in Curacao has improved considerably. However, adherence to treatment is still not optimal, and levels of retention in care are worryingly low.

## Recommendations

To allow for the correct interpretation of the data, it is important to eliminate as soon as possible the back log in data collection after the retirement of the previous data collector. Special attention should be paid to the collection of data of HIV-infected children. Further, adherence to treatment and retention in care need to be improved in order to reduce the number of patients failing on treatment [257]. Also, HIV infections need to be detected at an earlier stage, such that patients can start antiretroviral treatment in accordance with current recommendations.

# 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 Stichting HIV Monitoring website, *www.hiv-monitoring.nl*.

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# Publications & presentations

The publications and presentations listed below are those available since the publication of the previous Monitoring Report 2012.

## Publications

**Immunovirologic control 24 months after interruption of antiretroviral therapy initiated close to HIV seroconversion**
Lodi S, Meyer L, Kelleher AD, Rosinska M, Ghosn J, Sannes M, Porter K.
*Arch Intern Med. 2012 Sep 10;172(16):1252-5. doi: 10.1001/archinternmed.2012.2719.*

**Hepatitis C virus viremia increases the incidence of chronic kidney disease in HIV-infected patients**
Peters L, Grint D, Lundgren JD, Rockstroh JK, Soriano V, Reiss P, Grzeszczuk A, Sambatakou H, Mocroft A, Kirk O; EuroSIDA in EuroCoord.
*AIDS. 2012 Sep 24;26(15):1917-26.*

**Benchmarking HIV health care: from individual patient care to health care evaluation. An example from the EuroSIDA study**
Podlekareva DN, Reekie J, Mocroft A, Losso M, Rakhmanova AG, Bakowska E, Karpov IA, Lazarus JV, Gatell J, Lundgren JD, Kirk O; EuroSIDA study in EuroCoord.
*BMC Infect Dis. 2012 Sep 25;12:229. doi: 10.1186/1471-2334-12-229.*

**The clinical benefits of antiretroviral therapy in severely immunocompromised HIV-1-infected patients with and without complete viral suppression**
Mocroft A, Bannister WP, Kirk O, Kowalska JD, Reiss P, D'Arminio-Monforte A, Gatell J, Fisher M, Trocha H, Rakhmanova A, Lundgren JD; EuroSIDA Study in EuroCOORD.
*Antivir Ther. 2012;17(7):1291-300. doi: 10.3851/IMP2407. Epub 2012 Sep 26.*

**Predicting the short-term risk of diabetes in HIV-positive patients: the Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) study**
Petoumenos K, Worm SW, Fontas E, Weber R, De Wit S, Bruyand M, Reiss P, El-Sadr W, Monforte AD, Friis-Møller N, Lundgren JD, Law MG; D:A:D Study Group.
*J Int AIDS Soc. 2012 Oct 10;15(2):17426. doi: 10.7448/IAS.15.2.17426.*

**Temporal changes and regional differences in treatment uptake of hepatitis C therapy in EuroSIDA**
D Grint, L Peters, M Vogel, M Beniowski, C Pradier, M Battegay, D Jevtovic, V Soriano, J Lundgren, J Rockstroh, O Kirk, A Mocroft.
*J Int AIDS Soc. 2012 Nov 11;15(6):18118. doi: 10.7448/IAS.15.6.18118.*

**Heterogeneity in outcomes of treated HIV-positive patients in Europe and North America: relation with patient and cohort characteristics**
May MT, Hogg RS, Justice AC, Shepherd BE, Costagliola D, Ledergerber B, Thiébaut R, Gill MJ, Kirk O, van Sighem A, Saag MS, Navarro G, Sobrino-Vegas P, Lampe F, Ingle S, Guest JL, Crane HM, D'Arminio Monforte A, Vehreschild JJ, Sterne JA; Antiretroviral Therapy Cohort Collaboration (ART-CC).
*Int J Epidemiol. 2012 Dec;41(6):1807-20. doi: 10.1093/ije/dys164. Epub 2012 Nov 12.*

**Rate of CD4 decline and HIV-RNA change following HIV seroconversion in men who have sex with men: a comparison between the Beijing PRIMO and CASCADE cohorts**
Huang X, Lodi S, Fox Z, Li W, Phillips A, Porter K, Lutsar I, Kelleher A, Li N, Xu X, Wu H, Johnson AM; on behalf of the Beijing PRIMO cohort study and the CASCADE Collaboration in EuroCoord.
*J Acquir Immune Defic Syndr. 2012 Dec 6. [Epub ahead of print]*

**HIV-infected mental health patients: characteristics and comparison with HIV-infected patients from the general population and non-infected mental health patients**
Schadé A, van Grootheest G, Smit JH.
*BMC Psychiatry. 2013 Jan 23;13:35. doi: 10.1186/1471-244X-13-35.*

**Atazanavir is not associated with an increased risk of cardio or cerebrovascular disease events**
Monforte AD, Reiss P, Ryom L, El-Sadr W, Dabis F, De Wit S, Worm SW, Law MG, Weber R, Kirk O, Pradier C, Phillips AN, Lundgren JD, Sabin CA.
*AIDS. 2013 Jan 28;27(3):407-15*

**An internationally generalizable risk index for mortality after one year of antiretroviral therapy**
Tate JP, Justice AC, Hughes MD, Bonnet F, Reiss P, Mocroft A, Nattermann J, Lampe FC, Bucher HC, Sterling TR, Crane HM, Kitahata MM, May M, Sterne JA.
*AIDS. 2013 Feb 20;27(4):563-72. doi: 10.1097/QAD.0b013e32835b8c7f.*

**High incidence of intermittent care in HIV-1-infected patients in Curaçao before and after starting cART**
Hermanides HS, Holman R, Gras L, Winkel CN, Gerstenbluth I, de Wolf F, Duits AJ.
*AIDS Care. 2013 Feb 21. [Epub ahead of print]*

**Insurability of HIV positive people treated with antiretroviral therapy in Europe: collaborative analysis of HIV cohort studies**
Kaulich-Bartz J, Dam W, May MT, Lederberger B, Widmer U, Phillips AN, Grabar S, Mocroft A, Vilaro J, van Sighem A, Moreno S, Dabis F, Monforte AD, Teira R, Ingle SM, Sterne JA; Writing committee for the Antiretroviral Cohort Collaboration.
*AIDS. 2013 Feb 25. [Epub ahead of print]*

**Risk of tuberculosis following HIV seroconversion in high-income countries**
Lodi S, del Amo J, d'Arminio Monforte A, Abgrall S, Sabin C, Morrison C, Furrer H, Muga R, Porter K, Girardi E; CASCADE collaboration in EuroCoord.
*Thorax. 2013 Mar;68(3):207-13. doi: 10.1136/thoraxjnl-2012-201740. Epub 2012 Oct 31.*

**Antiretroviral drug-related liver mortality among HIV-positive persons in the absence of hepatitis B or C virus coinfection: the data collection on adverse events of anti-HIV drugs study**
Kovari H, Sabin CA, Ledergerber B, Ryom L, Worm SW, Smith C, Phillips A, Reiss P, Fontas E, Petoumenos K, De Wit S, Morlat P, Lundgren JD, Weber R.
*Clin Infect Dis. 2013 Mar;56(6):870-9. doi: 10.1093/cid/cis919. Epub 2012 Oct 22.*

**Predictors of CD4+ T-Cell Counts of HIV Type 1-Infected Persons After Virologic Failure of All 3 Original Antiretroviral Drug Classes**
The Pursuing Later Treatment Option II (PLATO II) Project Team of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE).
*J Infect Dis. 2013 Mar 1;207(5):759-67. doi: 10.1093/infdis/jis752. Epub 2012 Dec 7.*

**Durability of first ART regimen and risk factors for modification, interruption or death in HIV-positive patients starting ART in Europe and N. America 2002-2009**
Abgrall S; The Antiretroviral Therapy Cohort Collaboration (ART-CC).
*AIDS. 2013 Mar 13;27(5):803-13. doi: 10.1097/QAD.0b013e32835cb997. Epub 2012 Nov 28.*

**CD4 cell count and viral load-specific rates of AIDS, non-AIDS and deaths according to current antiretroviral use**
Mocroft A, Phillips AN, Gatell J, Horban A, Ledergerber B, Zilmer K, Jevtovic D, Maltez F, Podlekareva D, Lundgren JD; EuroSIDA study in EuroCOORD.
*AIDS. 2013 Mar 27;27(6):907-18. doi: 10.1097/QAD.0b013e32835cb766.*

**Impact of HIV-1 subtype on CD4 count at HIV seroconversion, rate of decline, and viral load set point in European seroconverter cohorts**
Touloumi G, Pantazis N, Pillay D, Paraskevis D, Chaix ML, Bucher HC, Kücherer C, Zangerle R, Kran AM, Porter K; CASCADE collaboration in EuroCoord.
*Clin Infect Dis. 2013 Mar;56(6):888-97. doi: 10.1093/cid/cis1000. Epub 2012 Dec 7.*

**Use of combination neonatal prophylaxis for the prevention of mother-to-child transmission of HIV infection in European high-risk infants**
Chiappini E, Galli L, Giaquinto C, Ene L, Goetghebuer T, Judd A, Lisi C, Malyuta R, Noguera-Julian A, Ramos JT, Rojo-Conejo P, Rudin C, Tookey P, de Martino M, Thorne C; European Pregnancy and Paediatric HIV Cohort Collaboration study group in EuroCoord.
*AIDS. 2013 Mar 27;27(6):991-1000. doi: 10.1097/QAD.0b013e32835cffb1.*

**Does hepatitis C viremia or genotype predict the risk of mortality in individuals coinfected with HIV?**
Rockstroh JK, Peters L, Grint D, Soriano V, Reiss P, d'Arminio Monforte A, Beniowski M, Losso MH, Ole K, Kupfer B, Mocroft A.
*Journal of Hepatology. 2013 April 10. [Epub ahead of print]*

**Effect of HCV Infection on Cause-Specific Mortality Following HIV Seroconversion Before and After 1997**
Van der Helm J, Geskus R, Sabin C, Meyer L, Del Amo J, Chêne G, Dorrucci M, Muga R, Porter K, Prins M; CASCADE collaboration in EuroCoord.
*Gastroenterology. 2013 Apr;144(4):751-760.e2. doi: 10.1053/j.gastro.2012.12.026. Epub 2012 Dec 22.*

**Prolonged decrease of CD4+ T lymphocytes in HIV-1 infected patients after radiotherapy for a solid tumor**
Sankatsing SU, Hillebregt MM, Gras L, Brinkman K, van der Ende M, de Wolf F, Stalpers LJ, Prins JM.
*J Acquir Immune Defic Syndr. 2013 Apr 15;62(5): 546-9. doi: 10.1097/QAI.0b013e318285d934. Epub 2013 Jan 10.*

**Lower incidence of Pneumocystis jirovecii pneumonia among Africans in the Netherlands; host or environmental factors?**
Schoffelen AF, van Lelyveld SF, Barth RE, Gras L, de Wolf F, Netea MG, Hoepelman AI.
*AIDS. 2013 Apr 24;27(7):1179-84. Epub 2012 Dec 31.*

**Association between antiretroviral exposure and renal impairment among HIV-positive persons with normal baseline renal function: the D:A:D study**
Ryom L, Mocroft A, Kirk O, Worm SW, Kamara DA, Reiss P, Ross M, Fux CA, Morlat P, Moranne O, Smith C, Lundgren JD; D:A:D Study Group.
*J Infect Dis. 2013 May 1;207(9):1359-69. doi: 10.1093/infdis/jit043. Epub 2013 Feb 4.*

**Hyaluronic Acid Levels Predict Risk of Hepatic Encephalopathy and Liver-Related Death in HIV/Viral Hepatitis Coinfected Patients**
Peters L, Mocroft A, Soriano V, Rockstroh J, Rauch A, Karlsson A, Knysz B, Pradier C, Zilmer K, Lundgren JD; for EuroSIDA in EuroCoord.
*PLoS One. 2013 May 27;8(5):e64283. doi: 10.1371/journal.pone.0064283. Print 2013.*

**Has the Rate of CD4 Cell Count Decline before Initiation of Antiretroviral Therapy Changed over the Course of the Dutch HIV Epidemic among MSM?**
Gras L, Geskus RB, Jurriaans S, Bakker M, van Sighem A, Bezemer D, Fraser C, Prins JM, Berkhout B, de Wolf F; for the ATHENA national observational cohort.
*PLoS One. 2013 May 27;8(5):e64437. doi: 10.1371/journal.pone.0064437. Print 2013.*

**Severe bacterial non-AIDS infections in HIV-positive persons: incidence rates and risk factors**
Søgaard OS, Reekie J, Ristola M, Jevtovic D, Karpov I, Beniowski M, Servitskiy S, Domingo P, Reiss P, Mocroft A, Kirk O for EuroSIDA in EuroCoord.
*J Infect. 2013 May;66(5):439-46.*

**Higher rates of AIDS during the first year of antiretroviral therapy among migrants: the importance of tuberculosis**
Antiretroviral Therapy Cohort Collaboration (ART-CC), Shepherd BS, Jenkins CA, Parrish DD, Glass TR, Cescon A, Masabeu A, Chene G, de Wolf F, Crane HM, Jarrin I, Gill J, del Amo J, Abgrall S, Khaykin P, Lehmann C, Ingle SM, May MT, Sterne JA, Sterling TR.
*AIDS. 2013 May 15;27(8):1321-9. doi: 10.1097/QAD.0b013e32835faa95.*

**Influence of geographical origin and ethnicity on mortality in patients on antiretroviral therapy in Canada, Europe and the United States**
The Antiretroviral Therapy Cohort Collaboration (ART-CC).
*Clin Infect Dis. 2013 Jun;56(12):1800-9. doi: 10.1093/cid/cit111. Epub 2013 Mar 1.*

**Computational models can predict response to HIV therapy without a genotype and may reduce treatment failure in different resource-limited settings**
Revell AD, Wang D, Wood R, Morrow C, Tempelman H, Hamers RL, Alvarez-Uria G, Streinu-Cercel A, Ene L, Wensing AM, Dewolf F, Nelson M, Montaner JS, Lane HC, Larder BA; on behalf of the RDI study group.
*J Antimicrob Chemother. 2013 Jun;68(6):1406-14. doi: 10.1093/jac/dkt041. Epub 2013 March 13.*

**Contribution of genetic background, traditional risk factors, and HIV-related factors to coronary artery disease events in HIV-positive persons**
Rotger M, Glass TR, Junier T, Lundgren J, Neaton JD, Poloni ES, van 't Wout AB, Lubomirov R, Colombo S, Martinez R, Rauch A, Günthard HF, Neuhaus J, Wentworth D, van Manen D, Gras LA, Schuitemaker H, Albini L, Torti C, Jacobson LP, Li X, Kingsley LA, Carli F, Guaraldi G, Ford ES, Sereti I, Hadigan C, Martinez E, Arnedo M, Egaña-Gorroño L, Gatell JM, Law M, Bendall C, Petoumenos K, Rockstroh J, Wasmuth JC, Kabamba K, Delforge M, De Wit S, Berger F, Mauss S, de Paz Sierra M, Losso M, Belloso WH, Leyes M, Campins A, Mondi A, De Luca A, Bernardino I, Barriuso-Iglesias M, Torrecilla-Rodriguez A, Gonzalez-Garcia J, Arribas JR, Fanti I, Gel S, Puig J, Negredo E, Gutierrez M, Domingo P, Fischer J, Fätkenheuer G, Alonso-Villaverde C, Macken A, Woo J, McGinty T, Mallon P, Mangili A, Skinner S, Wanke CA, Reiss P, Weber R, Bucher HC, Fellay J, Telenti A, Tarr PE; MAGNIFICENT Consortium; INSIGHT; Swiss HIV Cohort Study.
*Clin Infect Dis. 2013 Jul;57(1):112-21. doi: 10.1093/cid/cit196. Epub 2013 Mar 26.*

**Long-term response to combination antiretroviral therapy in HIV-infected children in the Netherlands registered from 1996-2012**
Cohen S, Smit C, van Rossum AM, Fraaij PL, Wolfs TF, Geelen SP, Schölvinck EH, Warris A, Scherpbier HJ, Pajkrt D; on behalf of the Dutch paediatric HIV study group.
*AIDS. 2013 Jul 9. [Epub ahead of print]*

**Stability of hepatitis C virus (HCV) RNA levels among interferon-naïve HIV/HCV-coinfected individuals treated with combination antiretroviral therapy**
Grint D, Peters L, Reekie J, Soriano V, Kirk O, Knysz B, Suetnov O, Lazzarin A, Ledergerber B, Rockstroh J, Mocroft A; EuroSIDA in EuroCoord.
*HIV Med. 2013 Jul;14(6):370-8.*

**Virologic and Immunologic Response to cART by HIV-1 Subtype in the CASCADE Collaboration**
Touloumi G, Pantazis N, Chaix ML, Bucher HC, Zangerle R, Kran AM, Thiebaut R, Masquelier B, Kucherer C, Monforte Ad, Meyer L, Porter K; for CASCADE Collaboration in EuroCoord.
*PLoS One. 2013 Jul 30;8(7):e71174. doi: 10.1371/journal.pone.0071174. Print 2013.*

**Natural History of HIV control since sero-conversion**
Madec Y, Boufassa F, Porter K, Prins M, Sabin C, Monforte AD, Amornkul P, Bartmeyer B, Sannes M, Venet A, Lambotte O, Meyer L; on behalf of the CASCADE Collaboration in Eurocoord.
*AIDS. 2013 Aug 1. [Epub ahead of print]*

**Association between ALT level and the rate of cardio/cerebrovascular events in HIV-positive individuals: The D:A:D Study**
Sabin CA, Ryom L, Kovari H, Kirk O, de Wit S, Law, Reiss P, Dabis F, Pradier C, El Sadr W, Monforte AD, Kamara D, Phillips AN, Lundgren JD.
*J Acquir Immune Defic Syndr. 2013 Aug 1;63(4):456-63*

**The Incidence of AIDS-Defining Illnesses at a Current CD4 Count ≥200 Cells/μL in the Post-Combination Antiretroviral Therapy Era**
Mocroft A, Furrer HJ, Miro JM, Reiss P, Mussini C, Kirk O, Abgrall S, Ayayi S, Bartmeyer B, Braun D, Castagna A, d'Arminio Monforte A, Gazzard B, Gutierrez F, Hurtado I, Jansen K, Meyer L, Muñoz P, Obel N, Soler-Palacin P, Papadopoulos A, Raffi F, Ramos JT, Rockstroh JK, Salmon D, Torti C, Warszawski J, de Wit S, Zangerle R, Fabre-Colin C, Kjaer J, Chene G, Grarup J, Lundgren JD; for the Opportunistic Infections Working Group on behalf of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study in EuroCOORD.
*Clin Infect Dis. 2013 Aug 6. [Epub ahead of print]*

**Loss to follow-up and mortality rates in HIV-1 positive patients in Curaçao before and after the start of combined anti-retroviral therapy**
Hermanides HS, Holman R, Gras L, Winkel C, Gerstenbluth I, de Wolf F, Duits A.
*AIDS Res Hum Retroviruses. 2013 Aug 8. [Epub ahead of print]*

**HIV-1 transmission networks amongst men having sex with men and heterosexuals in Kenya**
Bezemer D, Faria NR, Hassan AS, Hamers RL, Mutua G, Anzala O, Mandaliya KN, Cane PA, Berkley JA, Rinke de Wit TF, Wallis CL, Graham SM, Price MA, Coutinho R, Sanders EJ.
*AIDS Res Hum Retroviruses. 2013 Aug 15. [Epub ahead of print]*

**The effect of efavirenz versus nevirapine-containing regimens in the HIV-CAUSAL Collaboration: reply to Llibre and Podzamczer and additional results**
Cain, Lauren E.; Hernán, Miguel A.; on behalf of the HIV-CAUSAL Collaboration.
*AIDS. 2013 Aug 24;27(13):2169-2170.*

**Advanced chronic kidney disease, end-stage renal disease and renal death among HIV-positive individuals in Europe**
Ryom L, Kirk O, Lundgren J, Reiss P, Pedersen C, De Wit S, Buzunova S, Gasiorowski J, Gatell J, Mocroft A; EuroSIDA in EuroCoord.
*HIV Medicine. 2013 Sep;14(8):503-8.*

**The effect of statin therapy on pneumonia in an HIV-infected population in the Netherlands**
Janssen NE, van Lelyveld SF, Hoepelman AI, Gras L, Groenwold RH, Oosterheert JJ.
*J Infect. 2013 Sep;67(3):238-41. doi: 10.1016/j.jinf.2013.04.011. Epub 2013 Apr 19.*

**Missed Opportunities Among HIV-Positive Women to Control Viral Replication During Pregnancy and to Have a Vaginal Delivery**
Aebi-Popp K, Mulcahy F, Glass TR, Rudin C, Martinez de Tejada B, Bertisch B, Fehr J, Grawe C, Scheibner K, Rickenbach M, Hoesli I, Thorne C; for the European Collaborative Study in EuroCoord and the Swiss Mother & Child HIV Cohort Study.
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### Other printed materials

**Sexually transmitted infections, including HIV, in the Netherlands in 2012**
Soetens LC, Koedijk FDH, van den Broek IVF, Vriend HJ, Op de Coul ELM, van Aar F, van Sighem AI, Stirbu-Wagner I, van Benthem BHB.
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### Oral presentations

**SHM: Monitoring of HIV in the Netherlands**
De Wolf F, Van Sighem A.
*Support to the Republic of Kazakhstan in Infectious Disease Prevention and Control, Kick-off meeting, Almaty, Kazakhstan, 20-21 September 2012.*

**General overview of main approaches for estimating people living with HIV**
Van Sighem A.
*WHO technical consultation on HIV estimation methods in the Russian Federation and neighbouring countries: best approaches and challenges, Moscow, Russia, 25 September 2012.*

**Use of longitudinal case reporting data for estimation HIV prevalence**
Van Sighem A.
*WHO technical consultation on HIV estimation methods in the Russian Federation and neighbouring countries: best approaches and challenges, Moscow, Russia, 25 September 2012.*

**Computational models that predict response to HIV therapy may reduce virological failure and therapy costs in resource-limited settings**
Revell AD, Wang D, Alvarez-Uria G, Streinu-Cercel A, Ene L, Wensing AMJ, Hamers RL, Morrow C, Robin WOOD, Tempelman H, De Wolf F, Nelson M, Montaner JS, Lane HC[12], Larder BA on behalf of the RDI study group.
*11th International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, 11-15 November 2012.*

**CD4 count and viral load specific rates of AIDS, non-AIDS and deaths according to current antiretroviral use**
Mocroft A, Phillips A, Gatell J, Horban A, Ledergerber B, Zilmer K, Jevtovic D, Maltez F, Kirk O, Lundgren J et al for the EuroSIDA study in EuroCoord.
*11th International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, 11-15 November 2012.*

**Increases in acute hepatitis C (HCV) incidence across Europe: which regions and patient groups are affected?**
Rockstroh JK, Grint D, Boesecke C, Soriano V, Lundgren JD, d'Arminio Monforte A, Mitsura VM, Kirk O, Mocroft A and Peters L for EuroSIDA in EuroCoord.
*11th International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, 11-15 November 2012.*

**Immuno-virological discordance (ID) is associated with a higher frequency of fatal and non-fatal AIDS and non-AIDS**
Zoufaly A, Cozzi-Lepri A, Kirk O, Lundgren JD, Reiss P, Jetovic D, Machala L, Zangerle R, Mocroft A, van Lunzen J on behalf of EuroSIDA in EuroCoord.
*11th International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, 11-15 November 2012.*

**Advanced chronic kidney disease, end-stage renal disease and renal death in HIV-positive individuals in Europe**
Ryom L, Kirk O, Lundgren JD, Pedersen C, Reiss P, De Wit S, Buzunova S, Gasiorowski J, Gatell JM and Mocroft A on behalf of EuroSIDA in EuroCoord.
*11th International Congress on Drug Therapy in HIV Infection, Glasgow, Scotland, 11-15 November 2012.*

**Update on the HIV epidemic in the Netherlands**
De Wolf F, van Sighem A, Gras L, Smit C, Holman R, Bezemer D, Kesseling A, Zaheri S.
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**Pre-exposure prophylaxis amongst men who have sex with men in the Netherlands**
Van Sighem A, van den Hengel R, Bezemer D, de Wolf F.
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**Changes in first-line cART regimens and clinical outcome between 1996 and 2010 in the Netherlands**
Smit M, Smit C, Geerlings S, Gras L, Garnett G, Hallett T, de Wolf F.
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**Pre-exposure prophylaxis versus 'test and treat' amongst men who have sex with men in the Netherlands**
Van Sighem A, van den Hengel R, Bezemer D, de Wolf F.
*TasP, Vancouver, BC, Canada, 22-25 April 2013.*

**Association between Age and Long-Term CD4 Cell Count Trajectory in HIV-1 Infected Individuals with Sustained Viral Suppression Depends on CD4 Cell Count at Start cART**
Gras L, Kesselring A, van Lelyveld S, Prins JM, de Wolf F, Reiss P.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Pre-exposure prophylaxis amongst men who have sex with men in the Netherlands**
Van Sighem A, van den Hengel R, Bezemer D, de Wolf F.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**An individual-based stochastic simulation model of the natural history of HIV infection**
Fumiyo Nakagawa on behalf of the Stochastic Simulation of Outcomes of People with HIV in Europe (SSOPHIE) project working group in EuroCoord.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Accurate prediction of response to HIV therapy without a genotype a potential tool for therapy optimisation in resource-limited settings**
Larder BA, Revell AD, Wang D, Hamers R, TempelmanH, Barth R, Wensing AMJ, Morrow C, Wood R, van Sighem A, Reiss P, Nelson M, Emery S, Montaner JM, Lane HC, on behalf of the RDI study group.
*International Workshop on HIV & Hepatitis Drug Resistance and Curative Strategies, Toronto, Canada, 4-8 June 2013.*

**Cascade of HIV care**
Van Sighem A.
*RIVM/CIb Expertmeeting SOA HIV, Bilthoven, 14 June 2013.*

**Virale SOA – Surveillance 2012**
Op de Coul E.
*RIVM/CIb Expertmeeting SOA HIV, Bilthoven, 14 June 2013.*

**HIV delay studie – Tijd tot zorg**
Van Veen M.
*RIVM/CIb Expertmeeting SOA HIV, Bilthoven, 14 June 2013.*

**Use of longitudinal case reporting data for estimation HIV prevalence**
Van Sighem A.
*Meeting of experts on HIV surveillance and strategic information, Cairo, Egypt, 24-26 June 2013.*

**SHM: Monitoring of HIV in the Netherlands**
Van Sighem A, Zaheri S, Reiss P.
*Meeting of experts on HIV surveillance and strategic information, Cairo, Egypt, 24-26 June 2013.*

### Poster Presentations

**Impact of antiretroviral therapy (ART), viraemia and immunosuppression on lipid levels: the D:A:D Study**
Kamara DA, Sabin C, Reiss P, Rickenbach M, Smith C, De Wit S, Law M, Mocroft A, Pradier C, Lundgren JD.
*11th International Congress on Drug Therapy in HIV Infection, Glasgow, United Kingdom, 11-15 November 2012.*

**HIV-1 transmission networks on Curacao, a Caribbean Island**
Bezemer D, Hermanides G, van Sighem A, de Wolf F, Duits A.
*16th International Workshop on HIV Observational Databases, Athens, Greece, 29-31 March 2012.*
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**CD4 cell count changes following acute HCV infection in chronically HIV infected patients**
Gras L, Smit C, Prins M, de Wolf F, Schinkel J, Lambers F, van Hommerig J, van der meer J, Geskus R.
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**Long-term CD4 cell count improvement in HIV-1 infected individuals with long-term sustained viral suppression on combination antiretroviral therapy**
Gras L, Kesselring A, van Lelyveld S, Prins J, Reiss P, de Wolf F.
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**Response to anti-HCV treatment in HIV-infected patients chronically infected with Hepatitis C, the NVHB-SHM Hepatitis working group**
Smit C, van der Meer J, van der Ende M, Arends J, van der Valk M, Brinkman K, Schippers E, de Wolf F, Schutten M, Schinkel J, de Vries-Sluijs T, Hoepelman A, Richter C.
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**Decreased incidence of Pneumocystis jirovecii pneumonia among sub-Saharan African patients in the Dutch ATHENA cohort; genetic susceptibility or environmental factors?**
Schoffelen A, van Lelyveld S, Barth R, Gras L, de Wolf F, Netea M, Hoepelman A.
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**An overview of the Dutch pediatric vertically HIV-infected population in the era of cART**
Cohen S, Smit C, Pajkrt D, for the Dutch Pediatric HIV Study Group (PHON).
*6th Netherlands Conference on HIV Pathogenesis, Prevention and Treatment, Amsterdam, 27 November 2012.*

**Risk of non-AIDS-defining events amongst HIV-infected patients not yet on antiretroviral therapy**
Van Sighem A, Kesselring A, Gras L, Prins J, Hassink E, Kauffmann R, Richter C, Reiss P, de Wolf F.
*CROI 2013, Atlanta, USA, 3-6 March, 2013.*

**Response to anti-HCV treatment in HIV-infected patients chronically infected with Hepatitis C, the NVHB-SHM Hepatitis working group**
Smit C, van der Meer J, van der Ende I, Arends J, van der Valk M, Brinkman K, Schippers E, de Wolf F, Schutten M, Schinkel J, de Vries-Sluijs D, Hoepelman A, Richter C.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**The effect of antiretroviral penetration in the Central Nervous System on the incidence of AIDS-defining neurological conditions in a prospective observational study**
Caniglia E, on behalf of the HIV-CAUSAL Collaboration.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Immune reconstitution inflammatory syndrome: opportunistic infections and AIDS malignancies in patients initiating combination antiretroviral therapy**
Lodi S, on behalf of the HIV-CAUSAL Collaboration.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Differences in high HIV-1 viraemia following acute infection and cumulative burden over 2 years by HIV-1 subtype**
Touloumi G, on behalf of the CASCADE Collaboration in EuroCoord.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**The effect of boosted lopinavir versus boosted atazanavir-containing regimens on immunologic, virologic and clinical outcomes in a prospective observational study**
Cain L, on behalf of HIV-CAUSAL Collaboration.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Association of CD4 count at start of ART with long term mortality among patients who started ART before 2002**
Mirza S, on behalf of the ART Cohort Collaboration (ART-CC).
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Short and long term prognostic value of vitamin D for AIDS, non-AIDS defining events and all-cause mortality**
Shepherd L, on behalf of EuroSIDA for EuroCoord
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Defining self-reported and prescription measures of adherence to ART; multi-cohort analysis**
Ingle S, on behalf of the ART Cohort Collaboration (ART CC).
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**An Evaluation of 10 Elite Controller Definitions over ART Naïve Follow-up within a Large Seroconverter Cohort Collaboration**
Olson A, on behalf of the CASCADE Collaboration in EuroCoord.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Age and CD4 count increase on cART: a look behind the effect of older age on the average CD4 recovery to acquire additional insight on the phenomenon**
Cozzi-Lepri A, on behalf of EuroSIDA in EuroCoord.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Temporal trends in prognostic markers of HIV disease progression and transmission**
Pantazis N, on behalf of CASCADE Collaboration in EuroCoord.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Modelling the course of the HCV epidemic among HIV-positive MSM in the Netherlands**
Prins M, on behalf of the MOSAIC Study Group.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Is response to anti-HCV treatment predictive of mortality in HCV/HIV positive patients?**
Cozzi-Lepri A, on behalf of COHERE in EuroCoord.
*IWHOD, Cavtat, Croatia, 11-13 April 2013.*

**Transmission dynamics of the worldwide HIV-1 subtype B epidemic regarded from a Caribbean island**
Bezemer D, Hermanides G, Rodrigues Faria N, van Sighem A, Fraser C, de Wolf F, Duits A.
*20th International HIV Dynamics & Evolution, Utrecht, 8-11 May 2013.*

**HIV-1 subtype B transmission networks of heterosexually infected patients co-infected with HCV**
Bezemer D, Smit C, van Sighem A, de Wolf F.
*20th International HIV Dynamics & Evolution, Utrecht, 8-11 May 2013.*

**Higher rates of triple class virologic failure in perinatally HIV-infected teenagers compared to heterosexually infected young adults in the PLATO II study**
Gibb DM, on behalf of the PLATO II Project Team of COHERE.
*IAS 2013, Kuala Lumpur, Malaysia, 30 June – 3 July 2013.*

**Late HIV diagnosis, late initiation of combination ART and mortality in Europe: variation by educational level**
Lodi S, COHERE in EuroCoord.
*IAS 2013, Kuala Lumpur, Malaysia, 30 June – 3 July 2013*

# Terminology

**Acute Infection**
Any infection that begins suddenly, with intense or severe symptoms, is called acute (or primary). If the illness lasts more than a couple of weeks, it is called chronic.

**Adherence**
Adherence measures how faithfully a person takes all antiretroviral medications at the right time. Poor adherence is one of the main reasons antiretroviral combinations fail.

**AIDS**
Acquired Immunodeficiency Syndrome. A disease caused by a retrovirus, HIV (human immunodeficiency virus), and characterized by failure of the immune system to protect against infections and certain cancers.

**Antibody**
A substance in the blood formed in response to invading disease agents such as viruses, fungi, bacteria, and parasites. Usually antibodies defend the body against invading disease agents, however, the HIV antibody does not give such protection.

**Antigen**
An invading substance that may be the target of antibodies.

**Antiretroviral treatment (ART)**
A treatment that may prevent HIV from further damaging the immune system by blocking or hampering the reproduction of the HIV virus.

**Antiviral**
A substance that stops or suppresses the reproduction of a virus.

**ATHENA**
AIDS Therapy Evaluation in the Netherlands project (ATHENA). Stichting HIV Monitoring was founded in 2001 as a result of the successful ATHENA project.

**cART**
Combination antiretroviral treatment – a combination of drugs used to keep HIV infections under control.

**CD4 (T4) cell**
CD4+ T-lymphocyte, or T4-cell or T-helper cell. A white blood cell that plays a vital role within the immune system and can be infected by the HIV virus. In the course of the HIV infection the number of CD4 cells may drop from normal levels (more than 500 per $mm^3$) to dangerously low levels (fewer than 200 CD4 cells per $mm^3$ of blood).

**CIb**
Centre for Infectious Disease Control Netherlands, National Institute for Public Health and Environment *(www.rivm.nl/cib)*.

**DNA**
Deoxyribonucleic acid. A complex protein that carries genetic information. HIV can insert itself into the DNA molecules inside human cells and establish dormant infection.

**GGD**
Dutch Public Health Service
(*www.ggd.nl*).

**HAART**
Highly Active Antiretroviral Therapy, also known as combination antiretroviral therapy (cART).

**Hepatitis B virus (HBV)**
A viral infection that affects the liver and is transmitted only through blood-to-blood and sexual contact.

**Hepatitis C virus (HCV)**
A viral infection that is transmitted primarily by blood and blood products, as in blood transfusions or intravenous drug use, and sometimes through sexual contact.

**HIV**
Human Immunodeficiency Virus; the virus that causes the Acquired Immunodeficiency Syndrome (AIDS). HIV attacks and destroys the immune system by entering and destroying the cells that control and support the immune response system.

**HIV Type 1 (HIV-1)**
The HIV type responsible for the majority of HIV infections worldwide.

**HIV Type 2 (HIV-2)**
A virus very similar to HIV-1 that has been found to cause immune suppression. HIV-2 infections are found primarily in West Africa.

**MSM**
Men who have sex with men.

**Person-year**
A measure of time used in medical studies. A single person-year is 1 year lived by 1 person.

**Retrovirus**
A class of viruses which includes HIV. Retroviruses are so named because they carry their genetic information in RNA rather than DNA, and the RNA information must be translated "backwards" into DNA.

**Reverse Transcriptase**
After infecting a cell, HIV uses an enzyme called reverse transcriptase to convert its RNA into DNA and then replicates itself using the cell's machinery.

**RIVM**
Dutch National Institute for Public Health and the Environment *(www.rivm.nl)*.

**Seroconversion**
The change from an absence of HIV antibodies in the blood to the presence of those antibodies.

**Seroprevalence**
The incidence of disease in a given population based on blood serum specimens.

**SHM**
Stichting HIV Monitoring (the Dutch HIV monitoring foundation, *www.hiv-monitoring.nl*).

**Viral load**
The number of HIV particles in a millilitre of blood or another body fluid, such as semen or cerebrospinal fluid.

**VWS**
Dutch Ministry of Health, Welfare and Sport (*www.rijksoverheid.nl*).


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