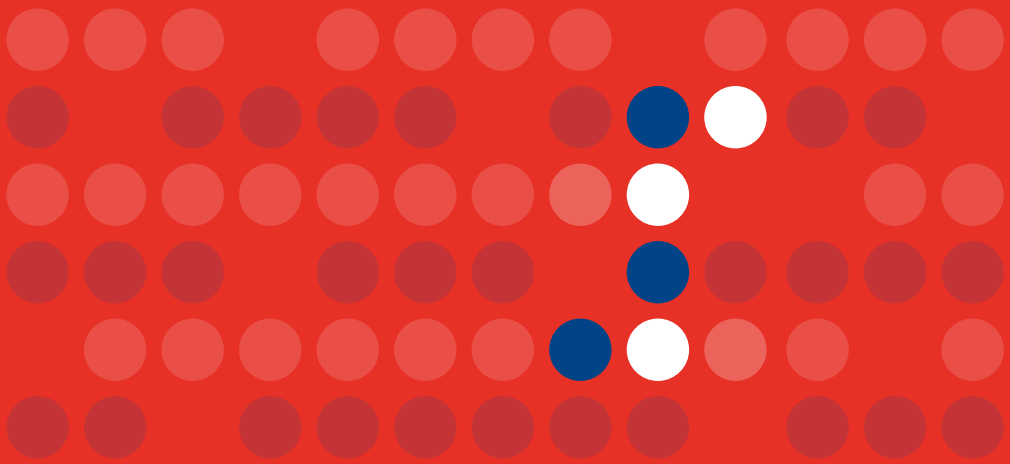
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2015



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 organisation for the registration and monitoring of HIV-infected patients in follow-up in Dutch HIV Treatment Centres.

Our mission

Stichting HIV Monitoring's mission is to monitor trends regarding all aspects of HIV infection, including comorbidities and co-infections, in the population of HIV-positive persons in care in the Netherlands. By collecting and analysing high-quality, nationwide data, SHM aims to inform all relevant stakeholders, including healthcare providers, government, researchers, and the community of people living with HIV about national and centre-specific trends, thereby continuing to make an important contribution to the national HIV quality of care standards and formal certification of HIV treatment centres in the Netherlands.

www.hiv-monitoring.nl

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HIV Monitoring

Monitoring Report 2015

Monitoring of Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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Reference numbers

Scroll over the reference numbers in the text to see the reference details.

Guide to buttons

Preceding page  Content page  Next page 

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by clicking the chapter buttons on the right side of the pages

The monitoring of HIV-infected adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 27 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 recognised as paediatric HIV treatment centres.

In 2015, the following health institutes were involved as centres for adult HIV care (in alphabetical order of town). By clicking on the names below or on the numbers and letters on the map you can visit the hospital websites:

1	Medisch Centrum Alkmaar (MCA)	Alkmaar
2	Flevoziekenhuis	Almere
3	Academic Medical Center of the University of Amsterdam (AMC-UvA)	Amsterdam
4	HIV Focus Centrum (DC Klinieken)	Amsterdam
5	Onze Lieve Vrouwe Gasthuis (OLVG)	Amsterdam
6	Sint Lucas Andreas Ziekenhuis	Amsterdam
7	MC Slotervaart	Amsterdam
8	Medisch Centrum Jan van Goyen (MC Jan van Goyen)	Amsterdam
9	VU medisch centrum (VUmc)	Amsterdam
10	Rijnstate	Arnhem
11	HagaZiekenhuis (Leyweg site)	Den Haag
12	Medisch Centrum Haaglanden (MCH, Westeinde site)	Den Haag
13	Catharina Ziekenhuis	Eindhoven
14	Medisch Spectrum Twente (MST)	Enschede
15	Admiraal De Ruyter Ziekenhuis	Goes
16	Universitair Medisch Centrum Groningen (UMCG)	Groningen
17	Spaarne Gasthuis	Haarlem
18	Medisch Centrum Leeuwarden (MCL)	Leeuwarden
19	Leids Universitair Medisch Centrum (LUMC)	Leiden
20	MC Zuiderzee	Lelystad
21	Maastricht UMC+ (MUMC+)	Maastricht
22	Radboudumc	Nijmegen
23	Erasmus MC	Rotterdam
24	Maasstad Ziekenhuis	Rotterdam
25	St Elisabeth Ziekenhuis	Tilburg
26	Universitair Medisch Centrum Utrecht (UMC Utrecht)	Utrecht
27	Isala (Sophia site)	Zwolle

Centres for the treatment and monitoring of paediatric HIV were:

A	Emma Kinderziekenhuis (EKZ), AMC-UvA	Amsterdam
B	Beatrix Kinderziekenhuis (BKZ), UMCG	Groningen
C	Erasmus MC-Sophia	Rotterdam
D	Wilhelmina Kinderziekenhuis (WKZ), UMC Utrecht	Utrecht


16
B
18
1
27
20
17
3
4
2
A
5
6
14
11
19
7
8
12
9
26
D
10
C
23
24
22
25
15
13
21

Table of contents

Introduction

The Monitoring Report 2015 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 14th in the series published by Stichting HIV Monitoring (SHM) since SHM was founded in 2001. The report 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 27 officially acknowledged HIV treatment centres throughout the country, SHM contributes significantly to the knowledge of HIV. SHM also makes 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. As such, SHM importantly facilitates the assessment of the quality of care provided by the treatment centres. This has become a key component of these centres' formal certification according to the process developed jointly between the Harmonisation of Quality in the Healthcare Sector (*Harmonisatie Kwaliteitsbeoordeling in de Zorgsector,* HKZ,) and the Dutch Association of HIV-treating Physicians (NVHB). Data from SHM can be used by individual treatment centres in collating and making available the key information required to support certification, whilst at the same time providing a nationwide benchmark. Moreover, once research proposals have been approved through appropriate procedures, treating physicians, as well as national and international researchers, can access aggregated data from all centres for scientific research purposes. 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.

After the Summary and Recommendations, the Monitoring Report includes a section on the HIV Monitoring Programme that provides an update 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. A new addition this year is a chapter on quality of care in the 27 HIV treatment centres in the Netherlands, by examining a number of quality of care indicators.

As in previous years, the Special Reports section includes a chapter on the results from the Amsterdam Cohort Studies and one on HIV in Curaçao.

In keeping with SHM's policy of reducing paper consumption, we will no longer be publishing the Monitoring Report 2015 as a printed book. Instead, it will be made available online, in a fully searchable and downloadable PDF. In addition, all figures and tables included

in the report will be made available in the form of a downloadable powerpoint presentation. The report and accompanying figures can be found on our website, www.hiv-monitoring.nl.

This year, we once again invited a small group of HIV treating physicians and experts in public health with an in-depth knowledge on relevant chapter topics to help shape content and act as reviewers. We are very grateful for their valuable input, which has further improved the report's clinical and public-health relevance. I thank them for their time and hope to continue this fruitful collaboration in the years ahead.

Finally, I would like to thank the HIV treating physicians, HIV nurse consultants and staff 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, we continue to not only improve the 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

As of May 2015, a total of 18,355 persons living with HIV in the Netherlands (18,149 adults, and 206 children and adolescents) were known to be retained in care in one of the 27 designated HIV treatment centres. Of these 18,355, 93% (17,071) had started combination antiretroviral therapy (cART), and of these 17,071, 92% (15,789) 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.

In 2014, the majority (69%) of newly diagnosed infections in adults were in men who have sex with men (MSM), 25% were acquired through heterosexual contact and around 7% through other or unknown modes of transmission. Of note, almost one quarter of all newly-diagnosed patients in 2014 were 50 years or older. Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to approximately 1,000 new diagnoses in recent years. Although this decreasing trend continued in 2014, the projected number of diagnoses may have been underestimated as registration of HIV diagnoses for this year has not yet been finalised. Nonetheless, this decreasing trend appears to be reflected in the MSM population aged 25-44 years, but remains less marked in MSM both 25 years and younger and 45 years and older, as well as in heterosexuals 45 years and older. Finally, overall, over 90 percent of persons newly diagnosed with HIV entered into specialised care within 6 weeks after diagnosis. There is little variation in these figures, regardless of where individuals were diagnosed.

The rates of testing for HIV appear to be increasing in certain settings. Interestingly, the proportion of patients with a previously negative HIV test has also increased (73% MSM and 40% heterosexuals had a known previous negative test in 2014). Moreover, fortunately, the proportion of patients who are identified and start cART earlier in their infection (including during primary HIV infection) continues to increase, particularly amongst MSM. This is reflected in the CD4 count, both at diagnosis and at start of cART, gradually having risen over time to a median of 385 and 410 cells/mm^3, respectively, in 2014.

The likelihood of patients starting cART at higher CD4 counts has also clearly increased. While in 2013, 49% of patients with a CD4 count of 500 cells/mm^3 had begun cART within 6 months of diagnosis, this proportion rose to 68% in 2014. Nonetheless, far too many patients continue to present late for care. In 2014, 44% of newly diagnosed patients presented late for care, i.e., with AIDS or a CD4 count less than 350 cells/mm^3, and 27% presented with advanced HIV disease, i.e., 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, individuals originating from South and South-East Asia and Sub-Saharan Africa, and individuals aged 45 years or older.

Continuum of HIV care in 2014

An important change compared to last year's Monitoring Report is that estimates of the number of people living with HIV, as well as of the number who are not yet diagnosed, are considerably lower than previously reported. The method recently developed by the European Centre for Disease Prevention and Control (ECDC) to estimate the total number of HIV-positive individuals, including those not yet diagnosed, revealed that 22,100 individuals were estimated to be living with HIV in the Netherlands by the end of 2014, of whom 2,700 were still undiagnosed. On the basis of this new estimated number of 22,100 people living with HIV, a continuum of HIV care has been constructed to depict engagement in HIV care in 2014 across a few key indicators, the last one being the number of individuals with suppressed viral load. By the end of 2014, 19,382 patients, or 88% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM. In total, 17,905 patients were considered to still be in care. The majority of these patients, 16,821 in total, had started cART, and 15,463 had a most recent HIV RNA measurement below 100 copies/ml, irrespective of treatment. Overall, 70% of the total estimated population living with HIV and 80% of those diagnosed and ever linked to care had a suppressed viral load.

This new estimate brings the Netherlands far closer to also reaching the first of the UNAIDS 90-90-90 targets than the less robust UNAIDS estimate used in previous years for constructing the continuum of care. ECDC is currently training public health surveillance staff from European countries in using the newly available methodology so that they can adopt and apply it when constructing their own HIV continuum of care. ECDC is also working together with UNAIDS on how this methodology could also be used for further improving estimates of the global burden of HIV.

Improved transdisciplinary strategies that target all factors sustaining the epidemic continue to be needed to achieve a significant decline in the rate of new infections. The aim of these strategies should be to simultaneously reduce the likelihood of HIV infection in key populations at risk, identify infected individuals early, rapidly link all infected persons to care, and immediately offer them the option of starting combination antiretroviral therapy.

Combination antiretroviral therapy in adults and quality of treatment and care

Guidelines for the choice of first-line cART are closely adhered to in the Netherlands. Most patients who first initiated cART in 2014 did so with a once-daily regimen, including tenofovir/emtricitabine as the backbone. Of note a clear shift can be observed towards including integrase strand transfer inhibitors (INSTI) as part of initial regimens. Over one-third of patients first initiating treatment in 2014 did so with the fixed-dose single-tablet regimen of tenofovir plus emtricitabine plus cobicistat-boosted elvitegravir (Stribild®). A similar trend may be expected to become visible in the use of the fixed-dose single-tablet regimen of abacavir plus lamivudine plus dolutegravir (Triumeq®).

Virological response to first-line cART continues to improve: over 95% of individuals who first initiated cART with one of the regimens recommended in 2014 achieved viral suppression to below the level of HIV-RNA quantification within 9 months. However, individuals <30 years of age, individuals infected through heterosexual transmission (compared with homosexual transmission), and individuals born in Sub-Saharan Africa compared with those born in the Netherlands were somewhat less likely to achieve this goal. Importantly, in contrast to what was seen in earlier periods, patients initiating treatment at CD4 counts >500 cells/mm^3 were no longer less likely to achieve initial suppression, which is an important observation in view of current guidelines recommending cART for all, regardless of CD4 count. Of the patients who first initiated cART from 1999 onwards and were continuously on treatment and still in follow up at 14 years, 99.6% had suppressed viraemia to less than 100 copies/ml.

Overall, 7.2% of the treatment-naive 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 according to this definition has declined over time to as little as 3%. Nonetheless, as expected, when virological failure does occur, it remains associated with a substantial risk of drug resistance.

Genotypic sequence data are only available to Stichting HIV Monitoring (SHM) from a suboptimal proportion of patients, both at the time of virological failure as well as at the time of HIV diagnosis prior to first initiating cART. With the introduction of new drug classes in recent years, including integrase and entry inhibitors, the collection of data on sequences needs to be extended to other parts of the viral genome. Increasingly, genotypic sequences of the relevant genes are being obtained during routine clinical care, but insufficient sequences are currently available in the SHM database to give a clear picture of resistance to these new drug classes. The collection of sequencing data needs to be improved to permit more complete monitoring of resistance. The first steps to achieve this have already been taken, and further progress is expected in the near future.

The proportion of patients achieving 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 2014, 12% of patients in care had a last available CD4 measurement below 350 cells/mm^3. The likelihood of achieving normalisation of CD4 counts and CD4/CD8 ratios is clearly dependent on the timely start of cART, and is much greater when treatment is started at a CD4 count greater than 500 cells/mm^3. Together with the results from the START trial, published earlier this year, this supports the need for early diagnosis and treatment of HIV infection.

Although tolerability of cART has continued to improve with time and larger numbers 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. The risk of a toxicity-driven therapy change in those starting cART in or after 2009 was higher in females, when cART was started at CD4 cell counts ≥500 cells/mm^3, and, when cART was started during primary infection, independent of CD4 cell count. When interpreting these findings it is, however, important to realise that, as the result of the increased availability of better tolerated and convenient fixed-dose combination regimens, in recent years there has been more proactive switching of regimens to reduce toxicity and intolerance.

As larger numbers of clinically asymptomatic, newly-identified patients with HIV are expected to start treatment earlier, continued development of even better-tolerated, convenient regimens, as well as improvements in individualised patient management remain necessary to improve the durability of initial treatment even further.

Quality of care

Generally speaking, a number of different quality of care indicators showed limited variability across the 27 adult HIV treatment centres. Retention in care and viral suppression rates in the first 6 months on cART, as well as during long-term use of cART, were high across all centres. Across most of the centres, an increasing proportion of patients is starting cART sooner after entering care, a trend we anticipate shall continue in light of the results of the START trial that now definitively supports the current guideline of offering cART to anyone with newly diagnosed HIV, regardless of their CD4 count. More substantial variation was observed regarding repeated screening in groups at risk for HCV. However, this may, to some extent, be explained by centres/physicians applying a policy of targeted screening guided by the presence of incident transaminase elevations. Continued, further monitoring of these trends seems warranted.

Morbidity and mortality

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, cardiovascular disease and chronic liver disease, comprise a sizable fraction of those other causes. Nonetheless, the proportion of patients dying of AIDS (nearly 27%) remained substantial between 2007 and 2014. Once more, this was largely driven by late presentation and late entry into care, and stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

Not surprisingly, older age was an important risk factor for co-morbidities that are traditionally associated with ageing, notably cardiovascular disease and non-AIDS malignancies. In this context, it is important to note that the proportion of older individuals with newly diagnosed HIV entering care in the Netherlands is substantial; in 2014, 24%

were 50 years or older. At the same time, the overall patient population with HIV in care in the Netherlands continues to age, with 42% currently older than 50 years. Of particular concern is the increasing proportion of patients with multiple co-morbidities, the risk of which appears to be increased in those with HIV, as demonstrated amongst others by data from the AGE$_h$iV 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.

Despite the increasing age of the HIV-infected population, the proportion at high or very high cardiovascular risk only increased slightly over the period 2000-2014. This suggests that cardiovascular risk management may have improved over time. Significant room for further improvement remains, however, given the suboptimal use of statin therapy, antihypertensive therapy and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit improving, uptake of these medications in the prevention of primary cardiovascular disease.

The crude incidence of non-AIDS malignancies in the Netherlands has remained stable over time, but the the absolute number and proportion of deaths due to these malignancies has increased. In men we observed a decline in age-standardised incidence of non-AIDS malignancies, including anal cancer, possibly as a result of a reduction in risk factors such as smoking and a higher proportion of individuals living with higher CD4 cell counts in more recent years. The most common non-AIDS malignancies continue to be lung, anal, head and neck cancers as well as Hodgkin's lymphoma, although the proportion of patients diagnosed with other non-AIDS malignancies increased with increasing age. Collaborative analyses conducted on much larger datasets as part of the D:A:D study showed a signal of protease inhibitor-based cART regimens possibly being associated with an increased risk of non-AIDS malignancies, and invasive anal cancer in particular. No such association was found for non-nucleoside reverse transcriptase inhibitor-based regimens.

Awareness of the role of modifiable, often lifestyle-related risk factors, such as smoking, and their management by both physicians and HIV-infected individuals, 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 ageing. 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. At the same time there is clear room for improvement in the use of known effective biomedical interventions for primary and secondary prevention according to general guidelines.

Hepatitis B and C co-infections

Screening for hepatitis B (HBV) and C (HCV) co-infection has, with time, increasingly become part of the standard of HIV care in the Netherlands. As a result, the presence or absence of HBV or HCV infection is now documented for virtually all HIV-infected patients in care in

the Netherlands. Approximately 12% of patients had evidence of ever having been exposed to HCV, 6% were documented as having chronic infection and 1.6% had acute infection. Seven percent of patients were shown to have chronic HBV infection.

An estimated 27% of HIV-infected patients overall and 21% of MSM either had not been exposed to HBV or had not been successfully vaccinated and may remain at risk of acquiring HBV. Although this does represent a reduction compared to our previous report, these findings illustrate the importance of continuing efforts to increase successful HBV vaccination rates amongst this subgroup of patients.

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. Importantly, the incidence of acute HCV infection observed in 2014 amongst MSM remains high at a rate of 3.7 diagnoses per 1,000 person years (4.2 per 1,000 person years in 2013). This clearly indicates the need for continued preventive efforts in these men, including the use of the novel, highly effective, short-course, well-tolerated and interferon-free combination therapies for HCV, which, by virtue of their high effectiveness, may not only benefit the individual patient but also markedly reduce the risk of onward transmission.

Our data clearly show that, with the advent of novel direct-acting antiviral agents (DAAs) in 2014 and 2015, peglyated interferon (PEG-IFN)-containing regimens are rapidly being replaced in clinical practice by a variety of all-oral DAA-based regimens and more patients with HCV co-infection are being treated. Based on data available up to 15 September 2015, more than 100 patients have received or are currently receiving treatment with regimens including one or more of the currently available novel DAAs sofosbuvir, simeprevir and daclatasvir. With the exception of one patient, all patients who completed their treatment with these new DAAs had a negative HCV RNA test result at the end of treatment, and 95% of all patients with sufficient follow-up data to calculate an SVR were found to have been cured. These results are markedly better than what was thus far feasible with previous PEG-IFN alpha-containing regimens. Very importantly, these developments have already resulted in a lower total number of HCV-co-infected patients who remain in need of effective treatment compared to last year's report (876 patients in 2014 vs. 907 in 2013), in spite of an increase in the total number of patients with HCV co-infection currently retained in care (1260 in 2014 vs. 1187 in 2013).

Overall, patients with HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. For patients with chronic HBV diagnosed after 2000, liver-related deaths have been significantly reduced, likely as a result of increasingly effective treatment for HBV through the use of tenofovir-containing cART.

The rapidly expanding availability of novel interferon-free regimens for HCV, together with optimised screening for HCV co-infection, with time will hopefully similarly limit the impact of HCV co-infection on long-term liver-related morbidity and mortality. In addition, when combined with additional preventive measures, it may be expected to contribute to reducing the rate of incident HCV infection among the key affected population of MSM.

HIV in pregnant women and in children

Universal first trimester screening for HIV in pregnant women and the increasingly effective use of cART during pregnancy has made perinatal transmission of HIV extremely rare in the Netherlands, although cases of incident HIV infection following a negative first trimester screen have been documented later during pregnancy.

Together with the observation that approximately 10% of HIV-infected pregnant women do not have fully suppressed viraemia around the time of delivery, this indicates the need for continued vigilance to ensure zero vertical transmissions of HIV.

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 vertically-infected children who started treatment below two years of age. More and more of these children, however, are transitioning into adult care. Almost 30% of the children who have transitioned into adult care and are retained in care currently do not have fully suppressed viraemia.

This illustrates that optimisation of long-term care for this particularly vulnerable and difficult-to-manage group of young individuals is sorely needed.

The Amsterdam Cohort Studies

The Amsterdam Cohort Studies on HIV infection and AIDS (ACS) are unique prospective longitudinal cohort studies initiated in 1984-1985 and focused on MSM and injecting drug users (IDU) with HIV or at risk for HIV infection. As of 31 December 2014, 2,649 MSM and 1,680 IDU had been enrolled. The ACS continues to provide important insights into both viral and host, including behavioural, 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. Moreover, the ACS continues to provide highly reliable information on HIV and HCV incidence over time in the key affected populations. Among MSM, incident HCV infections are observed only among those who are infected with HIV; with respect to incident HIV infections, following a rise in infections after 1999, numbers have levelled off to around 1 case per 100 person years in 2014. Data on risk behaviour collected within the framework of the ACS continue to demonstrate that HIV-uninfected participants in the cohort report high rates of unprotected anal intercourse, primarily with steady, but also with casual partners.

Together with the AMC Department of Infectious Diseases, Department of Global Health, the Amsterdam Institute of Global Health and Development, and SHM, the GGD Amsterdam (in part through the ACS), also importantly contributes to the ongoing follow-up of HIV-uninfected participants of the AGE$_h$iV Cohort Study. This study, started in 2010, continues to provide very detailed information regarding the incidence of a broad range of ageing-associated co-morbidities, as well as regarding risk factors and biomarkers associated with these conditions. It thereby provides important information to complement SHM's more general nationwide collection of data on clinical non-AIDS outcomes.

In collaboration with the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment, the GGD Amsterdam, the Jan van Goyen Medical Centre, the VU University Medical Center, and the AMC, the ACS also collaborates in the H2M (HIV and HPV in MSM) study, which aims to compare the prevalence, incidence, and clearance of high-risk (hr) human papillomavirus (HPV) infections between HIV-negative and HIV-infected MSM. Results thus far demonstrate that hrHPV infections are more common in HIV-infected than in HIV-uninfected men. This was true for both penile and anal infections. CD4 count (current or nadir) was found to have no effect on incidence or clearance.

Recent ACS research published in 2014 includes the characterisation of envelope glycoproteins and broadly neutralising antibodies from two individuals in the ACS who produced broadly neutralising antibodies in their first year after seroconversion (elite neutralisers). Other highlights of research in 2014 using ACS data included a study that found that naturally-occurring HPV antibodies failed to confer protection against subsequent type-specific anal and penile HPV infection within one year in highly sexually-active adult MSM.

HIV on Curaçao

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 Curaçao. In recent years, HIV-positive patients in Curaçao appear to be diagnosed increasingly earlier in their infection, as shown by a declining proportion of patients presenting late for care. As a consequence, cART is being started at increasingly higher CD4 cell counts. The quality of monitoring and treatment offered to HIV-positive patients has also improved considerably. However, adherence to treatment and retention in care do remain suboptimal.

Monitoring programme report

1. The HIV epidemic in the Netherlands

Ard van Sighem and Eline op de Coul

Introduction

As of May 2015, 24,263 HIV-infected patients had ever been registered by Stichting HIV Monitoring (SHM). Of those, 23,303 were followed in one of the HIV treatment centres in the Netherlands (*Figure 1.1*) and, all together, had a total follow-up time since diagnosis of 221,028 person years. The remaining 960 patients were registered in the St. Elisabeth Hospital in Willemstad, Curaçao (see *Chapter 10*). Of the 23,303 patients, the majority were infected with HIV-1 (22,963; 99%). A small group of patients, 97 in total, were infected with HIV-2, while 59 patients had antibodies against both HIV-1 and HIV-2. Serological results were not yet available in the SHM database for 184 recently registered patients.

This chapter will first focus on the HIV-infected patients who were still in care as of May 2015. The second part will discuss characteristics of HIV-1-infected patients at the time of diagnosis or at the time of entering HIV care. Finally, a brief overview will be given of the small group of patients infected with HIV-2.

Population – in care

Patients in clinical care

In total, 18,355 (79%) of the 23,303 registered patients, comprising 18,149 adults and 206 minors less than 18 years of age, were still under clinical observation (*Figure 1.1; Table 1.1; Appendix Table 1.1*) as of May 2015. This number of 18,355 patients is remarkably close to the 18,275 patients who were expected to be in care in 2015, according to a projection in our 2007 Monitoring Report[1]. Of the 4,948 patients who were no longer in clinical care, 2,396 (48%) were known to have died, and 1,134 (23%) to have moved abroad. Patients were considered to be in clinical care if data were available in 2014 or 2015 and they were known to be alive. This definition reflects present-day clinical practice in which some patients who respond well to treatment and have no complications from treatment are seen only once a year by their treating physician.

Figure 1.1: Overview of the HIV-infected population registered by Stichting HIV Monitoring (SHM) as of May 2015.

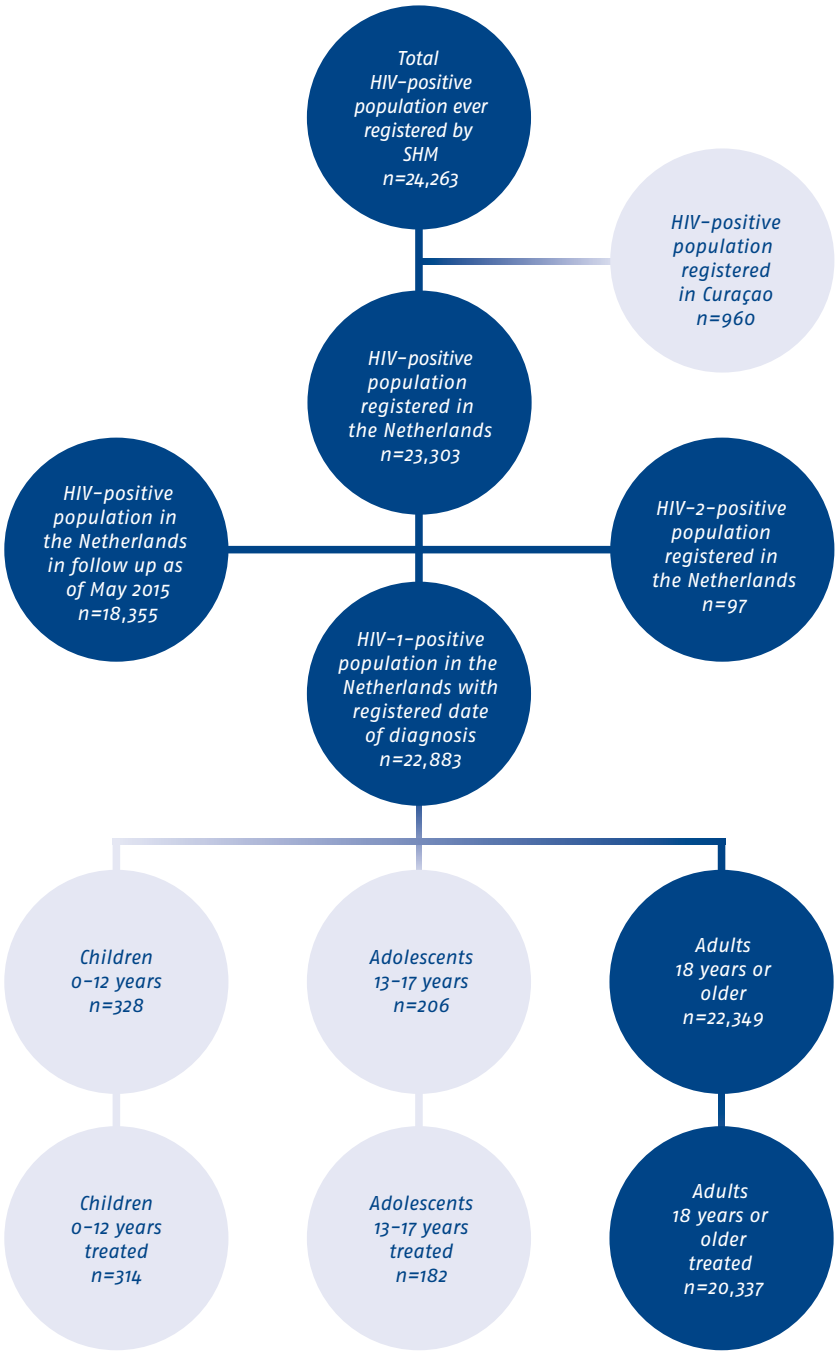


Table 1.1: Characteristics of the 18,355 HIV-positive patients in clinical care as of May 2015. An extended version of this table is presented in Appendix Table 1.1.

	Men (n=14,824, 81%)		Women (n=3,531, 19%)		Total (n=18,355)	
	n	%	n	%	n	%
Transmission						
MSM	11,204	76	-	-	11,204	61
Heterosexual	2,344	16	3,070	87	5,414	29
IDU	243	2	96	3	339	2
Blood (products)	150	1	91	3	241	1
Other/unknown	883	6	274	8	1,157	6
Current age (years)						
0-12	60	0	67	2	127	1
13-17	43	0	36	1	79	0
18-24	263	2	93	3	356	2
25-34	1,750	12	601	17	2,351	13
35-44	3,388	23	1,157	33	4,545	25
45-54	5,243	35	995	28	6,238	34
55-64	2,900	20	418	12	3,318	18
65-74	1,025	7	131	4	1,156	6
≥75	152	1	33	1	185	1
Region of origin						
The Netherlands	9,943	67	1,045	30	10,988	60
Sub-Saharan Africa	1,079	7	1,478	42	2,557	14
Western Europe	859	6	131	4	990	5
South America	966	7	323	9	1,289	7
Caribbean	566	4	172	5	738	4
Other	1,357	9	376	11	1,733	9
Unknown	54	0	6	0	60	0
Years aware of HIV infection						
<1	578	4	90	3	668	4
1-2	1,608	11	255	7	1,863	10
3-4	1,784	12	310	9	2,094	11
5-10	4,270	29	922	26	5,192	28
10-20	4,601	31	1,494	42	6,095	33
>20	1,863	13	418	12	2,281	12
Unknown	120	1	42	1	162	1

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

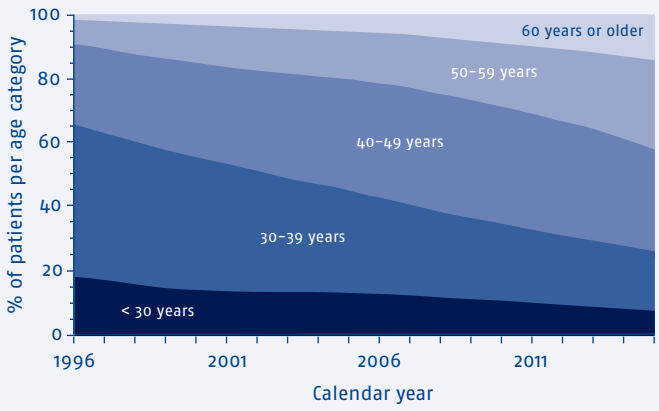
Retention in care

Of the 13,659 patients who enrolled in HIV care during the past 10 years, 683 (5%) were lost to care before 2014 and were not reported as having died or moved abroad. Retention in care was highest for patients of Dutch origin; 96% of those patients were estimated to still be in care after 10 years. Of the patients of Sub-Saharan African origin, 70% of men and 77% of women were still in care after 10 years, as were 88% of men and 87% of women originating from other regions. Retention in care improved with increasing age at the time of entry into care: for every additional five years of age at the time of entry, patients were 8% less likely to be lost to care.

Ageing population

The median age of the population in clinical care currently stands at 48 (interquartile range [IQR], 39-55) 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, 42% of patients currently in care (more than two out of five) are 50 years or older, including 45% of men and 29% of women; 14% of the patients are 60 years or older *(Appendix Table 1.1)*. As the HIV-infected population continues to age, it is to be expected that the number of patients with age-related co-morbidities will increase in coming years, thereby complicating the management of their HIV infection (see *Chapter 4*).

Figure 1.2: *Increasing age of the HIV-positive population in clinical care over calendar time. In 1996, 19% of the patients in care were younger than 30 years of age, whereas 9% were 50 years or older. In 2015, these proportions were 7% and 42%, respectively, while 14% of patients in care were 60 years of age or older. The proportion of patients in clinical care as of 1 May of each calendar year is shown according to those who were <30 years of age, 30 to 39 years, 40 to 49 years, 50 to 59 years, and 60 years or older.*



Duration of infection

On average, patients in clinical care as of May 2015 were diagnosed with HIV 10.7 years ago. Thus, a large group (46%) of those in care had been living with HIV for more than 10 years, while 12% had done so for more than 20 years. The average time since diagnosis was 10.2 years for men who have sex with men (MSM), 10.1 years for heterosexual men, and 11.3 years for heterosexual women. The majority of injecting drug users (87%) received their HIV diagnosis more than 10 years ago, which reflects the greatly decreasing number of new infections occurring via this mode of transmission.

Treatment combinations

In total, 93% of the patients in care were being treated with cART, compared with 91% in last year's report[2]. The most frequently prescribed regimens in current use, which accounted for 63% of all treatment combinations, were a combination of tenofovir/emtricitabine and either efavirenz (21%), nevirapine (14%), ritonavir-boosted darunavir (10%), rilpivirine (10%), or ritonavir-boosted atazanavir (7%). A backbone of tenofovir/emtricitabine was used by 74% of the patients, while abacavir/lamivudine was used by 13% and zidovudine/lamivudine by 4%. Additional drugs in the regimen included efavirenz (used by 25% of the patients), nevirapine (21%), atazanavir (11%), darunavir (17%), rilpivirine (10%), and raltegravir (8%). The majority of the patients (83%) used a once-daily regimen. Antiretroviral treatment is discussed in more detail in *Chapter 2*.

Clinical condition

The median current CD4 count was relatively high at 617 (IQR, 455-800) 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 MSM and women, but men infected via other modes of transmission had lower CD4 counts than their female counterparts (*Appendix Table 1.1*). For all patients in care, the most recent viral load measurement was below 500 copies/ml for 88% and below 100 copies/ml for 86%. About one-fifth (22%) of the patients had ever been diagnosed with an AIDS-defining disease; 57% of these patients were diagnosed with AIDS concurrently with their HIV diagnosis.

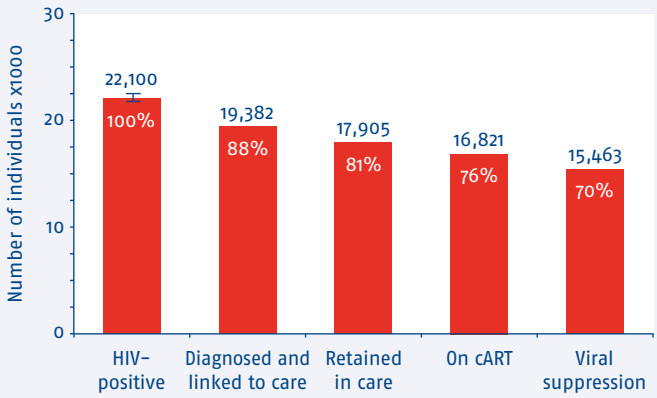
Continuum of HIV care

According to a recently developed method to estimate the total number of HIV-positive individuals, including those not yet diagnosed, 22,100 (95% confidence interval (CI) 21,700-22,800) individuals were estimated to be living with HIV in the Netherlands by the end of 2014, of whom 2,700 (2,300-3,400) were still undiagnosed[3]. This estimate is considerably lower, albeit within the reported uncertainty bounds, than a provisional estimate of 26,000 (19,000-37,000) individuals living with HIV by the Joint United Nations Programme on HIV/AIDS (UNAIDS). Our new method estimated a total of 21,300 (21,100-21,600) individuals with HIV in 2012, including 3,350 (3,100-3,650) still undiagnosed, which is lower than an independent estimate of 24,350 (95% credible interval 20,420-31,280) obtained with a different method that was based mainly on

prevalence surveys and HIV diagnoses at sexually transmitted infections (STI) clinics and registered cases in HIV care[4].

On the basis of this new estimated number of 22,100 people living with HIV, a continuum of HIV care has been constructed to depict engagement in HIV care in 2014 across a few key indicators, the last one being the number of individuals with suppressed viral load (*Figure 1.3;* continuum of HIV care for 2013 by the new method in *Appendix Figure 1.1*). By the end of 2014, 19,382 patients, or 88% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM. In total, 17,905 patients were considered to be retained in care (i.e., they had at least one HIV RNA or CD4 count measurement or a clinic visit in 2014). The majority of these patients (16,821 in total) had started cART, and 15,463 had a most recent HIV RNA measurement below 100 copies/ml, irrespective of treatment. Overall, 70% of the total estimated population living with HIV and 80% of those diagnosed and ever linked to care had a suppressed viral load. Note that using the UNAIDS estimate of 26,000 individuals, only 59% of the total estimated population living with HIV would have a suppressed viral load.

Figure 1.3: *Continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2014. According to a recently developed method, 22,100 people were living with HIV in the Netherlands. In total, 19,382 of these individuals were diagnosed, linked to care, and registered by SHM. Of these patients, 17,905 were still in care in 2014; 16,821 had started combination antiretroviral treatment (cART), and 15,463 patients had a most recent RNA measurement below 100 copies/ml. Percentages are calculated relative to the 22,100 people living with HIV.*



Legend: *cART=combination antiretroviral treatment.*

Population – diagnosis

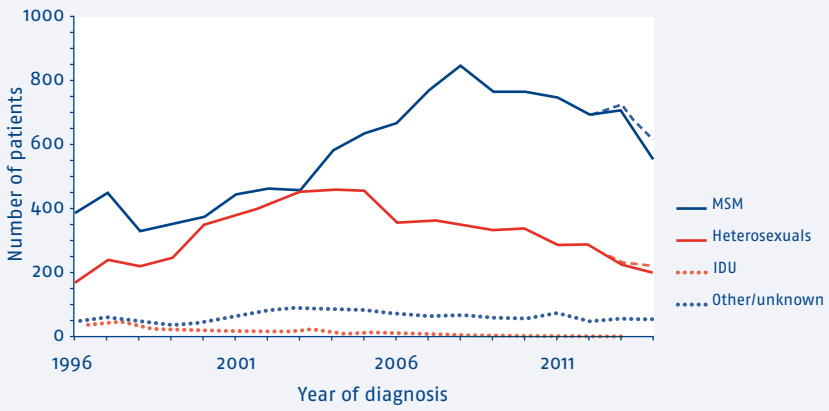
HIV-1-positive individuals

Having briefly discussed the HIV-positive population currently in clinical care, we will now focus on the 22,349 patients who were ever diagnosed with HIV-1 as adults with a recorded date of diagnosis (*Figure 1.1*). The majority of these patients were MSM (13,289 [59%]); the rest were infected mainly via heterosexual contact (3,084 men [14%] and 3,738 [17%] women) (*Appendix Table 1.2*). For 745 (3%) of the patients, the reported mode of transmission was injecting drug use, while 270 patients (1%) were infected by exposure to contaminated blood or blood products. Other and unknown modes of transmission accounted for the remaining 5% (1,223) of infections.

Decreasing number of diagnoses

From the 1990s, the annual number of new diagnoses among MSM steadily increased from approximately 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, thus marking an end to the trend of an increasing number of diagnoses. In fact, the increase may have slowed down as early as 2006, since the number of new diagnoses in 2007 and 2008 may have exceeded the long-term trend due to the introduction of opt-out testing for HIV at STI clinics across the country at about that time[5]. In 2014, the decreasing trend has continued, and the projected number of new HIV diagnoses in MSM, taking into account a backlog in registration of HIV cases, was between 600 and 650. A similar decrease in HIV diagnoses was observed in STI clinics, which reported 12% fewer diagnoses in MSM than in 2013[6].

Figure 1.4: Annual number of new HIV-1 diagnoses among adults, according to most likely mode of transmission. In 2014, men who have sex with men (MSM) accounted for 69% of new diagnoses, infections via heterosexual contact for 25%, infections via injecting drug use (IDU) for 0%, and infections via other or unknown modes of transmission for 7% of the annual tally. The dotted lines indicate the projected number of diagnoses when the backlog in registration of HIV cases (3% in 2013, 11% in 2014) is taken into account.



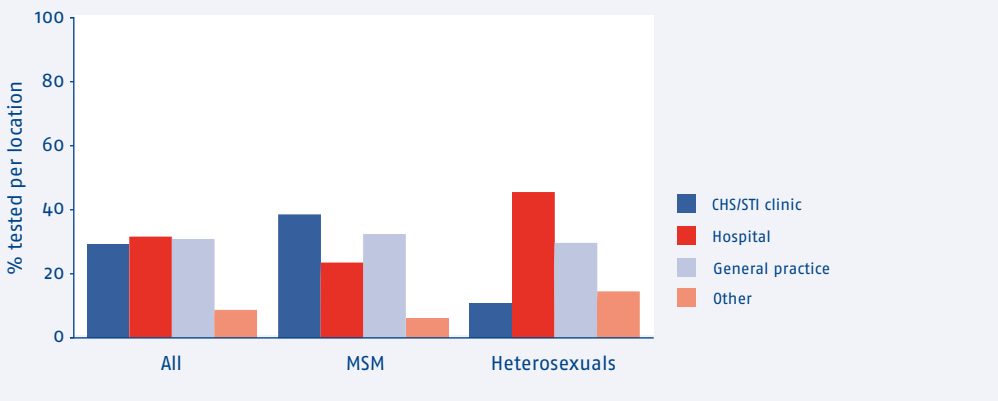
Legend: *MSM=men who have sex with men; IDU=injecting drug users.*

In the heterosexual population, the number of new diagnoses has declined to between 200 and 300 cases per year in the last few years. This decline, as shown later in this chapter, is largely the result of a reduced number of diagnoses in migrant populations. Finally, 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. Overall, 29% received their first HIV-positive test result at a community health service or STI clinic, 32% at a hospital, and 31% at a general practice (*Figure 1.5*). Among those tested at community health services or STI clinics, 89% were MSM, 5% were heterosexual men, and 5% were women. These numbers are comparable to those directly reported by STI clinics in 2014: 86% MSM, 8% heterosexual men, and 6% women[6].

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



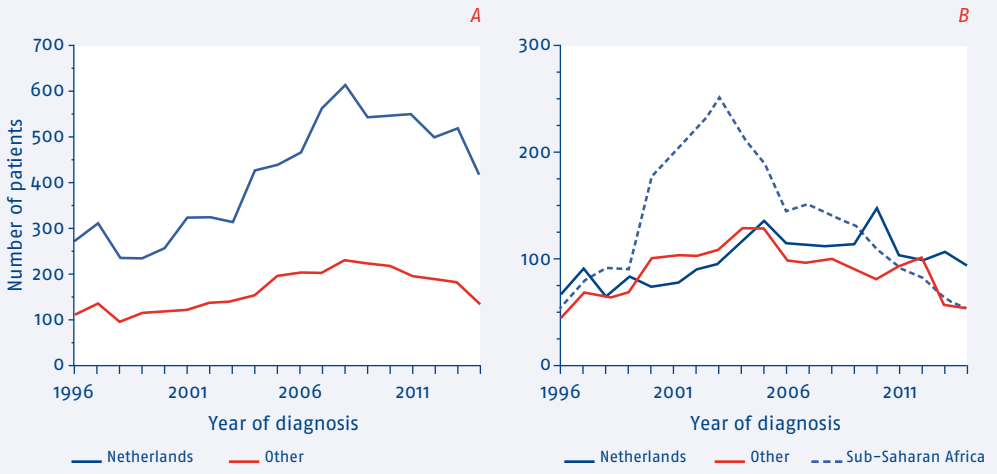
Legend: MSM=men who have sex with men; CHS=community health service; STI=sexually transmitted infection.

Geographical region of origin

In total, 71% of patients infected via homosexual contact originated from the Netherlands, 10% from other European countries, 7% from South America, and 3% from the Caribbean (*Figure 1.6A*). In recent years, the proportion of MSM of Dutch origin was 74% (*Appendix Table 1.3*). Minor changes over time have been observed in the proportion of patients from South America, which was 7% of the annual tally in the period before 2012 and 5% thereafter, and in the proportion of patients of western European origin, which was 8% before 2012 and 4% thereafter.

In the heterosexual population, only 32% originated from the Netherlands, while 40% originated from Sub-Saharan Africa, 10% from South America, 5% from the Caribbean, and 4% from South and South-East Asia (*Figure 1.6B*). However, the number of new diagnoses among Sub-Saharan Africans dropped sharply after 2003, probably partially as a result of stricter immigration laws that came into effect in the Netherlands at about that time. After 2011, 42% of the diagnosed heterosexual population was of Dutch origin, and 28% originated from Sub-Saharan Africa.

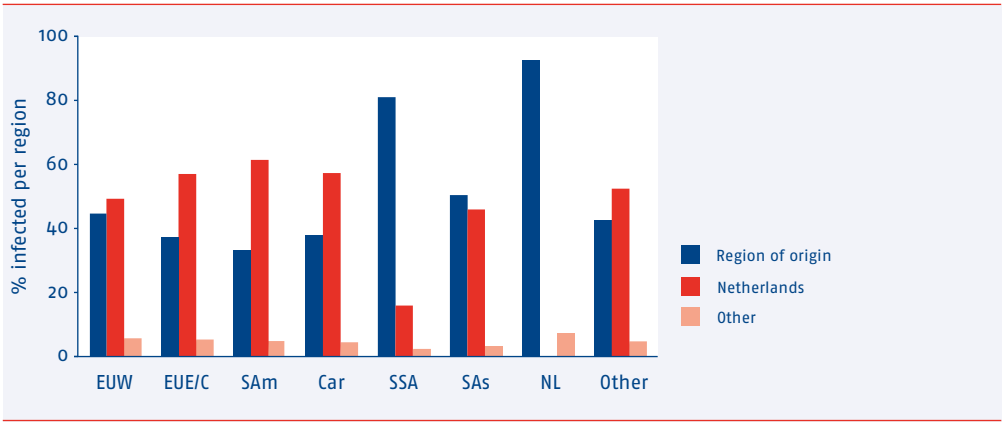
Figure 1.6: Annual number of diagnoses among (A) men who have sex with men (MSM) and (B) patients infected via heterosexual contact, by region of origin. Of the 13,289 MSM, 9,485 (71%) originated from the Netherlands, 1,374 (10%) from other European countries, 866 (7%) from South America, and 447 (3%) from the Caribbean. Among the 6,821 heterosexual patients, 2,707 (40%) originated from Sub-Saharan Africa, 2,216 (32%) from the Netherlands, 673 (10%) from South America, 370 (5%) from the Caribbean, and 287 (4%) from South and South-East Asia. Note: data collection for 2013 and 2014 has not yet been finalised.



Geographical region of infection

For 16,347 (73%) of the diagnosed adult population, 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 reported to likely have been infected in their region of origin (81%), and 16% to probably have been infected in the Netherlands. The majority of patients from other regions, except those from South and South-East Asia, were reported to have been infected in the Netherlands.

Figure 1.7: Proportion of HIV-1-positive adults per region of origin who were reported to have been infected in their own region of origin, in the Netherlands, or elsewhere.



Legend: EUW=Western Europe; EUE/C=Eastern and Central Europe; SAm=South America; Car=Caribbean; SSA=Sub-Saharan Africa; SAs=South and South-East Asia; NL=the Netherlands; Other=other regions of origin.

As may be expected from the heterogeneity in geographic region of origin, there were also major differences in the regions of infection between the major transmission groups. The majority of MSM (87%) were infected in the Netherlands. Furthermore, the majority of patients infected via injecting drug use (80%) were infected in the Netherlands, while 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 subtype of the infected patients. Overall, 93% 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.

Of the 4,767 heterosexual patients with a reported region of infection, 48% were infected in the Netherlands, while 34% reported having been infected in Sub-Saharan Africa. Of the 961 Dutch heterosexual men who reported a country of infection, 72% were infected in the Netherlands, 12% in South and South-East Asia, and 10% in Sub-Saharan Africa. Of the 809 Dutch women infected via heterosexual contact, 89% reported having been infected in the Netherlands and 7% in Sub-Saharan Africa, whereas less than 1% were infected in South and South-East Asia. Overall, 58% of the heterosexual patients with a known HIV-1 subtype were infected with a non-B subtype virus; for patients of Sub-Saharan African origin, this proportion was 98%.

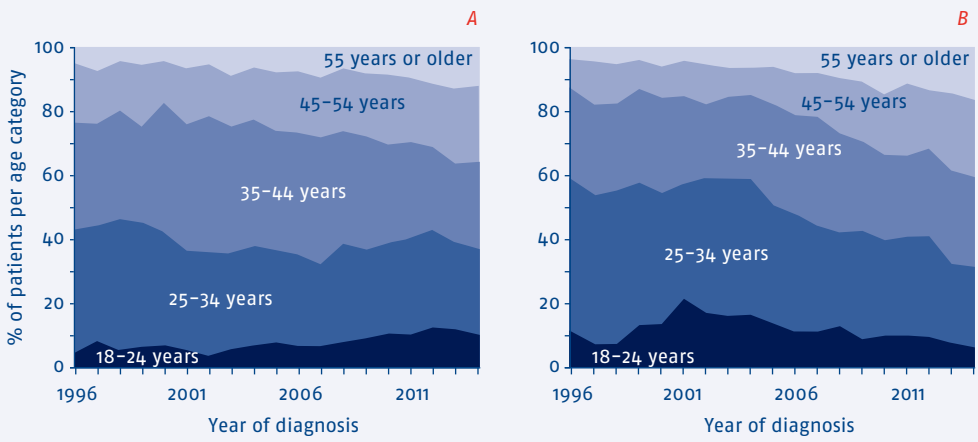
Increasingly older age at time of HIV diagnosis

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 37 years; in 2014, it was 41 years. Over the entire period from 1996 through 2014, 15% of adults who received a diagnosis of

HIV were 50 years or older; in 2014, 24% were 50 years or older. There were, however, considerable age differences between MSM and heterosexual men and women diagnosed in 2012 or later. MSM born in the Netherlands were diagnosed at a mean age of 41 years, while those of foreign origin were diagnosed at 35 years. Among heterosexual patients of Dutch origin, the average age at the time of diagnosis was 42 years for women and 45 years for men. Heterosexual patients born in Sub-Saharan Africa (women 35 years, men 41 years) or elsewhere (women 39 years, men 44 years) were substantially younger than their Dutch counterparts.

For MSM, the age distribution at the time of diagnosis has gradually changed over time, while for 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 among 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 among HIV-1-infected (A) men who have sex with men (MSM) and (B) heterosexual men and women. Between 1996 and 2014, the proportion of MSM aged 45 years or older at the time of diagnosis increased from 23% to 36%, while these proportions were 13% and 40% for heterosexuals. During the same period, the proportion of patients between 25 and 34 years of age decreased from 38% to 27% for MSM and from 47% to 25% for heterosexuals.*



Young adults

The number of diagnoses among young adults less than 25 years of age and infected via heterosexual contact was approximately 75 in the early 2000s and decreased to 19 in 2013, or to 8% of the annual tally (*Figure 1.8; Appendix Figure 1.2*). For 2014, 14 diagnoses have been registered so far, which is 7% of all diagnoses in heterosexuals in that year. Among MSM,

both the number and proportion of diagnoses among young adults increased over time, and, in 2013, young adults accounted for 13% of the annual tally, or 88 diagnoses. In 2014, 60 diagnoses in young adult MSM have been registered to date, which is 10% of all MSM diagnosed in that year.

Entry into care

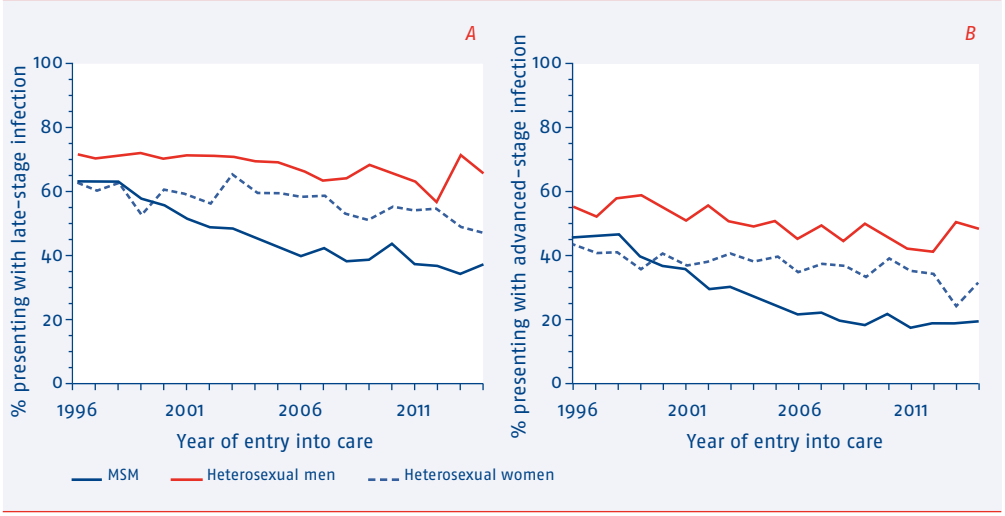
Of all patients diagnosed with HIV in 2008 or later for whom the location of testing was known, 83% had entered into care within four weeks, and 90% within six weeks of receiving their diagnosis. Overall, 91% of patients who received their first HIV-positive test at a community health service or STI clinic were in care within six weeks, as were 94% of those who tested HIV-positive in a hospital, 92% of those diagnosed at a general practice, and 87% of those diagnosed at other locations, excluding those diagnosed abroad. Overall, the proportion in care within six weeks was similar for MSM (90%) and for heterosexuals (89%). For heterosexuals, the proportion in care within six weeks did not differ by age at the time of diagnosis. On the other hand, more than 93% of MSM diagnosed at 35 years of age or older were in care within six weeks, compared with only 85% of those younger than 35 years.

Late presentation

Overall, 52% 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 2014, 44% of patients entered clinical care late in their infection (*Figure 1.9; Appendix Figure 1.3*). In addition, the proportion of patients presenting for care with advanced HIV disease (i.e., with a CD4 count below 200 cells/mm^3 or AIDS) has decreased over time and was 27% in 2014.

In total, 29% of the patients entering care from 1996 onwards had CD4 counts of 500 cells/mm^3 or higher, 20% had CD4 counts between 350 and 499 cells/mm^3, 20% had CD4 counts between 200 and 349 cells/mm^3, and 31% had CD4 counts below 200 cells/mm^3. For patients entering clinical care in recent years (2012 or later), these proportions were 35%, 22%, 19%, and 24%, respectively; 13% had already been diagnosed with AIDS.

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, 52% (44% from 2012) presented with late HIV disease: men who have sex with men (MSM) 45% (36% from 2012), heterosexual men 68% (64% from 2012), and heterosexual women 57% (50% from 2012). Overall, 34% (26%) were advanced presenters: MSM 26% (19% from 2012), heterosexual men 49% (46% from 2012), and heterosexual women 37% (29% from 2012). Late stage infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Advanced stage infection: CD4 counts below 200 cells/mm³ or having AIDS.



Legend: MSM=men who have sex with men.

Among patients entering clinical care in 2012 or later, 36% of MSM, 64% of heterosexual men, and 50% 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 (61%) compared with those of Dutch origin (52%). Late-stage infection at the time of entry into care was also often found in heterosexual patients originating from South America (62%) or from South and South-East Asia (62%). In this latter group, 59% presented for care with advanced HIV infection, compared to 37% of South Americans, 35% of Sub-Saharan Africans, and 35% of Dutch heterosexual patients.

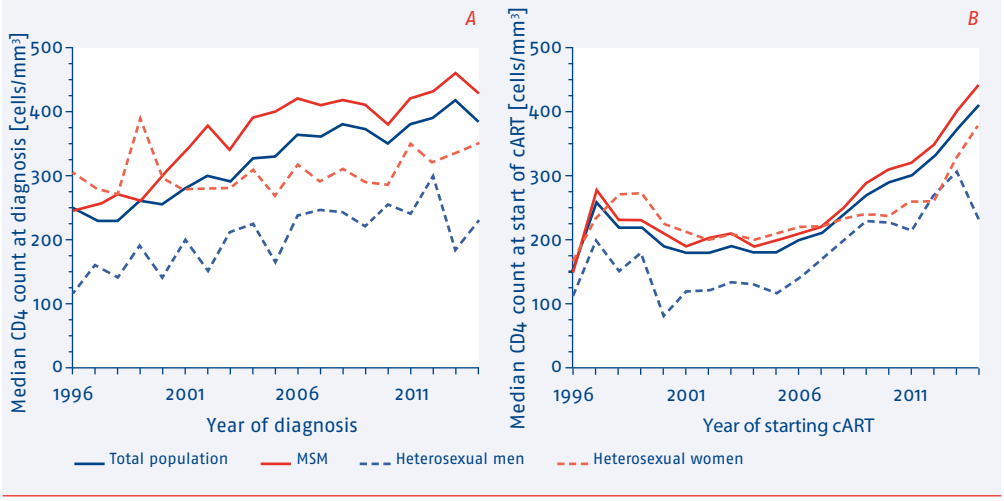
Late presentation was also more common in patients entering care at older ages. Late presentation was seen in 47% of MSM and 61% of heterosexuals entering care in 2012 or later at 45 years of age or older, compared with 19% of MSM and 36% of heterosexuals entering care at ages younger than 25 years. Although testing behaviour and frequency may differ between these two age groups, the relatively shorter period of sexual activity 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 at a hospital (67%) compared with those who were tested at a general practice (42%), a community health service or STI clinic (25%), or another testing location (36%).

Increasing CD4 cell counts

Between 1996 and 2014, median CD4 counts in the total adult population at the time of diagnosis increased from 250 to 385 cells/mm³ (*Figure 1.10A*). This overall increase was mainly the result of a rise in CD4 counts in both MSM and heterosexual men, whereas CD4 counts in women remained virtually unchanged.

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 2014, CD4 counts at the time of diagnosis increased from 250 (interquartile range [IQR], 80–440) to 385 (IQR, 190–580) cells/mm³ in the total adult population. The increase was most apparent for men who have sex with men (MSM): 245 (IQR, 80–450) cells/mm³ in 1996 and 430 (IQR, 259–610) cells/mm³ in 2014. During the same period, CD4 counts in heterosexual men increased from 115 (IQR, 30–395) to 225 (IQR, 53–410) cells/mm³, whereas CD4 count in heterosexual women was 300 (IQR, 120–500) cells/mm³ and did not change over time. (B) In the total adult population, CD4 counts at the start of cART rose to 260 (IQR, 130–400) cells/mm³ shortly after cART became available, decreased to a plateau of approximately 180 cells/mm³ between 2000 and 2005, and increased thereafter. In 2014, CD4 counts were 410 (IQR, 260–570) cells/mm³ in the total population, 442 (IQR, 320–598) cells/mm³ in MSM, 230 (IQR, 56–410) cells/mm³ in heterosexual men, and 380 (IQR, 250–530) cells/mm³ in heterosexual women.*



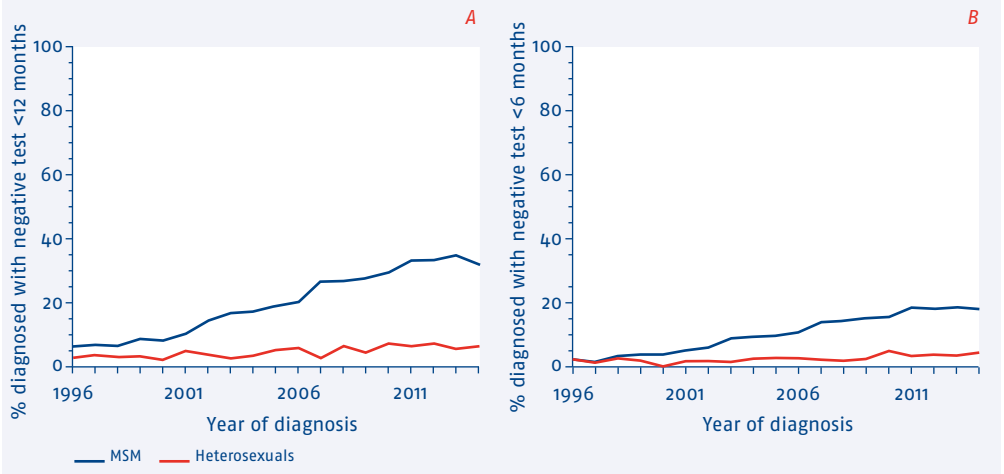
Legend: *MSM=men who have sex with men; cART=combination antiretroviral therapy.*

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, one-quarter of newly infected patients had CD4 counts below 350 cells/mm^3 within only one year after seroconversion[8].

A further, and arguably better, indication of earlier diagnosis is the increase in the proportion of MSM who were diagnosed with strong evidence of a recent infection, because they had a known negative HIV test six or, at most, 12 months before their first positive test (*Figure 1.11*). Among MSM diagnosed in 2012 or later, 33% had a negative test in the 12 months before diagnosis, while 18% had a negative test in the six months before diagnosis. For heterosexuals, these proportions were considerably lower; only 6% had a negative test in the 12 months before diagnosis, while 4% had a negative test in the six months before diagnosis. There has been no apparent improvement in these figures in the most recent calendar years.

Figure 1.11: *Proportion of patients diagnosed and having (A) a last negative test at most 12 months before diagnosis, or (B) a last negative test at most 6 months before diagnosis. All together, 32% of men who have sex with men (MSM) and 7% of heterosexuals (men 4%, women 9%) diagnosed in 2014 had a last negative test at most 12 months before diagnosis, whereas 18% of MSM and 5% of heterosexuals (men 4%, women 5%) had a last negative test at most 6 months before diagnosis.*



Legend: *MSM=men who have sex with men.*

Increasing frequency of testing

Since both the proportion of recent infections and CD4 counts at diagnosis have increased among 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 HIV test (*Appendix Figure 1.4*). In 2014, 73% of MSM and 40% of heterosexuals diagnosed with HIV had a known previous test with a negative result; in 2013, these proportions were 67% and 32%, respectively. The proportion with a previously known negative test was highest among those diagnosed at a community health service or STI clinic (78%), compared with 39% of those diagnosed in a hospital, 69% of those tested at a general practice, and 60% of those diagnosed elsewhere.

Population – start of cART

Treated population

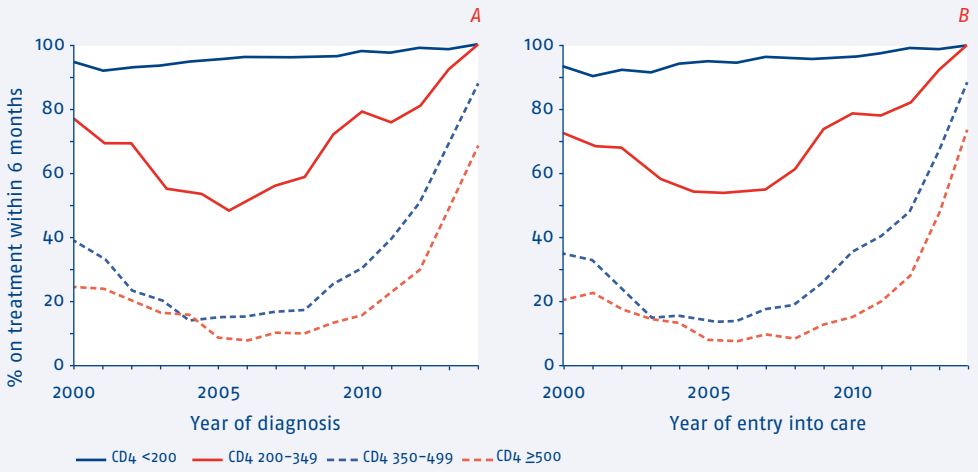
Of the 22,349 adult patients ever registered with an HIV-1 infection, 20,337 patients had started cART by May 2015. The majority of these patients (87%) started cART while being antiretroviral therapy-naive. For the entire group of adults, the total follow-up time since start of cART was 164,278 person years. Treatment and treatment outcomes are described in more detail in *Chapter 2*.

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 2014, median CD4 counts at the start of treatment had increased from 370 cells/mm^3 in 2013 to 400 cells/mm^3. Of those starting cART in 2014, 20% of patients started treatment at CD4 counts already below 200 cells/mm^3, 19% started at CD4 counts between 200 and 349 cells/mm^3, 27% started at CD4 counts between 350 and 499 cells/mm^3, and 34% started at CD4 counts of 500 cells/mm^3 or above.

The main reason for starting treatment too late (i.e., at low CD4 counts) appears to be a late diagnosis, because most patients who are able to start treatment on time do so. Patients with less than 200 CD4 cells/mm^3 at diagnosis or at the time of entry into care almost immediately started treatment; within 6 months after diagnosis, more than 95% had started cART (*Figure 1.12; Appendix Figure 1.5*). The proportion of patients who started treatment within 6 months was smaller for those with higher CD4 counts, but it has rapidly increased in recent years, reflecting changes in treatment guidelines towards starting treatment at higher CD4 counts.

Figure 1.12: (A) Proportion of patients who started combination antiretroviral treatment (cART) within six months after HIV diagnosis by CD4 count at the time of diagnosis. (B) Proportion of patients who started cART within six months after entry into care stratified by CD4 counts at the time of entry into care. Patients were considered only if they had more than six months of follow up after diagnosis or entry into care. Of all patients diagnosed in 2014, 100% of those with CD4 counts below 200 cells/mm³ or between 200 and 349 cells/mm³ had started cART within six months after receiving their diagnosis, while 87% of those with CD4 counts between 350 and 499 cells/mm³, and 68% of those with CD4 counts of 500 cells/mm³ or above had begun cART within six months of diagnosis. In patients who entered HIV care in 2014, 100% of those with CD4 counts below 200 cells/mm³ or between 200 and 349 cells/mm³ had started cART within six months after entry, while 89% of those with CD4 counts between 350 and 499 cells/mm³, and 74% of those with CD4 counts of 500 cells/mm³ or above had begun cART within six months of entry.



Population – HIV-2

HIV-2-positive population

In total, 97 of the 23,303 registered patients, including 45 men and 52 women, were infected with HIV-2. The majority (78 patients, or 80%) were infected via heterosexual contact. HIV-2 is endemic in Western Africa, and 64 patients originated from this region, mostly from Ghana (25 patients) or Cape Verde (24 patients). Only 20 patients were born in the Netherlands, 14 of whom were reported to have been infected in the Netherlands. A total of 69 patients were still in clinical care, 15 patients had died, and 5 had moved abroad. The mean age of the patients still in care was 55 years, and 77% were 50 years or older.

The mean age at the time of diagnosis was 44 years, which was considerably higher than for HIV-1-positive patients. For the 82 patients who were diagnosed in 1996 or later, the median CD4 count at the time of diagnosis was 336 (93-676) cells/mm^3. From 1996 onwards, 48% of the patients were late presenters, and 40% presented for care with advanced HIV disease[7]. The distribution of CD4 counts at entry into care appeared to be more bimodal than for HIV-1-positive patients: 37% had CD4 counts below 200 cells/mm^3, 38% had CD4 counts of 500 cells/mm^3 or higher, while relatively few patients (25%) had CD4 counts between 200 and 499 cells/mm^3.

Treatment

By May 2015, 55 HIV-2-positive patients had ever started cART. Of these, 38 were still care, 19 of whom used a backbone of abacavir/lamivudine, 8 tenofovir/emtricitabine, and 4 zidovudine/lamivudine. Additional drugs in the regimen included ritonavir-boosted darunavir in 16 patients, ritonavir-boosted lopinavir in 9, and atazanavir in 5 (all ritonavir-boosted, except one). At the start of cART, 23 patients had HIV-2 RNA levels above 500 copies/ml, while 13 had levels below 500 copies/ml.

Of the 69 patients who were still in care, 50 had a most recent viral load measurement below 500 copies/ml, 4 had a viral load above 500 copies/ml, and for 15 patients no HIV-2 RNA result was available. In total, 29 patients had not, or not yet, started treatment. These patients still had high CD4 counts (median 775 (510-970) cells/mm^3), and only one had an HIV-2 viral load above 500 copies/ml (11 not determined).

Conclusion

Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to approximately 1,000 new diagnoses in recent years. Although this decreasing trend continued in 2014, the projected number of diagnoses for that year may have been under-estimated because the data freeze for this Monitoring Report took place one month earlier than in previous years.

An important change compared to last year's Monitoring Report is that estimates of the number of people living with HIV, as well as the number who are not yet diagnosed, are considerably lower than previously reported. Until last year, we used estimates provided by UNAIDS, but these carry the disadvantage that the data and method on which they were based are unclear. Moreover, according to UNAIDS, there should be 25,640 HIV-positive patients on antiretroviral treatment. This would imply that almost 9,000 patients are not registered by SHM, which is impossible given the way care for HIV is organised in the Netherlands.

The new method, which is publicly available via the website of the European Centre for Disease Prevention and Control (ECDC), has the advantage that it uses only routine surveillance data. It is, therefore, relatively straightforward to provide annual updates of the

estimates, in contrast to methods that rely mainly on HIV prevalence surveys. Although the new method provided an estimate of a lower number of individuals living with HIV in 2012 than did an alternative method with HIV prevalence surveys, preliminary analyses showed that both methods gave very similar results for the size of the HIV population in Amsterdam. The higher estimate in the alternative method is mainly due to the relatively large uncertainty of the number of people with HIV living outside Amsterdam and Rotterdam[4].

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

In addition, in recent years, testing for HIV has appeared to become more frequent, because patients with a positive test are more likely to have had a previous negative test. Testing rates appear to be highest among patients who received a positive test result at community health services or STI clinics 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 clinics are more likely actively seeking testing for HIV on a regular basis than patients diagnosed in a hospital, who are more likely to be tested because they have a disease that may be caused by an HIV infection.

Patients tested early in their infection generally start treatment earlier and before CD4 counts have dropped to below 350 cells/mm^3. In the most recent years, treatment uptake has also increased in patients with high CD4 cells such that in 2014, almost three quarters of patients diagnosed with CD4 cells above 500 cells/mm^3 were on cART within 6 months after entering HIV care. As a result, 86% of patients in care and 70% of the total estimated population of persons living with HIV in the Netherlands, including those not yet diagnosed, have a suppressed viral load.

Recommendations

The decreasing trend in the number of new HIV diagnoses may, in part, be the result of the positive developments mentioned above (i.e., more testing, earlier diagnosis, earlier start of treatment, a large proportion of patients with viral suppression, and a smaller number living with undiagnosed HIV). To fully curb the epidemic and achieve a sustained further reduction in the number of new HIV infections, testing and treatment need to be scaled up even further. This should be part of an integrated approach on a national level, together with increasing awareness of sexual risk behaviour and extending the existing armoury of prevention measures with pre-exposure prophylaxis, as is currently being demonstrated in a project in Amsterdam as one of the components of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative.

2. Response to combination antiretroviral therapy (cART)

Luuk Gras, Kees Brinkman, Jan Prins and Peter Reiss

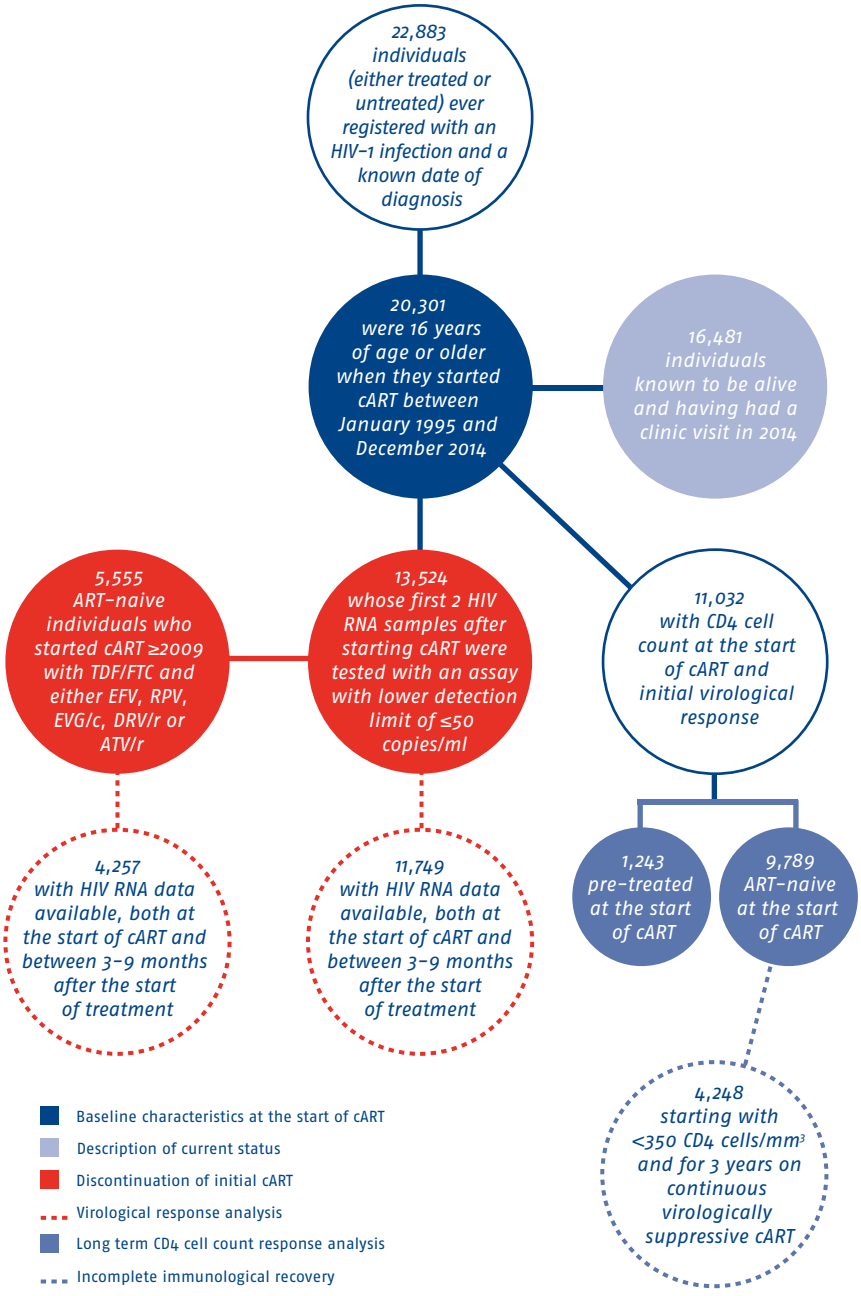
Introduction

The primary goal of combination antiretroviral therapy (cART) is to prevent HIV disease progression[9]. Another benefit of treatment is the prevention of onward HIV transmission. In studies in HIV-serodiscordant heterosexual couples, transmission has been shown to be more likely with higher HIV RNA levels[10-12]. Moreover, a randomised 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, besides preventing primary clinical events, AIDS, and tuberculosis[13], immediate start of ART is also more effective at preventing transmission of HIV than deferring treatment until the CD4 count has dropped to ≤250 cells/mm^3[14]. Thus, in addition to preventing disease progression in HIV-infected individuals, cART also benefits public health by preventing onward HIV transmission.

US guidelines on when to start cART, which are generally followed by the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB), currently recommend starting cART in all HIV-infected individuals[15]. Recent results from the Strategic Timing of Anti-Retroviral Treatment (START) trial, a randomised clinical trial on when to start cART, support these guidelines. The trial showed a 57% reduction in death, as well as AIDS-related and non-AIDS-related morbidity when cART is started while CD4 cell counts are still above 500 CD4 cells/mm^3 compared to deferring the start until counts are 350 cells/mm^3 or lower[16]. These findings imply that all HIV-infected individuals who are willing and ready to start treatment should be given the option of starting cART immediately after diagnosis. Finally, as adherence is better with once-daily regimens than with twice-daily regimens, all currently recommended first-line regimens in the Netherlands are once daily[17].

In this chapter we describe trends over time in the use of cART, trends in the virological and immunological responses to cART, as well as trends in toxicity-related therapy changes, according to demographic and clinical characteristics at the start of treatment. *Figure 2.1* gives an overview of the number of individuals included in the various analyses described in this chapter.

Figure 2.1: Flow diagram of the number of individuals included in analyses. Colours indicated in the legend refer to the various analyses described in this chapter.



Legend: *TDF=tenofovir; FTC=emtricitabine; EFV=efavirenz; RPV=rilpivirine; EVG/c=cobicistat-boosted elvitegravir; DRV/r=ritonavir-boosted darunavir; ATV/r=ritonavir-boosted atazanavir.*

Demographic and clinical characteristics at the start of cART

Of the 22,883 treated and untreated individuals with an HIV-1 infection and a known date of diagnosis registered by Stichting HIV Monitoring (SHM), 20,301 were 16 years of age or older when they started cART between January 1995 and December 2014 (*Figure 2.1*). Of these, 2,613 had had prior exposure to mono or dual ART at the start of cART, and 17,688 were ART-naive. The individuals described in this chapter include 188 individuals aged between 16 and 18 years at HIV diagnosis who are also described in *Chapter 6*.

We grouped individuals according to calendar year of starting cART: 6,052 started between 1995 and the end of 2001, 5,302 started between 2002 and the end of 2007, 7,884 started between 2007 and the end of 2013, and 1,063 started in 2014 (*Table 2.1*). Individuals starting in 2015 are not included because their follow up is currently too short to allow meaningful reporting of their virological and immunological response to cART.

***Table 2.1:** Baseline characteristics of 20,301 individuals starting combination antiretroviral therapy (cART) between 1 January 1995 and 31 December 2014.*

							Year of starting cART	
	1995–2001		2002–2007		2008–2013		2014	
Total (n, %)	6,052	100.0	5,302	100.0	7,884	100.0	1,063	100.0
DEMOGRAPHIC CHARACTERISTICS								
Male gender (n, %)	4,903	81.0	3,855	72.7	6,705	85.0	934	87.9
Age at start of cART (median, IQR)	37.5	32.0–44.4	38.5	31.8–45.7	40.5	32.7–48.2	39.9	31.5–48.7
Transmission risk group (n, %)								
MSM	3,513	58.0	2,506	47.3	5,264	66.8	770	72.4
Heterosexual contact	1,682	27.8	2,220	41.9	2,108	26.7	245	23.0
IDU	417	6.9	156	2.9	88	1.1	2	0.2
Blood or blood products	127	2.1	74	1.4	64	0.8	8	0.8
Vertical transmission	1	0.0			9	0.1		
Other/Unknown	318	5.21	346	6.6	351	4.5	38	3.6
Region of origin (n, %)								
Netherlands	3,633	60.0	2,556	48.2	4,889	62.0	714	67.2
W-Europe/N-America/Australia	685	11.3	383	7.2	485	6.2	54	5.1
Caribbean/S-America	581	9.6	671	12.7	862	10.9	112	10.5
Sub-Saharan Africa	768	12.7	1,243	23.4	892	11.3	88	8.3
Other	385	6.4	449	8.5	756	9.6	95	8.9
Socio-economic status (SES)*								
1	289	4.8	247	4.7	416	5.3	44	4.1
2	1,268	21.0	1,056	19.9	1,735	22.0	205	19.3
3	1,471	24.3	1,503	28.3	2,260	28.7	314	29.5
4	1,455	24.0	1,294	24.4	1,875	23.8	242	22.8
5	966	16.0	1,039	19.6	1,410	17.9	191	18.0
Missing	603	10.0	163	3.1	188	2.4	67	6.3

	Year of starting cART							
	1995–2001		2002–2007		2008–2013		2014	
CLINICAL CHARACTERISTICS								
CD4 cell count at start of cART, cells/mm³ (median, IQR)	200	80–340	190	90–280	294	181–390	410	260–570
HIV RNA at start cART, log_{10} cps/ml (median, IQR)	4.82	4.15–5.31	5.00	4.47–5.34	4.91	4.37–5.35	4.70	4.09–5.23
AIDS diagnosis at start of cART (n, %)	1,947	32.2	1,399	26.4	1,243	15.8	125	11.8
HCV status at start of cART (n, %)								
Negative	4,876	80.6	4,658	87.9	7,230	91.7	974	91.6
HCV RNA positive	105	1.7	164	3.1	264	3.3	18	1.7
HCV Ab positive	326	5.4	84	1.6	25	0.3	5	0.5
Unknown	745	12.3	396	7.5	365	4.6	66	6.2
HBV status at start of cART** (n, %)								
Negative	5,213	86.1	4,758	89.7	7,226	91.7	964	90.7
Positive	427	7.1	350	6.6	380	4.8	28	2.6
Unknown	412	6.8	194	3.7	278	3.5	71	6.7
TREATMENT CHARACTERISTICS								
ART-naive at start cART	3,807	62.9	5,057	95.4	7,770	98.6	1,054	99.2
cART started during pregnancy	142	2.3	391	7.4	230	2.9	12	1.1
cART started during primary infection***	98	1.6	203	3.8	629	8.0	144	13.5

** Socio-economic status: a combined measure based on income, employment, and level of education obtained by interviewing one household in each six-position postal code and aggregated into a single score for each four-position postal code by principal component analysis. Scores were classified in five groups such that they contained approximately 7%, 24%, 38%, 24%, and 7% of all postal codes; 1 indicates high SES and 5 indicates low SES [18].*

*** Measured by hepatitis B surface antigen.*

**** cART started within six months of estimated date of seroconversion (midpoint between last negative and first positive HIV test or, in case of laboratory evidence of acute infection, the date of HIV diagnosis).*

***Legend:** cART=combination antiretroviral therapy; ART=antiretroviral therapy; MSM=men who have sex with men; IDU=injecting drug use; W Europe=Western Europe; N America=North America; S America=South America; CDC-C=Centers for Disease Control category C; HCV=hepatitis C virus; HBV=hepatitis B virus; IQR=interquartile range.*

Of the 20,301 individuals who had ever started cART after January 1995, 3,904 were women (19%) of whom 27% were born in the Netherlands. Of the 1,063 individuals who started cART in 2014, 770 (72%) were MSM, similar to 2013 (71%). Among the 112 individuals of Caribbean or South American origin who started cART in 2014, 46 originally came from Surinam (41%), 22 from the former Netherlands Antilles (20%), 15 from Brazil (13%), and 7 from Colombia (6%). The 95 individuals from other regions of origin who started in 2014 were from Central and Eastern Europe (n=45), Southeast Asia (n=26), North Africa and the Middle East (n=15), and Oceania and the Pacific (n=6), while the region of origin was unknown for 3 individuals.

The percentage of individuals with an AIDS diagnosis at the start of cART declined over time (test for trend p<0.0001). This was accompanied by an increase in the median CD4 cell count at the start of cART: from 210 cells/mm^3 in 2007 to 373 cells/mm^3 in 2013 and 410 cells/mm^3 in 2014 (Cuzick test for trend p<0.0001). *Chapter 1* gives more detailed information on trends in CD4 cell count at the start of cART over time and additional aspects of the continuum of HIV care. More than 13% of individuals starting cART in 2014 did so during primary infection, compared to 10% in 2013. The prevalence of hepatitis B co-infection significantly declined over time (p<0.0001).

Virological response to cART

The key goal of cART is to achieve and maintain durable viral suppression. The definition of viral suppression has changed over the years with the introduction of more sensitive viral load assays, and nowadays a cut-off of 40 or 50 HIV RNA copies/ml is most often used. Here we have defined virological success as any plasma viral load measurement <100 copies/ml taken between three and nine months after starting cART. We used a cut-off of 100 copies/ml, 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 of plasma viral load when the load is at levels close to the lower limit of detection[19, 20].

In the Netherlands, a total of 20,301 individuals have started cART since January 1995. In this report, we will focus on ART-naive individuals starting cART who were monitored with sensitive viral load assays (i.e., the first two plasma viral loads available after the start had to be measured with an assay with a lower detection limit of 50 copies/ml or less), which have been gradually introduced into routine clinical practice since 1999. Of the 13,524 individuals selected by these criteria, we further excluded 1,023 individuals without a viral load measurement three and nine months after starting cART, as well as 620 women who started cART during pregnancy and 203 participants of the primo-SHM study because cART may have been interrupted at the end of the pregnancy or as part of the study protocol. Results in the following section on virological response to cART are therefore restricted to the remaining 11,749 individuals.

Short-term virological response

Of these 11,749 individuals, 10,935 (93.1%) achieved initial virological success (a plasma viral load <100 HIV RNA copies/ml between three and nine months). The percentage of individuals with initial virological success has improved over time and was 87.9% (95% CI 86.2-89.5%) in those starting between 1999 and 2002, 92.9% (95% CI 91.8–93.9%) in those starting between 2003 and 2006, 93.7% (95% CI 92.8-94.4%) in those starting between 2007 and 2010, and 94.5% (95% CI 93.8-95.2%) in those starting between 2011 and 2014 (Cochran-Armitage test for trend p<0.0001).

To study factors associated with initial virological suppression to <100 copies/ml, we performed a logistic regression analysis using demographic and clinical data from the 11,749 individuals, as well as data on the frequency of daily ART intake (once, twice, three times daily, or more often), type of initial regimen (non-nucleoside reverse transcriptase inhibitor (NNRTI)-based, protease inhibitor (PI)-based, ritonavir-boosted PI [PI/r]-based, triple-NRTI, and other), use of an integrase inhibitor, and type of viral load assay (CAP/CTM v2.0 vs. other assays). In adjusted analyses, the probability of suppression to <100 copies/ml was lower in individuals infected through heterosexual or intravenous transmission of HIV (as compared to homosexual transmission), those with a higher plasma viral load at the start of cART, those from Sub-Saharan Africa, those with a lower CD4 cell count, and those aged less than 30 years at the start of cART *(Table 2.2)*. On the other hand, socio-economic status was not significantly associated (p=0.61) with the probability of achieving initial viral suppression. In addition, both a starting regimen that included an integrase inhibitor and a once-daily regimen as compared to a twice-daily regimen were significantly independently associated with a shorter time to suppression. Finally, there was a trend towards a lower probability of initial virological success when cART was started during primary infection (p=0.07).

Table 2.2: Unadjusted and adjusted odds ratios (95% confidence interval) of initial virological success (HIV RNA <100 copies/ml between three and nine months after starting combination antiretroviral therapy) by logistic regression analysis in 11,749 previously ART-naive individuals. The probability of virological success is higher compared to the reference group when the odds ratio is higher than 1.00.

				Unadjusted				Adjusted*
	OR	HR	(95% CI)	(overall) p-value	OR	HR	(95% CI)	(overall) p-value
Gender								
Male	1.00				1.00			
Female	0.80	0.66	0.97	0.02	1.18	0.94	1.49	0.16
Transmission risk group				(<0.0001)				(<0.0001)
MSM	1.00				1.00			
Heterosexual	0.65	0.56	0.76	<0.0001	0.81	0.65	1.00	0.0555
IDU	0.34	0.23	0.52	<0.0001	0.37	0.24	0.58	<0.0001
Region of origin				(<0.0001)				(0.07)
Netherlands	1.00				1.00			
Caribbean & South America	0.81	0.65	1.02	0.08	0.85	0.67	1.08	0.19
Sub-Saharan Africa	0.54	0.45	0.65	<0.0001	0.70	0.55	0.89	0.004
Western Europe / North America	0.95	0.69	1.31	0.7568	0.99	0.71	1.37	0.95
Socio-Economic Status**								(0.61)
1	1.06	0.73	1.52	0.77	0.95	0.66	1.38	0.80
2	1.00	0.82	1.24	0.96	0.92	0.74	1.14	0.43
3	1.00				1.00			
4	0.93	0.76	1.14	0.49	0.93	0.76	1.14	0.49
5	0.77	0.63	0.95	0.01	0.82	0.66	1.02	0.07
Age (years)				(<0.0001)				(0.003)
16-29	0.75	0.61	0.91	0.004	0.74	0.60	0.91	0.004
30-39	1.00				1.00			
40-49	1.20	1.00	1.45	0.05	1.11	0.92	1.35	0.27
≥50	1.09	0.89	1.34	0.42	0.99	0.79	1.23	0.90
CD4 cell count (cells/mm^3)				(<0.0001)				(0.03)
<50	0.48	0.37	0.62	<0.0001	0.68	0.54	0.87	0.002
50-200	0.68	0.53	0.86	0.001	0.81	0.66	1.00	0.05
200-350	1.09	0.86	1.39	0.48	0.84	0.66	1.08	0.18
350-500	1.00				1.00			
>500	1.03	0.75	1.42	0.86	0.89	0.65	1.22	0.48
HIV RNA ($\log_{10}$ copies/ml)				(<0.0001)				(<0.0001)
<4	1.07	0.77	1.49	0.70	1.08	0.77	1.51	0.65
4-5	1.00				1.00			
≥5	0.43	0.36	0.51	<0.0001	0.46	0.38	0.55	<0.0001

				Unadjusted				Adjusted*
	OR	HR	(95% CI)	(overall) p-value	OR	HR	(95% CI)	(overall) p-value
Year of starting				(<0.0001)				(0.04)
1999–2002	0.49	0.40	0.60	<0.0001	1.01	0.77	1.32	0.94
2003–2006	0.89	0.73	1.10	0.28	1.30	1.03	1.63	0.03
2007–2010	1.00				1.00			
2011–2013	1.17	0.97	1.41	0.11	1.20	0.96	1.51	0.11
HBV co-infection								
HBsAg –	1.00							
HBsAg +	1.06	0.63	1.31	0.67				
HCV co-infection								
–	1.00							
RNA +	0.89	0.60	1.32	0.56				
Ab +	0.65	0.35	1.21	0.17				
Integrase inhibitor included in regimen	1.75	1.15	2.68	0.009	3.48	1.98	6.12	<0.0001
Daily frequency of initial cART intake				(<0.0001)				(<0.0001)
Once	1.00				1.00			
Twice	0.49	0.42	0.57	<0.0001	0.61	0.49	0.76	<0.0001
Three or more times	0.14	0.07	0.26	<0.0001	0.30	0.15	0.63	0.001
Start during primary infection	0.82	0.62	1.09	0.17	0.75	0.55	1.02	0.07
HIV RNA assay								
CAP/CTM v2.0	1.16	0.98	1.38	0.08	0.78	0.63	0.97	0.03
Other assay	1.00				1.00			

**In addition to all variables listed, type of initial regimen was also included in the adjusted analyses.*

***Socio-economic status (SES): a combined measure based on income, employment, and level of education obtained by interviewing one household in each six-position postal code and aggregated into a single score for each four-position postal code by principal component analysis. Scores were classified in five groups such that they contained approximately 7%, 24%, 38%, 24%, and 7% of all postal codes; 1 indicates high SES and 5 indicates low SES [18].*

***Legend:** CI=confidence interval; OR=odds ratio; MSM=men who have sex with men; IDU=injecting drug users; HBV=hepatitis B virus; HCV=hepatitis C virus; cART= combination antiretroviral therapy; HBsAg=hepatitis B surface antigen; Ab=antibody; CAP/CTM v2.0=COBAS AmpliPrep COBAS TaqMan HIV-1 assay, version 2.0.*

We also found a significant interaction between the CD4 cell count at the start of cART and the year of starting cART (p=0.002, *Table 2.3*). In individuals who started cART between 2003 and 2006, starting at 500 CD4 cells/mm^3 or higher (1,148 out of 11,749 individuals [10%]) was associated with a significantly lower probability of initial viral suppression compared to starting at 200-350 cells/mm^3; however, this effect was no longer seen when cART was

started in or after 2011. In individuals who started cART in or after 2007, starting at 200 CD4 cells/mm^3 or lower was associated with a significantly lower probability of initial viral suppression. These findings remained the same when individuals who started cART during primary infection were excluded from the analysis. There was no evidence that the association between starting cART during primary infection and virological success had changed over time (test for interaction, p=0.80).

Table 2.3: *Selected odds ratios (95% confidence intervals) of reaching initial virological suppression <100 HIV RNA copies/ml by logistic regression analysis, after including an interaction term between year of starting cART and CD4 cell count at the start of cART. An odds ratio greater than 1.00 indicates a higher probability of having <100 HIV RNA copies/ml compared to the reference group.*

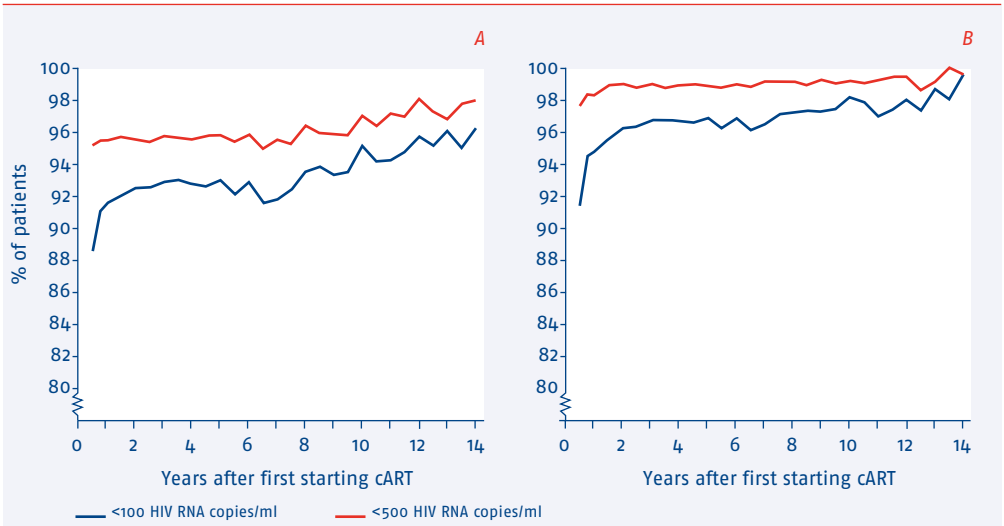
	Year of starting cART			
	1999–2002	**2003–2006**	**2007–2010**	**2011–2014**
CD4 cell count at start of cART (cells/mm^3)				
<200	1.05 (0.70–1.58)	1.08 (0.74–1.58)	0.58 (0.42–0.80)	0.57 (0.40–0.83)
200–350	1.00	1.00	1.00	1.00
350–500	0.65 (0.36–1.15)	1.11 (0.50–2.44)	0.61 (0.40–0.95)	1.05 (0.69–1.59)
≥500	1.16 (0.53–2.54)	0.42 (0.19–0.94)	0.60 (0.30–1.19)	1.07 (0.68–1.69)

Legend: *cART=combination antiretroviral therapy.*

Long-term virological response

Figure 2.2 shows that the percentage of individuals with a viral load <100 copies/ml increased from 92% at 1 year after starting cART to 96% at 14 years after starting cART and, likewise, increased from 95% (year 1) to 99.6% (year 14) for those continuously on cART. To some extent, the increasing trend in percentages with time after starting cART may reflect a bias towards individuals who do well and remain in follow up.

Figure 2.2: The percentage of individuals with a plasma HIV RNA concentration <100 (red line) and <500 copies/ml (blue line) at months 9, 12, 18, and at every 6 months of follow up thereafter. Plot A shows results from all individuals after first starting combination antiretroviral therapy (cART), and plot B shows a subgroup of individuals who remained on cART continuously, allowing for a therapy interruption of <2 weeks. A total of 11,794 treatment-naive individuals starting cART were included in this analysis, but this number diminished over time due to differences in length of follow up.



Legend: cART=combination antiretroviral therapy.

Analyses regarding the occurrence of virological failure are described in *Chapter 3*.

Immunological response

After initiation of cART, most HIV-infected 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. Normal CD4 cell counts in the general population are, on average, approximately 800 cells/mm^3, but vary according to factors such as age, ethnicity, gender, and smoking status. Failure to suppress viraemia is associated with poorer recovery of CD4 cell count[21, 22]. However, incomplete recovery of CD4 cell count may also occur despite sustained suppression of plasma viral load to levels below the limit of detection, a situation reported to be associated with an increased risk of progression to AIDS and development of non-AIDS-related diseases[23]. Furthermore, although the CD4 cell count is considered the key prognostic factor for mortality and AIDS-defining endpoints, recent evidence has emerged suggesting that other immunological measures, such as a low CD4/CD8 ratio, may also

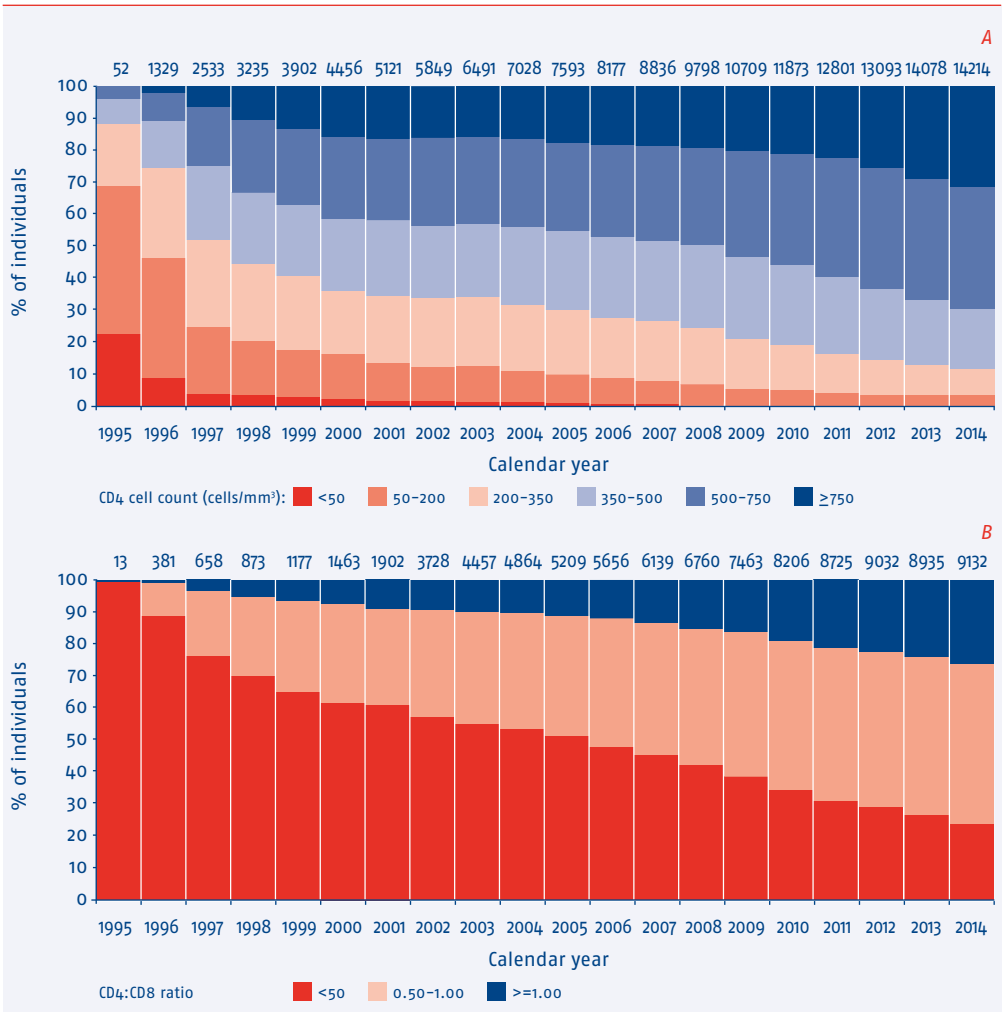
independently predict time to death and non-AIDS-defining endpoints[24-27]. In the general population, a low CD4/CD8 ratio has been found to be associated with immunosenescence and all-cause mortality[28-30].

As the clinical benefit of cART is strongly related to the level of recovery of the immune status, in particular, the CD4 cell count (*Chapter 4*)[31-36], we report on the immune status of the 20,301 individuals who started cART from 1995 onwards, and we describe long-term CD4 cell count and CD4/CD8 ratio responses after the start of cART, including a description of patients with incomplete immunological recovery three years after having started cART.

Immune status in the treated population by calendar year

Figure 2.3 shows the last known immune status of individuals in each calendar year after the start of cART. After starting cART, the percentage of individuals with counts <350 cells/mm^3 (a level placing them at higher risk of both AIDS and non-AIDS co-morbidity) dropped from 74% in 1996 to 12% in 2014 (*Figure 2.3.A*). Likewise, the number of individuals with CD4 cell counts <350 cells/mm^3 at the end of each calendar year decreased from 2,427 in 2008 to 1,703 in 2014 (numbers for 2014 may increase slightly because data collection is not yet complete; *Appendix Figure 2.1.A*). The drop in absolute number of individuals with low CD4 cell counts at the end of each calendar year may partly reflect the trend of starting cART at higher CD4 cell counts, which has been observed since 2007. Finally, *Figure 2.3.B* shows that among individuals who had ever started cART, the percentage of those with a CD4/CD8 ratio of 1 or above increased from 7% in 2000 to 26% in 2014.

Figure 2.3.A and B: Last available CD4 cell count (cells/mm³) (A) and CD4:CD8 ratio (B) in each calendar year after the start of cART. The last available CD4 cell count and CD4:CD8 ratio in each year and after the start of cART was selected for each patient. The percentage of individuals in each CD4 cell count and CD4:CD8 ratio category is shown.



Longitudinal CD4 cell count changes after starting cART

Of the 20,301 individuals who first started cART (including both ART-naive and ART-experienced individuals), a CD4 cell count at the start of therapy or thereafter was available for 18,500 (91%) individuals. Of these, only 11,032 individuals (1,243 ART-experienced, 9,789 ART-naive individuals) who had achieved initial virological suppression within nine months

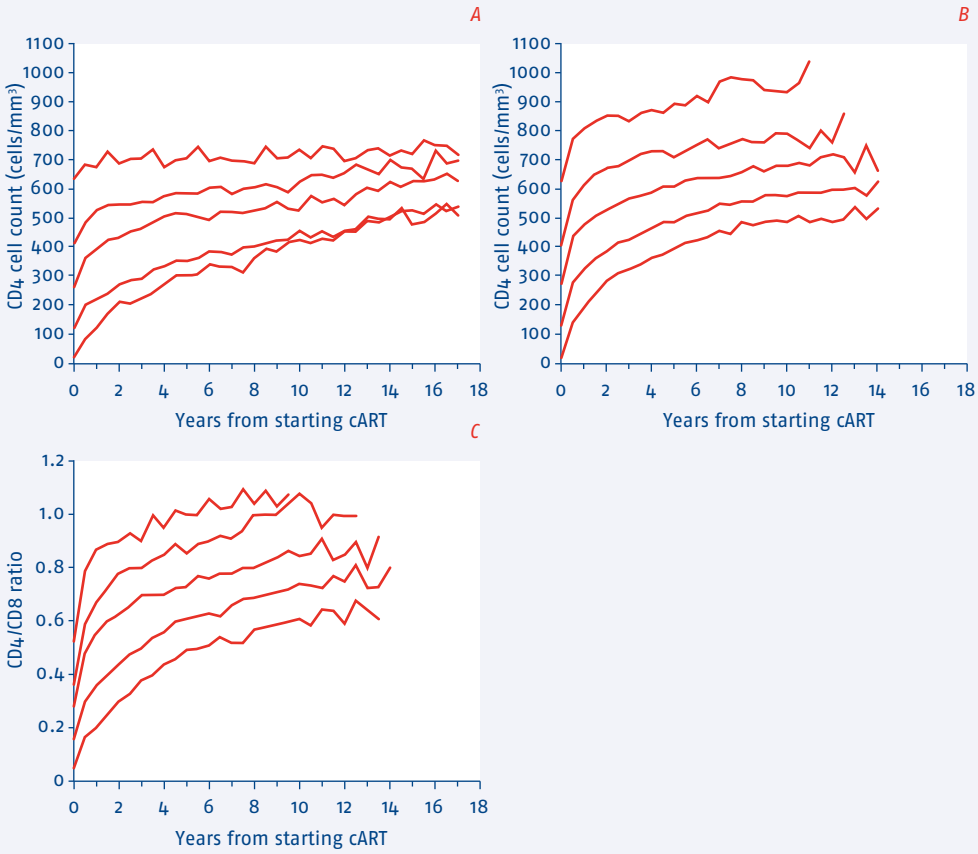
after starting cART (<500 HIV RNA copies/ml for ART-experienced individuals, <50 copies/ml for therapy-naive individuals) were included in further analyses. In this group, we studied CD4 cell count changes during continuous virologically suppressive cART (allowing for therapy interruptions of less than two weeks). In ART-experienced individuals, we excluded CD4 cell counts after a confirmed viral load >500 copies/ml, and, in ART-naive individuals, we excluded CD4 cell counts after a confirmed viral load >200 copies/ml. The different cut-offs for ART-experienced and ART-naive individuals were used because ART-experienced individuals had started cART in earlier calendar years and their plasma samples had therefore been tested predominantly with viral load assays with a lower detection limit of 400 copies/ml or higher. Finally, we also excluded CD4 cell counts after the start of immunosuppressive therapy (chemotherapy, interferon). Data on radiotherapy is not part of routine data collection. We thus obtained a stringently-selected group of individuals whose changes in CD4 cell count reflect the best possible response to cART, especially when cART was started without previous exposure to antiretroviral therapy.

In individuals who had had previous exposure to mono or dual antiretroviral therapy when cART was started, median CD4 cell counts at 16 years from the start of cART were 530 cells/mm^3 for those starting with <50 cells/mm^3, 560 cells/mm^3 for those starting between 50 and 200 cells/mm^3, 660 cells/mm^3 for those starting between 200 and 350 cells/mm^3, 710 cells/mm^3 for those starting between 350 and 500 cells/mm^3, and 710 cells/mm^3 for those starting with 500 or more cells/mm^3 (*Figure 2.4.A*). The CD4 trajectories for individuals starting with less than 50 cells/mm^3 and those starting with between 50 and 200 cells/mm^3 converged after approximately 12 years.

In ART-naive individuals, median CD4 counts at 11 years were 480 cells/mm^3 for individuals starting with <50 cells/mm^3, 580 cells/mm^3 for those starting between 50 and 200 cells/mm^3, 670 cells/mm^3 for those starting between 200 and 350 cells/mm^3, 730 cells/mm^3 for those starting between 350 and 500 cells/mm^3, and 1,030 cells/mm^3 for those starting with 500 or more cells/mm^3 (*Figure 2.4.B*). Although median CD4 cell counts fluctuated over time and did occasionally decrease, the trend over time reflects an increase in median CD4 cell counts in individuals remaining virologically suppressed on cART. Median CD4 cell counts for subgroups of individuals within each of the five categories of CD4 cell count at the start of cART did not converge.

Similar to the CD4 cell count response in ART-naive individuals, median CD4/CD8 ratios during sustained virological suppression on cART in the five baseline CD4 cell count strata did not seem to converge (*Figure 2.4.C*). 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 CD4 counts at the start were ≥500 cells/mm^3, and after 8 years when counts were 350-500 cells/mm^3.

Figure 2.4.A-C: Median CD4 count over time in antiretroviral therapy (ART)-experienced individuals (A) and ART-naive individuals (B), and CD4/CD8 ratio in ART-naive individuals (C), according to the CD4 count at the start of combination antiretroviral therapy (cART) (<50, 50-200, 200-350, 350-500 and ≥500 cells/mm³). Because plot A is limited to treatment-experienced individuals who started cART during calendar years when less sensitive viral load assays were used in routine clinical practice, different cut-offs were used in plot A compared to those in plots B and C. Trend lines stopped when the number of individuals in a subgroup dropped below 40 individuals.



Legend: cART=combination antiretroviral therapy.

Incomplete immunological recovery

Compared to a continued CD4 cell count recovery, incomplete CD4 cell count recovery during cART despite long-term successfully suppressed viral load is associated with an increased risk of mortality, AIDS, and non-AIDS-related diseases [23, 37, 38]. We therefore investigated the

CD4 cell count response in individuals who started cART with ≤350 cells/mm³, had not received prior monotherapy or dual therapy, and had sustained suppression of viraemia at two and three years. The CD4 cell counts between 1.5 and 2 years (closest to 2 years), and between 2.5 and 3 years (closest to 3 years) were selected. Median CD4 cell count at two years was 450 cells/mm³ (IQR 330-580) and at three years 480 (360-620). *Table 2.4* shows the distribution of CD4 cell counts in individuals at two and three years after starting cART, according to whether counts at the start of cART were <200 or 350 cells/mm³.

Table 2.4: *CD4 cell count at two and three years of continuous virologically successful cART in individuals starting cART with <200 and <350 CD4 cells/mm³. Therapy interruptions of less than 2 weeks were allowed. Virologically successful cART was defined as having supressed viral load of ≤100 copies/ml within nine months from starting cART and not having had a confirmed viral load of >200 copies/ml after initial suppression; single blips between 200 and 500 copies/ml were allowed.*

		CD4 cell count at start of cART (cells/mm³)		
		<200		<350
CD4 cell count at 2 / 3 years (cells/mm³)	2 years	3 years	2 years	3 years
<200	347 (14%)	160 (8%)	359 (7%)	169 (4%)
200–350	920 (36%)	650 (30%)	1,144 (22%)	796 (19%)
350–500	757 (30%)	690 (32%)	1,645 (31%)	1,262 (30%)
500–750	440 (17%)	507 (24%)	1,702 (33%)	1,558 (37%)
≥750	101 (4%)	126 (6%)	377 (7%)	463 (10%)
Total	2,565	2,133	5,227	4,248

Legend: *cART=combination antiretroviral therapy.*

At three years, 38% of individuals (820 out of 2,133 individuals) who started cART at <200 CD4 cells/ mm³ and 23% (965 out of 4,248 individuals) who started with <350 CD4 cells/mm³ still had values <350 cells/mm³, and thus remained at an increased risk of an AIDS or non-AIDS defining event.

Independent risk factors significantly associated with still having <350 CD4 cells/mm³ after three years of virologically suppressive cART when cART was started at <350 cells/mm³ were found to be older age, lower CD4 cell count at the start of cART, an HIV RNA <100,000 copies/ml at the start, place of birth being Sub-Saharan Africa, the Caribbean or South America in contrast to the Netherlands, and co-infection with hepatitis B (HBV) or hepatitis C (HCV) *(Table 2.5)*. There was a lower risk of incomplete immunological recovery when cART was started between 2007 and 2010 as compared to between 1999 and 2002, and when cART was initiated with a ritonavir-boosted PI regimen as compared to an NNRTI-based regimen.

Chapter 4 further describes an analysis of the potential association between incomplete CD4 cell count recovery and the risk of mortality, AIDS, and non-AIDS diseases.

Table 2.5: Adjusted odds ratios of the risk of incomplete immunological recovery <350 CD4 cells/mm³ after three years of continuous virologically successful combination antiretroviral therapy (cART) in individuals starting treatment at <350 CD4 cells/mm³.*

	OR (95% CI)	(Overall) p-value
Gender		
Male	1.00	
Female	0.48 (0.36-0.63)	<0.0001
Age (per 10 years older)	1.30 (1.19-1.42)	<0.0001
CD4 cell count at the start of cART (per 50 cells/mm³ increase)	0.52 (0.50-0.55)	<0.0001
Region of origin		(0.0002)
Netherlands	1.00	
Caribbean & South America	0.74 (0.55-0.99)	0.05
Sub-Saharan Africa	1.54 (1.15-2.07)	0.003
Western Europe / North America	0.82 (0.57-1.16)	0.21
HIV RNA at the start of cART (log_{10} copies/ml)		(<0.0001)
<4	1.15 (0.83-1.59)	0.41
4-5	1.00	
≥5	0.62 (0.51-0.75)	<0.0001
HBV at the start of cART		
HBsAg negative	1.00	
HBsAg positive	1.41 (1.01-1.98)	0.04
HCV at the start of cART		(0.001)
Negative	1.00	
HCV RNA positive	1.99 (1.28-3.11)	0.002
HCV Ab positive	1.70 (0.95-3.04)	0.08
Initial regimen		(0.15)
NNRTI	1.00	
PI	0.92 (0.58-1.45)	0.72
PI/r	0.77 (0.64-0.94)	0.01
3 NRTI	0.96 (0.53-1.76)	0.90
Other	0.93 (0.59-1.48)	0.77
Transmission risk group		(0.57)
MSM	1.00	
Heterosexual	1.05 (0.82-1.33)	0.70
IDU	1.62 (0.83-3.15)	0.16
Calendar year at the start of cART		(0.05)
1999-2002	1.41 (1.11-1.80)	0.005
2003-2006	1.21 (1.00-1.48)	0.05
2007-2010	1.00	
2011-2014	1.04 (0.72-1.51)	0.81

	OR (95% CI)	(Overall) p-value
Socio-economic status**		
1-2	1.04 (0.83-1.31)	0.72
3	1.00	
4-5	1.13 (0.92-1.38)	0.24

** Adjusted for all variables listed.*

*** Socio-economic status (SES): a combined measure based on income, employment, and level of education obtained by interviewing one household in each six-position postal code and aggregated into a single score for each four-position postal code using principal component analysis. Scores were classified in five groups such that they contained approximately 7%, 24%, 38%, 24%, and 7% of all postal codes; 1 indicates high SES and 5 indicates low SES [18].*

***Legend:** cART=combination antiretroviral therapy; OR=odds ratio; CI=confidence interval;3 NRTI=triple nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor; PI/r=ritonavir-boosted protease inhibitor; IDU=injecting drug user; HBV=hepatitis B virus; HCV=hepatitis C virus; HBsAg: hepatitis B surface antigen; Ab=antibody.*

The Efavirenz, Obesity Project Team on behalf of the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord assessed the virological and immunological responses to initial efavirenz-containing regimens according to weight in HIV-infected individuals[39]. Outcomes considered were time to first undetectable viral load (<50 HIV RNA copies/ml) after treatment initiation, time to a confirmed viral rebound (>50 HIV RNA copies/ml) after initial suppression, and difference from baseline CD4 cell count at 6 and 12 months on cART. Among 19,968 individuals, 81% attained virological suppression, of whom 34% subsequently experienced a viral rebound. In adjusted analyses no significant differences were found between heavier individuals compared to normal-weight individuals. Mean absolute counts at baseline and thereafter were higher among heavier individuals. However, the difference at 6 and 12 months compared to baseline was not significantly different from that of normal-weight individuals. These results suggest that the standard 600 mg efavirenz dosage is appropriate across a wide weight range.

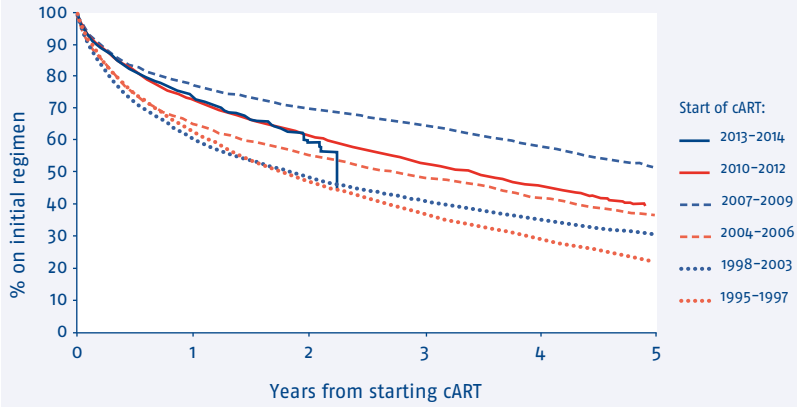
Therapy switches and incidence of toxicity-driven regimen change during the first three years after the start of cART

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[40-42]. In this section we report on trends over time in treatment switches and especially treatment-limiting toxicities during the first three years after the start of cART.

Discontinuation of the initial regimen

Of the 20,301 individuals who ever started cART, 13,427 discontinued the initial regimen. *Figure 2.5* reveals a trend over time towards a longer interval before discontinuing the initial cART regimen until 2007-2009. A lower percentage of individuals starting cART in or after 2010 were still on their initial regimen three years after starting cART, compared to those who started cART between 2007 and 2009. The percentage of individuals still on the initial cART regimen two years after starting was 47% for those starting in 1995-1997, 48% in 1998-2003, 55% in 2004-2006, 70% in 2007-2009, 61% in 2010-2012, and 59% for those starting in 2013 or 2014. These figures may reflect increased rates of substitutions or switches to non-standard regimens in recent years due to the recent availability of well tolerated once-daily drugs[43].

Figure 2.5: *Kaplan–Meier estimates of the percentage of individuals remaining on their 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.*



Legend: *cART=combination antiretroviral therapy.*

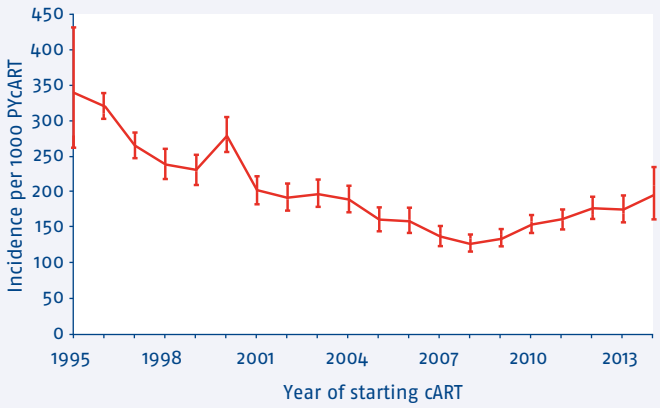
Toxicity-driven therapy changes

As toxicity is the most common reason for discontinuing not only the first regimen but also subsequent regimens, we will focus further on trends over time in toxicity-driven therapy changes during the first three years of cART. These changes are importantly influenced by the extent to which, over time, less toxic alternatives have become available to replace regimen components associated with particular toxicities.

During the first three years after the start of cART, individuals were followed for a total of 48,952 person years (PY), of which 47,772 person years (97.6%) on cART (PYcART). The overall

incidence of toxicity-driven regimen changes was 194 (95% CI 190-198) per 1000 PYcART. Individuals could change the regimen more than once. During follow up, 14,155 of the 20,301 individuals (70.0%) did not change the regimen because of toxicity. The maximum number of changes due to toxicity in a single patient was 14.

Figure 2.6: *Toxicity-driven changes in therapy during the first three years after the start of combination antiretroviral therapy (cART) presented as incidence per 1000 person years on cART for each starting year of cART (blue line; vertical lines are 95% Poisson confidence intervals).*



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

The incidence of toxicity-driven therapy changes was highest (494 per 1000 PYcART) during the first three months after the start of cART, thereafter declining to 218 per 1000 PYcART between 3 and 6 months, 173 per 1000 PYcART between 6 and 12 months, 149 per 1000 PYcART between 12 and 24 months, and 128 per 1000 PYcART between 24 and 36 months ($p<0.0001$). The incidence of toxicity-driven therapy changes during the first three years following cART initiation declined from 2000 to 2008 (*Figure 2.6*). The subsequent increase from 2009 onwards can be largely attributed to the introduction of new medications associated with minimal toxicity that offered more options to switch to a regimen with fewer toxicities than the older regimens and to individuals starting in or after 2013 who have not yet been in follow up for three years. The risk of a toxicity-driven therapy change in individuals is highest in the initial few months after first starting cART and decreases with a longer time on cART.

In an adjusted Poisson regression analysis of the risk of a toxicity-driven therapy change during the first three years after the start of cART, the risk was 23% higher in women than in men, independent of weight at the start of cART ($p<0.0001$, *Appendix Table 2.1*). Starting cART at ≥500 CD4 cells/mm^3 was associated with a 28% increased risk, compared to starting

at 350-500 cells/mm^3 (p=0.0002). Independent of CD4 cell count at the start, initiation of cART during primary infection was also associated with an increased risk (risk ratio [RR] 1.25, 95% CI 1.09-1.42, p=0.001). Individuals with a previous toxicity-driven therapy change had an increased risk of another toxicity-driven therapy change compared to those without a previous change, presumably because of unmeasured characteristics that put them at higher risk of toxicity. After adjustment for duration of follow up after starting cART, the risk of toxicity-driven therapy change was lower in individuals starting in 2014 compared to those who started in 2009 (RR 0.73, 95%CI 0.59-0.90, p=0.003). Finally, transmission risk group (p=0.40), age (p=0.42) and weight at the start of cART (p=0.15) were not significantly associated with a toxicity-driven therapy change.

We have shown that, although the incidence of toxicity-driven therapy changes declined up to 2008, toxicity remained the major reason for regimen change. In the next paragraph we give an overview of patterns of the most frequently-recorded adverse events associated with these therapy changes.

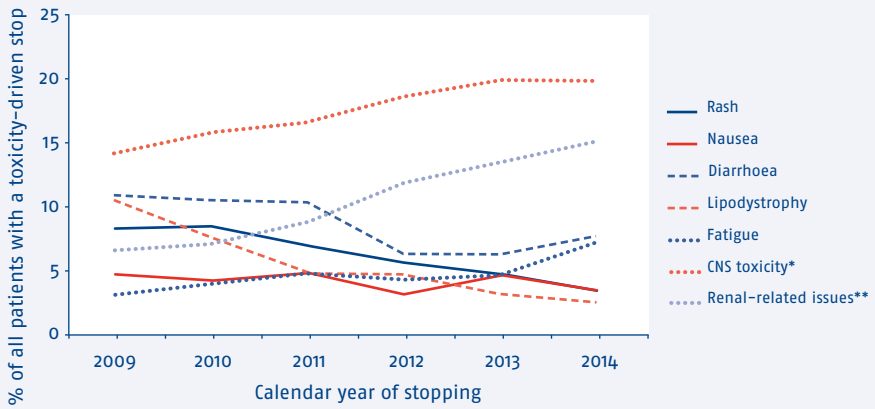
Adverse events associated with a toxicity-driven therapy change

Appendix Table 2.2 provides an overview of adverse events associated with a toxicity-driven therapy change. Although stable between 2008 and 2011, the absolute number of individuals with at least one toxicity-driven therapy change increased to 1,349 in 2012 and 1,376 in 2013, while the figure for 2014 (currently 1,079) is also expected to rise to a similar number once data for 2014 is complete. In addition to an increasing number of individuals on cART over time, the availability of new drugs associated with less toxicity has probably driven the increase during the last three years.

Figure 2.7 shows the change in distribution of the seven most frequently-registered adverse events associated with a regimen change over time. Central nervous system (CNS) toxicity was the type of adverse event most frequently associated with a toxicity-driven therapy change. The percentage of CNS toxicity-driven stops increased from 14% (142 out of 1,001 individuals with a toxicity-driven therapy stop) in 2009 to 20% (488 out of 2,455 individuals) in 2013 and 2014 combined. Among those 488 individuals, 448 (92%) stopped using efavirenz due to CNS toxicity. Of the 440 individuals (98%) who subsequently switched to another cART regimen, 54% switched to rilpivirine, 16% to nevirapine, 14% to a regimen including an integrase inhibitor, 10% to ritonavir-boosted darunavir, and 5% to ritonavir-boosted atazanavir.

There was also a relative increase in treatment changes because of renal-related issues over time, which accounted for 16% of all toxicity-driven therapy changes in 2014. Most of the discontinuations in 2014 involved tenofovir (79% of cases, either as a single drug or as part of fixed-dose combinations) or lamivudine (16% of cases). The new regimen was most likely to contain abacavir/lamivudine (76% of cases who stopped tenofovir). Finally, the percentage of changes because of rash and lipodystrophy declined over time.

Figure 2.7: 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 combination antiretroviral therapy (cART) regimen. For every toxicity-driven therapy change, one to three adverse events can be recorded; therefore, percentages do not add up to 100%.



** Central nervous system (CNS) toxicity includes the following adverse events in the database: dizziness, sleeplessness, nightmares, mood changes, concentration disorders, and confusion.*

*** Renal-related issues include the following adverse events recorded in the database: elevated creatinine, renal insufficiency, proteinuria, and dialysis.*

Status of HIV-infected individuals currently known to be in care

Of the 20,301 individuals who ever started cART, 2,074 died during follow up and another 1,746 did not have a clinical visit in or after January 2014. The clinical status of the remaining 16,481 individuals is described in this section. *Table 2.6* shows the current status of these 16,481 individuals in terms of treatment and clinical characteristics. *Appendix Table 2.3* shows the current status according to demographic characteristics. Among individuals alive and in follow up, for those who had started cART between 1995-2001, 2002-2007, and 2008-2013, the percentage currently not on a cART regimen was 3.3%, 2.4%, and 1.2%, respectively. The majority of these individuals are currently on an NNRTI-based regimen, whereas most individuals who started in 2014 are now on an integrase inhibitor-based regimen. Of those individuals who started cART between 1995 and 2013, 90% to 92% currently have a suppressed viral load <50 copies/ml. The number of individuals who first started cART in 2014 is, at present, only 68% because not all have yet reached initial virological suppression. The percentage of individuals with a viral load <50 copies/ml was higher among men, MSM, and individuals originating from the Netherlands, Western Europe, and North America compared to those from Sub-Saharan Africa, the Caribbean, and South America. Median current CD4 cell count was higher for those who had started cART in earlier calendar years, while the

CD4/CD8 ratio was similar for those who had started cART between 1995 and 2001, 2002 and 2007, and 2008-2013. Current CD4 cell count and current CD4/CD8 ratio were higher in women.

Table 2.6: Treatment and clinical characteristics of 16,481 individuals currently in follow up.

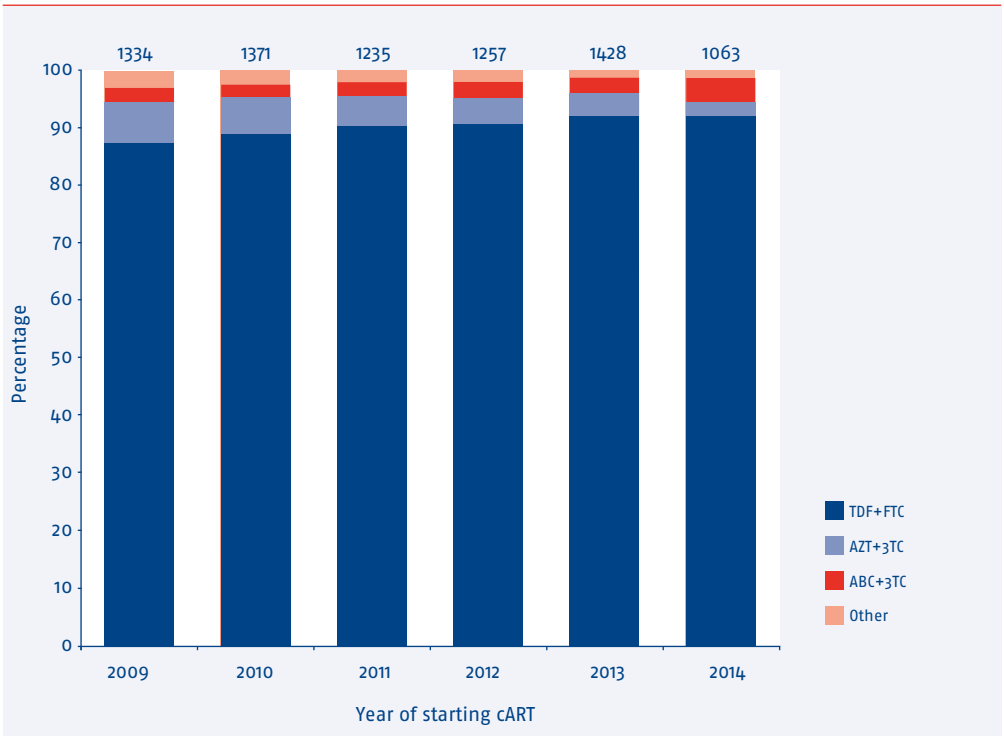
	Year start cART							
	1995–2001		2002–2007		2008–2013		2014	
	n	%	n	%	n	%	n	%
Total (n, %)	4,118	100.0	4,098	100.0	7,210	100.0	1,055	100.0
Current regimen								
Not on ART	62	0.5	23	0.6	29	0.4	17	1.6
Mono/dual	116	2.8	74	1.8	56	0.8	3	0.3
NNRTI	2,068	50.2	2,410	58.8	4,269	59.2	332	31.5
NNRTI+integrase	81	2.0	23	0.6	22	0.3	1	0.1
PI	977	23.7	1,097	26.8	2,021	28.0	196	18.6
PI+integrase	195	4.7	67	1.6	69	1.0	9	0.9
NRTI+integrase	269	6.5	276	6.7	594	8.2	491	46.5
other	350	8.5	74	1.8	36	0.5	6	0.6
HIV RNA <50 copies/ml	3,761	91.3	3,684	89.9	6,558	91.0	714	67.7
Ever AIDS diagnosis	1,524	37.0	1,223	29.8	1,209	16.8	121	11.5
	Median	IQR	Median	IQR	Median	IQR	Median	IQR
Age on 1 May 2015	54	49–60	49	42–55	45	37–52	41	32–49
Last CD4 cell count (cells/mm^3)	660	480–870	620	466–803	610	460–780	550	390–720
Last CD8 cell count (cells/mm^3)	865	630–1,180	829	600–1,120	850	630–1,130	990	730–1,330
Last CD4/CD8 ratio	0.75	0.50–1.05	0.73	0.50–1.00	0.70	0.50–1.00	0.51	0.35–0.78

Legend: *ART=antiretroviral therapy; NNRTI=non-nucleoside reverse transcriptase inhibitors; PI=protease inhibitors; NRTI=nucleoside reverse transcriptase inhibitors.*

Initial cART regimens between 2009 and 2014

Figure 2.8 provides an overview of the initial cART components used between 2009 and 2014. In 2014, the combination of tenofovir and emtricitabine was used in 982 of the 1,063 initial cART regimens (92%). The fixed-dose combination of abacavir and lamivudine (ABC+3TC), which according to current guidelines may be used as a starting regimen in individuals with <100,000 HIV RNA copies/ml, was used in only 44 (4%) of the initial regimens in 2014.

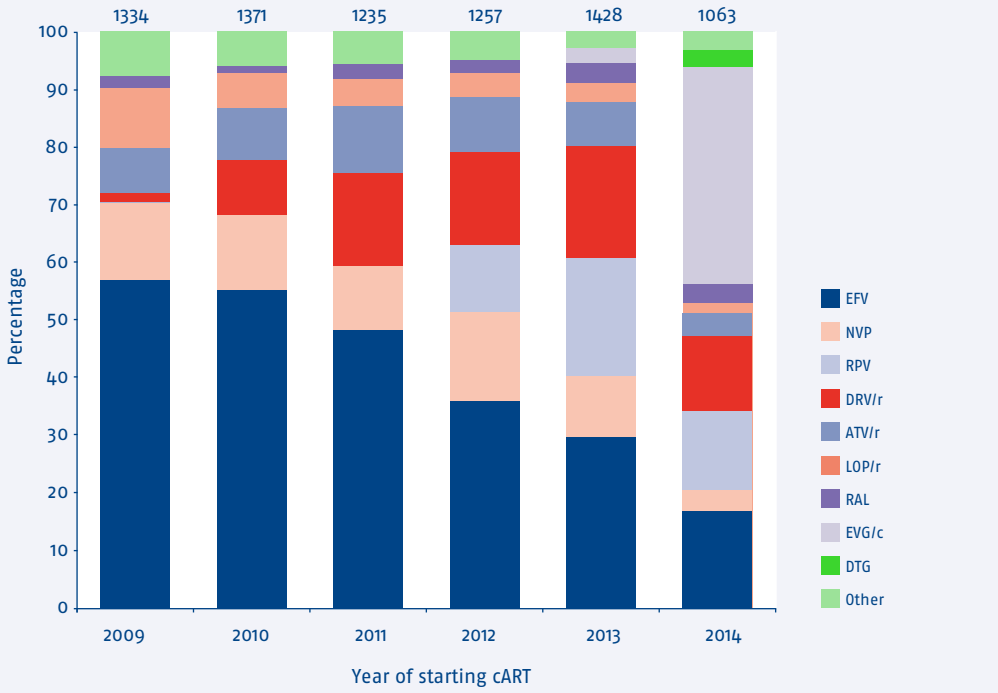
Figure 2.8: *Trends in the use of initial combination antiretroviral therapy (cART) NRTI backbones.*



Legend: *cART=combination antiretroviral therapy; TDF=tenofovir; FTC=emtricitabine; AZT=zidovudine; 3TC=lamivudine; ABC=abacavir.*

Figure 2.9 shows the trends over time in third-drug additions to the NRTI backbone used as part of the initial cART regimen. In particular, the use of efavirenz as third drug to the NRTI backbone has declined from 57% of all starting regimens in 2009 to 17% in 2014. Moreover, in 2014, the most frequently-used third drug was cobicistat-boosted elvitegravir in 395 (37%) out of 1,063 starting regimens.

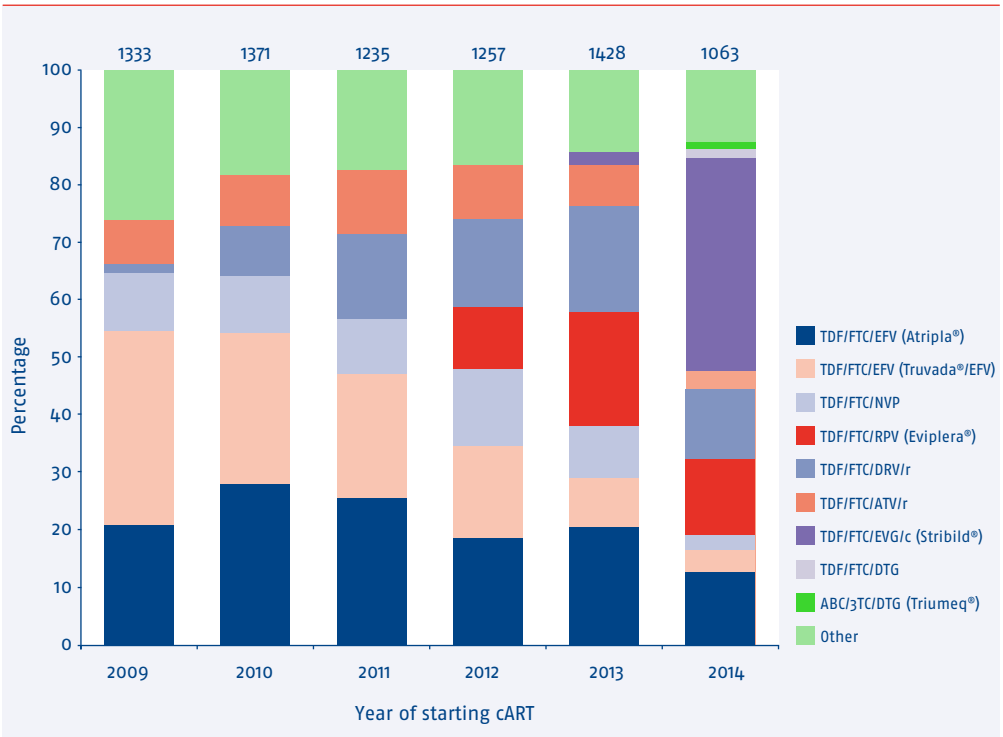
Figure 2.9: Trends in the use of additions to the NRTI backbone as part of initial combination antiretroviral therapy (cART) regimens.



Legend: *cART=combination antiretroviral therapy; EFV=efavirenz; NVP=nevirapine; RPV=rilpivirine; DRV/r=darunavir plus ritonavir; ATV/r=atazanavir plus ritonavir; LOP/r=ritonavir boosted lopinavir; RAL=raltegravir; EVG/c=elvitegravir/cobicistat; DTG=dolutegravir.*

Figure 2.10 shows that the fixed-dose single-tablet regimen of tenofovir plus emtricitabine plus cobicistat-boosted elvitegravir (Stribild®) has been increasingly chosen (in 37% of all starting regimens in 2014) instead of the fixed-dose single-tablet regimen of tenofovir plus emtricitabine plus efavirenz (Atripla®) (13%), tenofovir and emtricitabine plus efavirenz (3%), fixed-dose single-tablet regimen of tenofovir and emtricitabine plus rilpivirine (Eviplera®)(13%), tenofovir and emtricitabine plus darunavir/ritonavir (12%), tenofovir and emtricitabine plus nevirapine (3%), or tenofovir and emtricitabine plus atazanavir/ritonavir (3%). Finally, the integrase inhibitor raltegravir, not recommended in starting regimens because it needs to be taken as part of a twice-daily regimen, has been used in only 4% of starting regimens since 2009. *Appendix Table 2.4* shows a more comprehensive overview of the most frequently-used initial cART regimens in 2009-2014. Patterns in the choice of initial cART over time in the Netherlands have previously been shown to follow treatment guidelines[44].

Figure 2.10: Trends in initial combination antiretroviral therapy (cART) regimens. Eviplera®, Stribild®, and Triumeq® were added to the Netherlands drug reimbursement system in June 2012, December 2013, and November 2014, respectively.



Legend: *cART=combination antiretroviral therapy; TDF=tenofovir; FTC=emtricitabine; EFV=efavirenz; NVP=nevirapine; RPV=rilpivirine; DRV/r=darunavir plus ritonavir; ATV/r=atazanavir plus ritonavir; RAL=raltegravir; EVG/c=elvitegravir/cobicistat; DTG=dolutegravir; ABC=abacavir; 3TC=lamivudine.*

We analysed the short-term virological efficacy and durability of initial cART regimens in individuals who started cART on one of the regimens recommended in or after 2014, provided there was a sufficient number of individuals starting on these regimens. We thus selected 5,555 individuals who started in or after 2009 on one of the following five regimens: tenofovir and emtricitabine plus a third drug, specifically, efavirenz, rilpivirine, elvitegravir/cobicistat, darunavir/ritonavir or atazanavir/ritonavir.

Initial virological suppression

To compare the initial virological response between the above-mentioned starting regimens, we selected 4,257 individuals out of the 5,555 individuals who were not pregnant at the start of cART, were not participants in the primo-SHM study, and had an HIV RNA result available both at the start of cART and between three and nine months after the start of treatment. When cART was started at <100,000 HIV RNA copies/ml, there were no significant differences in the percentage of individuals with initial virological success (*Table 2.7*). However, when cART was started at ≥100,000 HIV RNA copies/ml, the percentage of individuals with virological success was lower with atazanavir/ritonavir as compared to those with efavirenz (p=0.03) or elvitegravir plus cobicistat (p=0.02).

Table 2.7: Initial virological suppression to <100 copies/ml in a subgroup of individuals starting combination antiretroviral therapy (cART) from 2009 onwards using one of the regimens recommended in or after 2014.

Third drug alongside tenofovir and emtricitabine	HIV RNA at start cART <100,000 copies/ml: Initial virological success / total starting	% virological success	p-value*	HIV RNA at start cART ≥100,000 copies/ml: Initial virological success / total starting	% virological success	p-value*
efavirenz	1,334/1,359	98.2	1.00	968/1,035	93.5	1.00
rilpivirine	382/393	97.2	0.24	Not recommended		
darunavir/ritonavir	299/306	97.7	0.61	389/426	91.3	0.66
atazanavir/ritonavir	222/230	96.5	0.11	209/235	88.9	0.03
elvitegravir/cobicistat	159/163	97.5	0.59	77/80	96.2	0.15

** p-values after each third drug reflect the probability that the proportion of individuals with initial virological success differs from that seen with efavirenz, obtained by logistic regression analysis. Because of the high proportion of individuals with virological success, models were only adjusted for log_{10} transformed HIV RNA at the start of cART.*

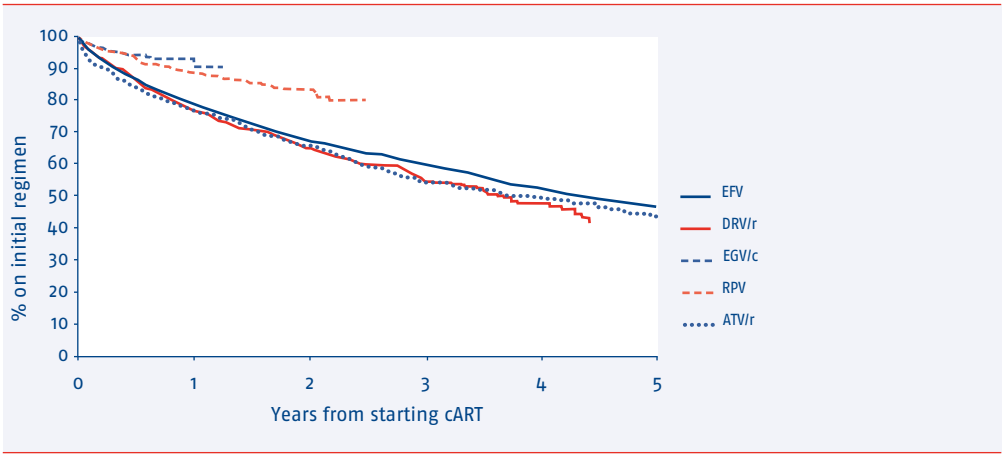
***Legend:** cART=combination antiretroviral therapy.*

Discontinuation of the initial regimen

In the subset of 5,555 individuals starting cART in or after 2009 with tenofovir plus emtricitabine plus either a third drug (efavirenz, rilpivirine, atazanavir/ritonavir, darunavir/ritonavir, or elvitegravir/cobicistat), a significantly higher proportion of individuals starting on tenofovir and emtricitabine plus rilpivirine continued on the regimen compared to those whose regimen included efavirenz, darunavir/ritonavir or atazanavir plus ritonavir (all p-values <0.0001). Although the duration of follow up for those starting on tenofovir and emtricitabine plus elvitegravir/cobicistat was still relatively short, a significantly higher proportion of individuals also continued on this regimen compared to those whose regimen included efavirenz (p<0.0001). As rilpivirine has only been available in the Netherlands

since 2012 and elvitegravir/cobicistat has been available since 2014, follow up for these regimens is shorter than for the other three regimens. Time to discontinuation was not significantly different between regimens containing efavirenz, darunavir/ritonavir, or atazanavir/ritonavir and those including rilpivirine or elvitegravir/cobicistat (*Figure 2.11*).

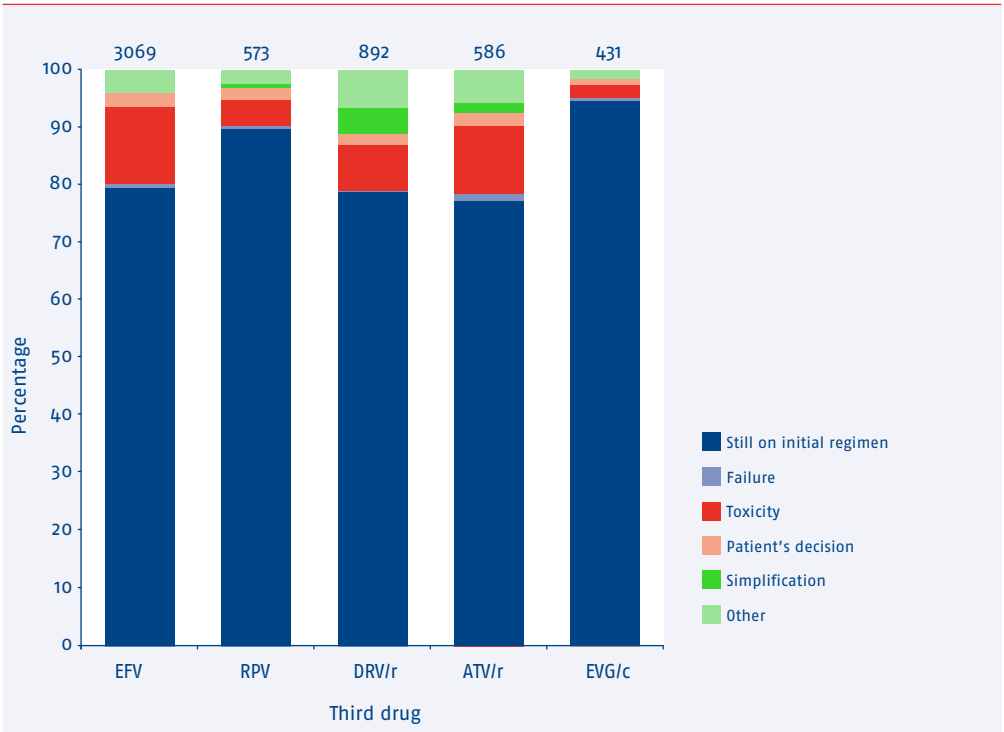
***Figure 2.11:** Kaplan–Meier estimates of the percentage of individuals remaining on their initial combination antiretroviral therapy (cART) regimen according to cART regimen in individuals starting in or after 2009 on tenofovir and emtricitabine plus a third drug (starting regimens currently recommended or recommended during 2014). 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.*



***Legend:** cART=combination antiretroviral therapy; ATV/r=atazanavir plus ritonavir; DRV/r=darunavir plus ritonavir; EFV=efavirenz; RPV=rilpivirine; EGV/c=elvitegravir/cobicistat.*

Overall, 1,034 of 5,555 individuals discontinued the initial regimen within 1 year. The most common reasons for discontinuing were: toxicity (58%), patient request (10%), and simplification (6%). *Figure 2.12* shows the distribution of reasons for discontinuation of the various third-drug additions to the tenofovir and emtricitabine NRTI backbone. The high proportion of individuals still on the initial regimen among those who had started using rilpivirine and elvitegravir/cobicistat is partly because, compared to the other regimens, a higher proportion of individuals have not yet had one year of follow up.

Figure 2.12: Relative distributions of reasons for stopping or switching at least one of the drugs in the regimen within one year of cART initiation, according to the third drug in addition to tenofovir and emtricitabine. (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], problems with adherence and unknown reasons).



***Legend:** ATV/r=atazanavir plus ritonavir; DRV/r=darunavir plus ritonavir; EFV=efavirenz; RPV=rilpivirine; EVG/c=elvitegravir/cobicistat.*

In those individuals who discontinued one of the five initial cART regimens within one year, the main reason for stopping was toxicity. Another reason for stopping one or more drugs in a high percentage of individuals on tenofovir and emtricitabine plus darunavir/ritonavir was simplification (22% of discontinuations within one year of starting cART); most of these individuals switched to a fixed-dose single-tablet regimen of tenofovir and emtricitabine plus rilpivirine (68%) or tenofovir and emtricitabine plus efavirenz (24%).

In an adjusted Cox regression analysis of time to a toxicity-driven therapy change restricted to individuals starting cART in or after 2009 on a combination of tenofovir and emtricitabine

with either efavirenz, rilpivirine, atazanavir/ritonavir, darunavir/ritonavir, or elvitegravir/cobicistat, the cause-specific hazard of a toxicity-driven regimen change was significantly lower when cART included rilpivirine or elvitegravir/cobicistat (hazard ratio [HR] compared to efavirenz, darunavir/ritonavir, or atazanavir/ritonavir (all p-values<0.0001).

Summary and conclusion

cART is currently recommended for all HIV-infected individuals. The CD4 cell count at which cART is initiated in the Netherlands has increased steadily since 2007, reaching a median of 370 cells/mm^3 in 2013 and 410 cells/mm^3 in 2014.

The combination of tenofovir and emtricitabine was used in 92% of all starting regimens in 2014, and the most frequently-used initial cART regimen in the Netherlands was tenofovir and emtricitabine plus elvitegravir/cobicistat (in 37% of starting regimens in 2014), which was added to the Netherlands drug reimbursement system in December 2013. Other frequently-used starting regimens in 2014 were tenofovir and emtricitabine, combined with efavirenz (16%), rilpivirine (13%), darunavir/ritonavir (12%), nevirapine, (3%), or atazanavir/ritonavir (3%). As dolutegravir in combination with abacavir plus lamivudine (as a single-tablet fixed-dose combination regimen) was added to the Netherlands drug reimbursement system only in December 2014, the percentage of individuals starting on this regimen in 2014 was small, but it is likely to increase in 2015.

Virological response

Of all individuals who started cART on one of the regimens recommended in or after 2014 and who had an available plasma HIV RNA sample taken between three and nine months after starting cART, 95.3% had initial virological success (HIV RNA <100 copies/ml between 3 and 9 months). The probability of initial virological success was higher when the viral load at the start of cART was <100,000 copies/ml. There were no significant differences in the probability of initial success between tenofovir and emtricitabine plus efavirenz, compared to the more recently-introduced combinations of tenofovir and emtricitabine plus rilpivirine, tenofovir and emtricitabine plus ritonavir-boosted darunavir, tenofovir and emtricitabine plus ritonavir-boosted atazanavir, and tenofovir and emtricitabine plus cobicistat-boosted elvitegravir, except when tenofovir and emtricitabine plus ritonavir-boosted atazanavir was started at 100,000 HIV RNA copies/ml or more. As these results were obtained by observational data, residual confounding may play a role, and thus, these findings need to be interpreted with caution. Ensuring rapid 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 increases in CD4 cell count, higher probability of treatment failure, and emergence of drug resistance. The probability of initial virological success was lower in younger individuals (<30 years of age), in individuals infected through heterosexual transmission (compared with homosexual transmission), in those born in Sub-Saharan Africa compared with those born in the Netherlands and in those who started cART in or after 2007 with a CD4 cell count lower than 200 cells/mm^3. Conversely, the

probability of initial viral success was higher when the viral load at the start was lower and when an integrase inhibitor was included in the initial regimen.

Immunological response

A timely start of cART is important because, on average, CD4 cell counts approach those seen in the general population after eight years of virologically suppressive cART only if cART is started at ≥350 CD4 cells/mm^3. In individuals who started cART at CD4 cell counts <200 cells/mm^3 or <350 cells/mm^3, 38% and 23% still had CD4 cell counts <350 cells/mm^3 at three years of treatment, respectively, despite virologically successful cART, and thus remained at an increased risk of AIDS and non-AIDS morbidity.

Similar to CD4 cell count changes, normalisation of the CD4/CD8 ratio towards one or above seems to be strongly related to the CD4 cell count at the start of cART. With a starting CD4 cell count ≥500 cells/mm^3, the median CD4/CD8 ratio exceeded 1 after three and a half years of suppressive cART, and with a starting CD4 cell count between 350 and 500 cells/mm^3, median CD4/CD8 ratio exceeded 1 one after eight years. However, individuals with starting CD4 cell counts below 350 cells/mm^3 failed to achieve median CD4/CD8 ratios greater than 1 during follow up. Lower CD4/CD8 ratios have been suggested to be associated with increased immune activation markers during sustained viral suppression[45], non-AIDS-related events[26], and subclinical atherosclerosis[27]. If the clinical significance of these findings is confirmed by larger cohorts, then the findings in this report provide further evidence of the need to start cART at high CD4 cell counts.

Durability and toxicity

Lifelong use of ART requires tolerable and durable regimens. Approximately 50% of individuals currently starting cART are able to remain on their first-line regimen for more than three years. The main reason for changing treatment remains toxicity, although the incidence of toxicity-driven therapy changes has dramatically declined since the introduction of cART. The risk of a toxicity-driven therapy change in those starting cART in or after 2009 was higher in women, when cART was started at CD4 cell counts ≥500 cells/mm^3, and when cART was started during primary infection, independent of CD4 cell count. Among those individuals switching therapy due to toxicity, the most frequently recorded adverse event in 2014 was CNS toxicity, which led to substitution of efavirenz with rilpivirine in many individuals. As the result of the availability of rilpivirine, it is likely that more individuals with only minor CNS toxicity on efavirenz are now switching to rilpivirine, while previously these individuals would have continued on efavirenz. The newer combinations of tenofovir and emtricitabine plus either rilpivirine or cobicistat-boosted elvitegravir are currently associated with lower rates of substitution when used as initial regimens. As the need for better tolerated drugs and more individualised strategies for patient management continue, the availability of new drugs such as rilpivirine, dolutegravir, and elvitegravir is likely to contribute to further improvements in the durability of cART regimens.

3. Virological failure and resistance

Ard van Sighem, Luuk Gras, Anne Wensing, Jan Prins, Kees Brinkman and 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[46]. Moreover, 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. Monitoring of longer-term virological response is, therefore, of importance as high-level viraemia has been associated with a poorer clinical outcome and smaller increases in CD4 cell count[21, 22, 47-49]. In addition, frequent or persistent periods of low-level viraemia have been reported to be associated with the emergence of drug resistance and treatment failure[50, 51].

Here we report on the long-term virological response in antiretroviral therapy-naive patients starting cART from 1999 onwards whose short-term response is described in the preceding chapter. We also look at the presence of resistance in the total treated HIV-infected population followed by Stichting HIV Monitoring (SHM) and the extent to which resistant virus strains are transmitted to uninfected individuals.

Virological failure

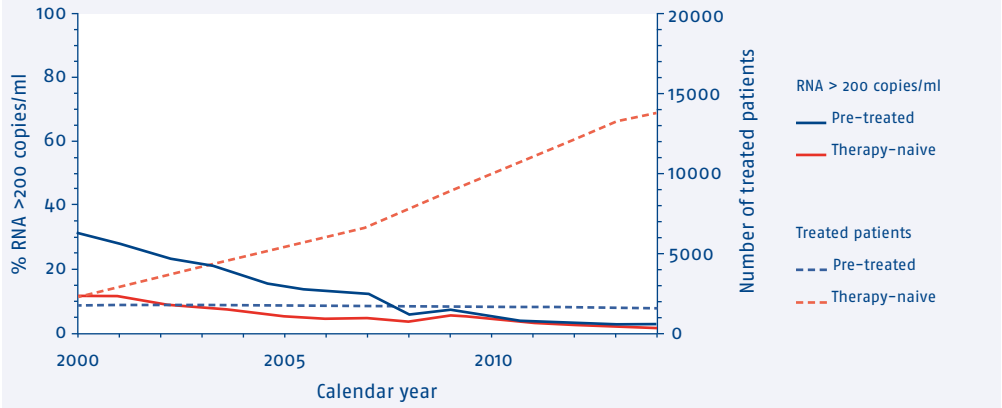
Low-level viraemia

After having achieved initial virological suppression, more than 30% of patients on cART experience episodes of viraemia[47]. Often, these episodes are limited to a single measurement above the quantification limit of the viral-load assay, so-called blips[52, 53]. However, the clinical significance of infrequent low-level viraemia remains less clear. Short-term low-level viraemia is not associated with AIDS, non-AIDS-defining events, death, or CD4 cell count response[47, 54-57]. Although short-term low-level viraemia is assay-dependent[58] and more frequently detected by new assays with a lower limit of detection[59, 60], resistance-associated mutations have also been found in patients with plasma viral-load levels below 50 copies/ml[51, 61]. In addition, even at plasma viral-load levels below 50 copies/ml, patients with low, but detectable, levels had a lower probability of sustained viral suppression than patients with completely undetectable viral loads[62].

Less virological failure

To minimise the effect of blips and of the new quantification assay, we used a viral-load threshold of 200 copies/ml as a marker of virological failure[15]. Since 2000, the annual proportion of patients with a viral load above 200 copies/ml has decreased to approximately 3%. During the same time, the difference between patients pre-treated with monotherapy or dual therapy and those starting cART while antiretroviral therapy-naive has disappeared (*Figure 3.1; Appendix Figure 3.1*). From 2008 onwards, approximately equal proportions of patients in these two groups experienced a viral load above 200 copies/ml, 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.

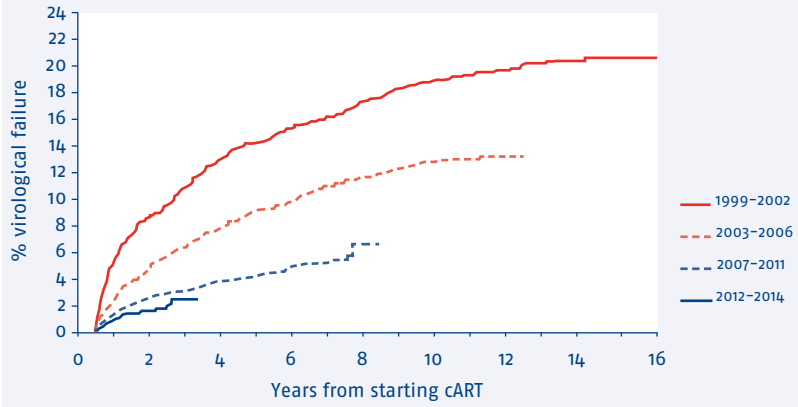
Figure 3.1: *Annual number of treated patients with a viral-load measurement while on treatment (dashed lines), and the proportion of patients with virological failure (solid lines) (i.e., a viral load above 200 copies/ml while on treatment and measured at least four months after start of cART or four months after resuming treatment following a treatment interruption). Among approximately 1,700 pre-treated patients, the proportion with failure by a threshold of 200 copies/ml decreased from 32% in 2000 to 3% in 2014. Among previously therapy-naive patients, virological failure was less common and decreased from 11% to 2% during the same period, while the number of such patients increased from 2,365 to 13,730.*



Virological failure was defined as time to the first of two consecutive plasma viral HIV RNA levels above 200 copies/ml after 24 weeks on antiretroviral therapy, as defined in the US Department of Health and Human Services (DHHS) guidelines[15]. cART interruptions shorter than two weeks did not count as interruptions. In total, 969 (7.2%) out of 13,524 treatment-naive patients who started cART from 1999 onwards met the definition of virological failure.

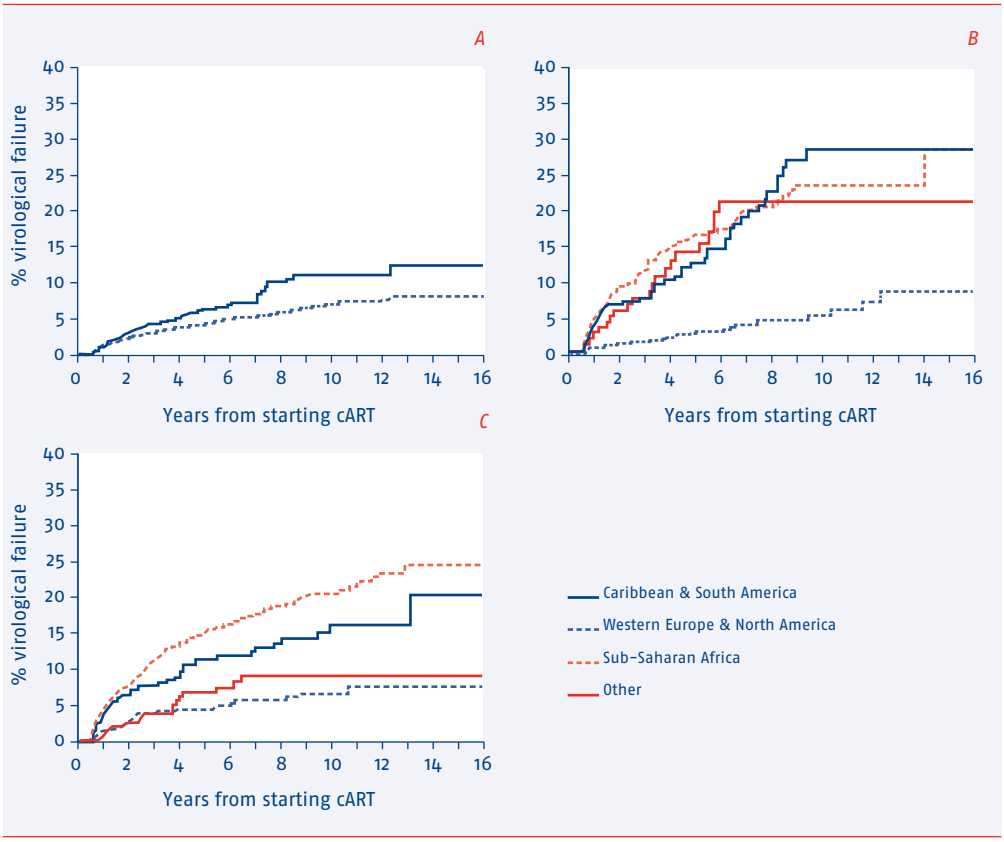
The Kaplan–Meier estimate of the percentage of patients with virological failure within 15 years after first starting cART was 13% (95% confidence interval [CI] 12-14%). The probability of virological failure was lower when cART was started during later calendar-year periods. The probability of failure at three years after starting cART was 11.0% when cART was started between 1999 and 2002, 6.6% when cART was started between 2003 and 2006, 3.1% when cART was started between 2007 and 2010, and 2.5% when cART was started in or after 2012 (*Figure 3.2*, p<0.0001). Men who have sex with men (MSM) from Western Europe (including the Netherlands) and North America were significantly less likely to experience virological failure than those from the Caribbean/South America (*Figure 3.3.A*, overall log rank p=0.007). Among heterosexuals, differences in the risk of failure were more pronounced. The risk was higher among heterosexual men from Sub-Saharan Africa and the Caribbean/South America than among those from Western Europe/North America (middle plot in *Figure 3.3.B*, overall log rank p<0.0001). Although less pronounced than in heterosexual men, the risk was also higher in women from Sub-Saharan Africa, the Caribbean and South America compared to those from Western Europe and North America (*Figure 3.3.C*, overall log rank p<0.0001).

Figure 3.2: *Kaplan–Meier estimates of the percentage of patients with virological failure according to calendar period of starting combination antiretroviral therapy (cART).*



Legend: *cART=combination antiretroviral therapy.*

Figure 3.3: Kaplan–Meier estimates of the percentage and 95% confidence intervals of patients with virological failure according to transmission risk group (A: men who have sex with men [MSM], B: heterosexual men, and C: heterosexual women) and region of origin. No lines are shown for the subgroups of MSM from Sub-Saharan Africa and other regions of origin because of limited numbers of individuals.



Legend: cART=combination antiretroviral therapy.

In adjusted analyses, the risk of failure decreased with later calendar years of starting cART (*Table 3.1*). This is likely to be a reflection of changes in HIV care and cART regimens over time. The risk of virological failure was higher in individuals less than 30 years of age at the start of cART. Those with higher viral load at the start and those starting with CD4 cell counts below 200 cells/mm^3 had an increased risk of failure compared with those

with higher CD4 cell counts. There was no significant difference in risk between starting at 350-500 CD4 cells/mm^3 and starting at 500 CD4 cells/mm^3 or more (p=0.36). There was no evidence that virological failure was more likely when cART was started during primary infection (p=0.97); however, it should be noted that time was censored when individuals interrupted cART for longer than two weeks. There was evidence that the risk of failure according to region of origin was different in patients who had started cART before and after 2012 (test for interaction, p=0.02). When cART was started before 2012, the risk of failure in individuals born in the Caribbean or South America was significantly higher than in those born in Western countries (hazard ratio [HR] 1.89, 95% CI 1.55-2.31), but not when cART was started in or after 2012 (HR 1.17, 95% CI 0.44-3.06). In contrast, the risk of failure in individuals born in Sub-Saharan Africa remained significantly increased compared to the risk in those born in Western countries, both when cART was started before 2012 (HR 2.40, 95% CI 1.97-2.92) and in or after 2012 (HR 2.59, 95% CI 1.25-5-36). Finally, there was insufficient statistical power to compare time to virological failure between currently-recommended initial cART regimens.

Table 3.1: Adjusted hazard ratios (95% confidence intervals) of time to virological failure. Time to virological failure is shorter compared to the reference group when the hazard ratio is higher than 1.00.*

	HR (95% CI)	(Overall) p-value
Risk group		(0.03)
MSM	1.00	
Heterosexual men	1.17 (0.96-1.43)	0.11
Heterosexual women	1.26 (1.03-1.54)	0.007
Region of origin		(<0.0001)
Netherlands /Western Europe / North America	1.00	
Caribbean/South America	1.86 (1.53-2.27)	<0.0001
Sub-Saharan Africa	2.36 (1.94-2.87)	<0.0001
Age at the start (years)		(<0.0001)
16-29	1.53 (1.30-1.80)	<0.0001
30-39	1.00	
40-49	0.91 (0.77-1.08)	0.27
≥50	0.97 (0.78-1.21)	0.51
CD4 cell count at the start (cells/mm^3)		(<0.0001)
<50	1.88 (1.39-2.54)	<0.0001
50-200	1.64 (1.25-2.16)	0.0003
200-350	1.12 (0.85-1.47)	0.44
350-500	1.00	
>500	0.83 (0.55-1.24)	0.36
Start during primary infection	0.99 (0.68-1.44)	0.97

	HR (95% CI)	(Overall) p-value
HIV RNA at the start (log_{10} copies/ml)		(<0.0001)
<4	0.56 (0.41–0.76)	0.0002
4–5	1.00	
≥5	1.54 (1.20–1.97)	0.0007
Year of starting		(<0.0001)
1999–2002	2.48 (2.08–2.96)	<0.0001
2003–2006	1.52 (1.28–1.81)	<0.0001
2007–2011	1.00	
2012–2014	0.82 (0.60–1.14)	0.24
HCV status at start cART		(0.27)
HCV RNA negative	1.00	
HCV RNA positive	1.03 (0.68–1.57)	0.88
HCV Ab positive	1.16 (0.79–1.70)	0.46
HBV status at start cART		
HBsAg negative	1.00	
HBsAg positive	1.38 (1.09–1.73)	0.007
AIDS diagnosis at the start	1.16 (0.99–1.35)	0.07

** Apart from the variables listed in the table, hazard ratios were also adjusted for hepatitis C status at the start of cART and for socio-economic status.*

Legend: *HR=hazard ratio; CI=confidence interval; MSM=men who have sex with men; HCV=hepatitis C virus; HBsAg=hepatitis B surface antigen; cART=combination antiretroviral therapy.*

Resistance during treatment

Scanning for drug resistance

In patients who experienced virological failure, resistance to antiretroviral drugs was ascertained by scanning genotypic sequences (obtained at the time of failure) of the reverse transcriptase (RT) and protease genes for specific mutations known to be associated with resistance to the three originally most commonly-used classes of drugs, including lamivudine plus emtricitabine, other nucleoside RT inhibitors (NRTI), non-nucleoside RT inhibitors (NNRTI), and protease inhibitors (PI)[63]. In recent years, new drug classes have also been introduced, including integrase and entry inhibitors, and genotypic sequences of the relevant genes are increasingly obtained during routine clinical care. However, only approximately 50 sequences of the integrase gene were available in the SHM database, all coming from only one treatment centre, and we did not consider them for further analysis. A genotypic resistance interpretation algorithm by Stanford University (version 7.0) 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[64].

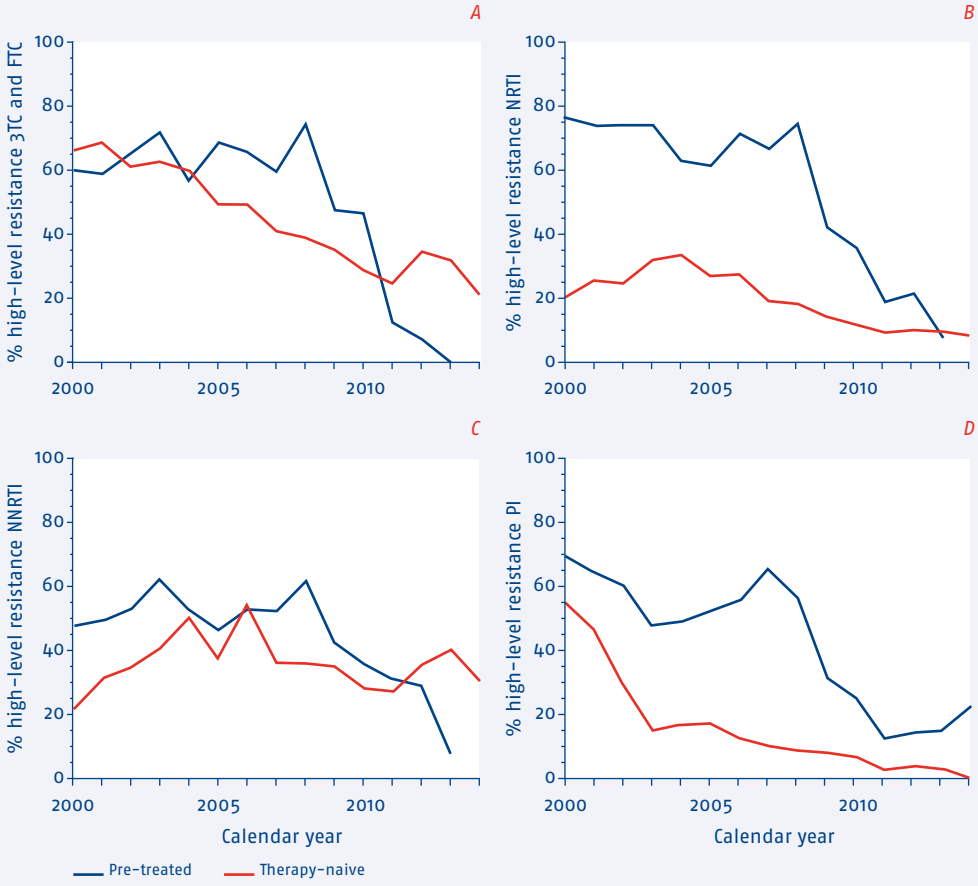
Sequences

In total, 4,369 sequences were obtained from 2,734 patients after the start of cART in 1996 or later. Overall, pre-treated patients were disproportionally represented with 1,656 sequences (38%), even though pre-treated patients represented only 10% of all treated patients in clinical care. However, from 2008 onwards, this discrepancy became less marked, with only 16% of the sequences from pre-treated patients. Overall, 3,553 sequences (81%) were obtained while patients were receiving treatment, whereas the other 816 (19%) sequences were from patients who had a treatment interruption. High-level resistance to at least one antiretroviral drug was found in 72% of these 3,553 sequences, including in 88% of the sequences obtained from pre-treated patients and in 61% of those from patients who had started cART while being antiretroviral therapy-naive. It is interesting that 8% of the sequences from pre-treated patients and 24% of those from previously therapy-naive patients were susceptible to all antiretroviral drugs, probably indicating that the patients were not taking their prescribed medication at the time the blood sample was obtained.

Less resistance

All together, the proportion of sequences with high-level resistance at the time of virological failure decreased from 91% in 2000 to 41% in 2014 (*Appendix Figure 3.2*). Generally, patients who were pre-treated with monotherapy or dual therapy had higher levels of resistance at the time of failure compared to previously therapy-naive patients. Differences in proportions with resistance were most apparent for PIs and NRTIs, whereas the proportions with resistance to lamivudine plus emtricitabine and to NNRTIs were comparable between pre-treated and previously therapy-naive patients (*Figure 3.4; 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 3.4: Annual proportion of available sequences with high-level resistance to (A) lamivudine (3TC) plus emtricitabine (FTC), (B) other nucleoside/nucleotide reverse transcriptase inhibitors (NRTI), (C) non-nucleoside reverse transcriptase inhibitors (NNRTI), and (D) protease inhibitors (PI). In total, 3,553 sequences were obtained from patients while they were on treatment, with a distinction made between patients who started combination antiretroviral therapy (cART) while being antiretroviral therapy-naive and those who were pre-treated with non-cART regimens. High-level resistance was found in 2,566 (72%) sequences, including 1,258 (88%) sequences from pre-treated patients and 1,308 (61%) sequences from previously therapy-naive patients. Note that in recent years the number of sequences from pre-treated patients is very small and in 2014 the number of sequences in pre-treated patients was too low to give meaningful proportions.



Legend: 3TC=lamivudine; FTC=emtricitabine; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

Type of regimen

In total, 294 sequences were obtained from previously antiretroviral therapy-naive 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 (54%). Of the patients on an NNRTI-based regimen, 60% had high-level resistance to an NNRTI, while 36% were fully susceptible to all NNRTIs. In contrast, only 18% of the patients on a PI-based regimen had high-level resistance to a protease inhibitor, and 62% were fully susceptible to all PIs. High-level resistance to lamivudine and emtricitabine was found in 48% of patients on a PI-based regimen and in 45% of those on NNRTI-based regimens, while high-level resistance to other NRTIs was observed in 5% and 21%, respectively.

Overall prevalence of resistance

In total, as of May 2015, resistance-associated mutations had been found in 2,070 (11%) of the 18,355 HIV-infected patients who had been still in clinical care[65]. For 1,545 patients (8%), including 601 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 24% of patients with virological failure in or after 2002 and for 17% with virological failure in or after 2008, the true prevalence of resistance may be higher.

Of the 1,545 patients with evidence of high-level resistance, 71% had resistance to lamivudine plus emtricitabine, while 50% had resistance to at least one other NRTI. Resistance to at least one PI was found in 31% of cases and to at least one NNRTI in 61% of cases. High-level resistance to drugs from one drug class was observed in 39% of patients, resistance to drugs from two classes was seen in 46%, and resistance to all three original drug classes was seen in 15%. Predicted levels of resistance for each antiretroviral drug are shown in *Appendix Tables 3.1* and *3.2*.

Transmission of drug resistance

Limited treatment options

Treatment options may be more limited when patients become infected with a strain of HIV 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 for the possible presence of drug resistance so that the patient's initial treatment regimen can be optimised[66, 67].

Back mutation

Although a resistant virus strain may evolve to a drug-susceptible virus (a process sometimes referred to as back mutation), resistant variants may remain dormant in resting CD4 cells

and other reservoirs, awaiting more favourable conditions for replicating after treatment has started. The presence of transmitted resistance, therefore, needs to be established as close to the moment of infection as possible[68-70]. In particular, the M184V mutation in RT, which is associated with high-level resistance to lamivudine plus emtricitabine, can disappear relatively quickly after transmission. Other mutations disappear at a much slower rate 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[71].

Screening for resistance

In 2003, screening for resistance at the time of entry into care was incorporated into the Dutch treatment guidelines. Since then, SHM has collected pre-treatment sequences for 5,015 patients who have been screened for transmitted drug resistance, which comprise 37% of all 13,611 patients diagnosed with HIV during that period, but only 22% of patients diagnosed in 2012 or later. To reduce a possible effect of back mutation on observed levels of resistance, only patients who had a genotypic sequence within one year of diagnosis and who had not started antiretroviral treatment were included in this total number. In addition, patients were divided into two complementary groups: one including patients with a recent infection (32%) and the other 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 12 months at most. Patients without a previously negative test or with a negative test more than 12 months before the first positive test were considered non-recent infections. These two groups differed markedly regarding patient characteristics. Dutch homosexual men represented 68% of the recently infected group, but only 41% of the group of more long-standing infections. In contrast, patients of Sub-Saharan African origin accounted for only 3% of those with recent infections and 17% of those with long-standing infections.

Transmitted drug resistance

Overall, at least one resistance-associated mutation was found in 11% of the 5,015 patients with a genotypic sequence within one year of diagnosis, including 4% with NRTI mutations, 5% with NNRTI mutations, and 2% with mutations in the protease gene[63]. Between 2003 and 2014, there were no significant changes in these proportions, nor were there changes in specific mutations.

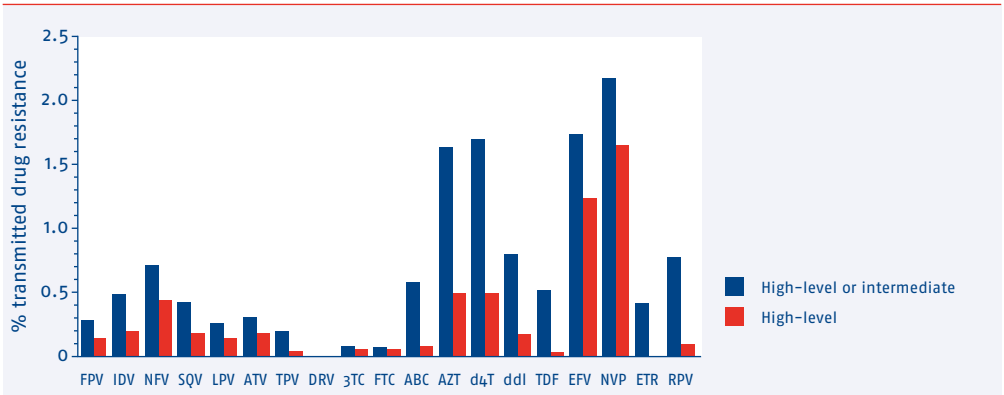
In total, 97 patients had high-level resistance to drugs from one class, 13 patients had high-level resistance to drugs from two classes, and 4 patients had high-level resistance to drugs from three classes. It should be emphasised that this does not mean that entire drug classes are rendered unsuitable 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 three classes, fully efficacious cART combinations can often still be constructed[72].

High-level resistance to at least one antiretroviral drug was found in 2.3% of the 5,015 patients, while intermediate levels of resistance were found in 2.1% of this group (*Table 3.2*). The proportion of patients with resistance and a recent infection was similar to the proportion with resistance and a 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 3.5*). In addition, 1.2% of the patients had high-level resistance to efavirenz, while 1.7% were resistant to nevirapine. In recent years, no changes were observed in the proportion of patients with predicted high-level resistance.

Table 3.2: *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 (64). 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 12 months at most.*

	Recent infection n=1,618		Non-recent infection n=3,397		All diagnoses n=5,015	
	n	%	n	%	n	%
Any drug						
Intermediate	32	2.0	74	2.2	106	2.1
High-level	34	2.1	80	2.4	114	2.3
PI						
Intermediate	5	0.3	10	0.3	15	0.3
High-level	8	0.5	14	0.4	22	0.4
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	19	1.2	49	1.4	68	1.4
High-level	7	0.4	19	0.6	26	0.5
NNRTI						
Intermediate	11	0.7	21	0.6	32	0.6
High-level	21	1.3	64	1.9	85	1.7

Figure 3.5: The predicted proportion of patients with high or intermediate levels of transmitted drug resistance, according to the Stanford interpretation algorithm, was 1.6% for zidovudine and 1.7% for stavudine (two drugs that are no longer commonly used) and 2.2% for nevirapine and 1.7% for efavirenz [64]. 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 among men (91%) than among women (97%). In contrast, virus strains susceptible to all PIs were observed in 89% of men, but in only 63% of women.

These differences between the sexes can largely be explained by the HIV-1 subtype with which patients were infected. Overall, 84% of men, but only 35% of women, were infected with a subtype B virus. Intermediate or high-level resistance to NRTIs was seen in 2.4% of subtype B viruses, compared with only 0.3% of non-B viruses. These higher levels of resistance to NRTIs were largely due to subtype B strains with revertant mutations in RT such as 215S or 215D, which have established themselves as sub-epidemics [73]. Revertant mutations at position 215 in RT were found in 212 (6%) subtype B infections, but in only four out of 1,185 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 additional resistance-associated mutations. Between 2011 and 2014, 5% of all sequences had this specific mutation compared to 1% before that time. However, due to a backlog in data collection, it is not possible to determine if this increase was a regional phenomenon or occurred at a national level.

Full susceptibility to all protease inhibitors was found in 95% of subtype B sequences, but only 51% of non-B viruses. This difference is likely due to naturally occurring polymorphisms at minor resistance-associated positions in the protease gene that are not considered clinically relevant[63].

Conclusions

In terms of percentages, virological failure is less common nowadays than it was in 2000, due to improvements in combination treatment itself and the availability of more treatment options. This appears to hold true even for patients pre-treated with monotherapy or dual therapy, who now have the same rates of virological failure as previously therapy-naive patients. Nevertheless, due to a growing volume of treated HIV-infected patients, approximately 300 to 400 patients per year still experience virological failure. The risk of virological failure remains higher in younger individuals (<30 years), individuals with low CD4 cell counts (<200 cells/mm^3) or high viral load (>100,000 copies/ml) at the start of cART, heterosexually infected men and women as compared to MSM, and patients from Sub-Saharan Africa, the Caribbean, and South America.

Resistance patterns in sequences obtained around the time of failure seem to indicate that in about one-quarter of previously therapy-naive patients, virological failure is the result of patients failing to take their prescribed medication, which could be due to drug-related toxicity. In patients with a sequence obtained while 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 because of the larger number of mutations necessary to render the virus fully resistant[74]. In patients on a PI-based regimen, resistance to lamivudine plus emtricitabine is most commonly observed, whereas in patients on NNRTI-based regimens, resistance to NNRTIs and, to a lesser extent, lamivudine plus emtricitabine is most frequent.

Unfortunately, in recent years sequences have been made available to SHM for only 17% of the patients with virological failure. As such, it is difficult to draw firm conclusions on the prevalence of resistance in the entire HIV-infected population in care in the Netherlands. Furthermore, 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.

Only 11% of patients with a pre-treatment sequence within one year of HIV diagnosis were infected with a virus that harboured any resistance-associated mutations. This proportion is most likely 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[75, 76]. The transmitted mutations have given 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 the present, 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 such a low proportion of patients with virological failure. The collection of sequencing data needs to be improved to permit more complete monitoring of resistance. The first steps to achieve this have already been taken, and further progress is expected in the near future.

With the introduction of new drug classes in recent years, including integrase and entry inhibitors, the collection of data on sequences needs to be extended to other parts of the viral genome. Increasingly, genotypic sequences of the relevant genes are being obtained during routine clinical care, but insufficient 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 increase the risk of development of virological failure. Moreover, even though no resistance-associated mutations are currently found in many patients, there is no guarantee that this situation will remain unchanged. 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 formulate tailor-made intervention strategies to reduce HIV incidence.

4. HIV and non-HIV-related morbidity and mortality

Luuk Gras, Colette Smit, Ard van Sighem, Ferdinand Wit and Peter Reiss

Introduction

Of the 22,883 adults and children infected with HIV-1 ever registered in the Dutch national HIV registration and monitoring database, 91% are currently on combination antiretroviral therapy (cART). The life expectancy of HIV-infected patients has markedly improved since the introduction of cART, and, in a subgroup of recently diagnosed, effectively treated patients, has been shown to be similar to that of the general population in the Netherlands[77].

Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased[78], morbidity and/or mortality associated with non-AIDS-related diseases such as renal and liver disease, diabetes mellitus, myocardial infarction, osteoporosis, stroke and non-AIDS-defining malignancies, has increased among HIV-1 infected individuals during the cART era[34, 79-83].

Various reports suggest that the risk of non-AIDS morbidity may be higher among HIV-infected individuals treated with antiretroviral therapy (ART) than among uninfected individuals of comparable age[84-86]. For example, pulmonary hypertension[87], bone disease and non-traumatic bone fractures[88-90] have been reported to be more common in HIV-infected patients. There is also a concern that HIV-related neurocognitive impairment may persist or even progress, despite otherwise effective long-term cART[91-93]. Furthermore, traditional risk factors (e.g., tobacco use[94], alcohol abuse, and viral hepatitis co-infection[95]) are likely to also importantly contribute to the increased risk of certain non-AIDS co-morbidities in HIV, similar to in uninfected individuals.

Importantly, one of the most prevalent co-morbidities in HIV is cardiovascular disease (CVD). In addition to traditional risk factors such as smoking, probable additional risk factors with high prevalence among HIV-infected patients include metabolic abnormalities, including dyslipidaemia, insulin resistance, hypertension, diabetes, and changes in body fat distribution (lipodystrophy), which may partly be driven by use of cART, as well as by sustained HIV-associated immune activation and inflammation, despite effective cART[32, 96].

In this chapter, we report on rates of mortality and causes of death for HIV-1-infected patients using updated Stichting HIV Monitoring (SHM) data. In addition, we report on 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.

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[97]). A CD4 count below 200 cells/mm^3 in the absence of an AIDS-defining condition, which is considered to be an AIDS-defining condition in the United States, 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.

Cardiovascular disease, including myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy, was defined according to criteria established by the D:A:D study.

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, except that Castleman's disease was also defined as a non-AIDS-defining malignancy. Histological confirmation of malignancies is part of standard clinical practice in the Netherlands and, therefore, pathology reports have been used as much as possible to establish the presence of any malignancy.

Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate (eGFR) below 60 ml/min (estimated with the Cockcroft-Gault equation), confirmed after three months or longer. Creatinine levels have been routinely collected by SHM since April 2007 and, therefore, here we report on CKD from 2007 onwards.

Methods

For the analyses of incidence per calendar year and period, we consider all events after an individual was diagnosed with HIV-1 or after the start of routine collection of data on the condition of interest, whichever occurred most recently. For instance, data on CKD were analysed from April 2007 onwards because that was when laboratory data became available. As the average age of the Dutch HIV population increased over time, we also estimated the incidence rates for the periods 2000-2005, 2006-2010, and 2011-2014, while standardising

these according to the age distribution of the population during the period 2011-2014 (divided into age classes 18-35, 35-45, 45-55, 55-65, and ≥65 years) using the indirect method [98]. We investigated risk factors for AIDS and death and for each of the non-AIDS events, as well as a combined non-AIDS endpoint (first occurrence of cardiovascular diseases, diabetes mellitus, or non-AIDS malignancy). CKD was not included as creatinine was not part of routine data collection before 2007. Baseline for treated and untreated HIV-1-infected individuals was defined as the date of HIV-1 diagnosis or July 2000, whichever occurred most recently. Subsequent follow-up time was divided into three-monthly periods. Poisson regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for most recent CD4 cell count (lagged by three months), body mass index, gender, region of birth, most likely HIV-1 transmission route, current age, known time with CD4 count <200 cells/mm^3, known time with plasma HIV RNA >1000 copies/ml, time on cART, prior diagnosis of AIDS, and presence of chronic active hepatitis B and C virus infection.

Mortality and AIDS

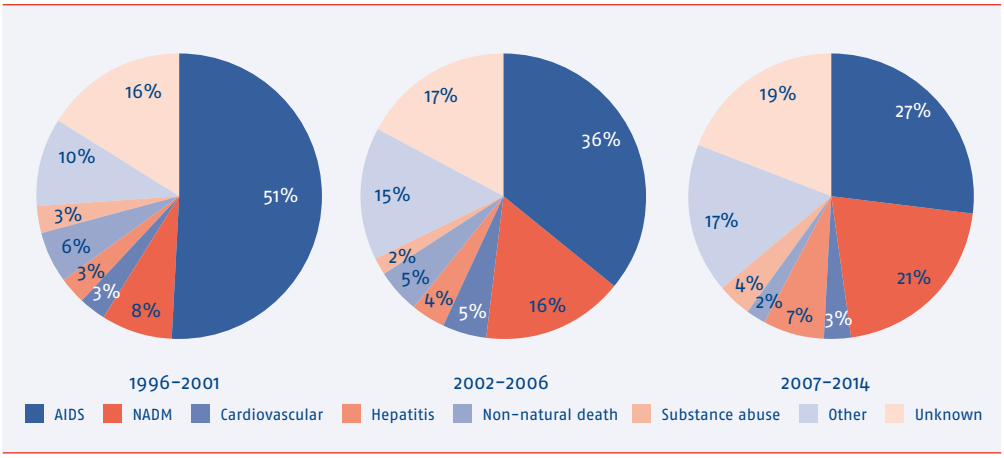
From 1996 onwards, the overall mortality rate in all 22,883 HIV-1-infected adults and children ever registered in the SHM database with a recorded date of HIV diagnosis was 11.2 (95% confidence interval [CI], 10.8-11.7) per 1,000 person years and declined over time to 8.3 (6.9-9.8) per 1,000 person years in 2014 (*Appendix Figure 4.1A; Appendix Table 4.1*). Although the mortality rate has improved over time, it is well above the rate that would be expected for the general population in the Netherlands, namely, 5.2 per 1,000 person years in 2014, when gender and age are taken into account. The excess mortality rate can be partly ascribed to patients who already had AIDS at the time of their HIV diagnosis. When these patients were excluded, the mortality rate was 9.7 per 1,000 person years overall and 7.5 (6.2-9.1) per 1,000 person years in 2014. The overall mortality rate was even lower, 8.9 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 nucleoside reverse transcriptase inhibitor (NRTI) therapy in the period before cART first became available. In the same group of 22,883 patients, the incidence of AIDS decreased sharply to approximately 8 cases per 1,000 patients per year in the most recent years (*Appendix Figure 4.1B*).

Likewise, the mortality rate after the start of cART has substantially decreased over calendar time to 8.5 (7.1-10.1) per 1,000 person years in 2014 (*Appendix Figure 4.1C*). 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 has decreased dramatically and

was 4.6 (3.6-5.9) per 1,000 person years in 2014 (*Appendix Figure 4.1D*). The incidence of AIDS after starting cART was lower with higher latest CD4 cell counts and was 464.1 (95% CI 395.0-541.9) per 1,000 person years of follow up; additionally, it was 64.0 (56.4-72.3), 17.0 (14.8-19.4), 7.6 (6.5-8.8), 4.0 (3.4-4.8), and 3.2 (2.5-4.1) at latest CD4 cell counts of <50, 50-200, 200-350, 350-500, 500-750, and ≥750 cells/mm^3, respectively.

Observed underlying causes of death are presented in *Appendix Table 4.2*. Although the proportion of patients who die of AIDS has decreased significantly since the advent of cART, it still remains substantial and is probably driven largely by the high number of patients still presenting late for care with already advanced immune deficiency. Forty-one percent of all patients who died of AIDS between 2010 and 2015 had a CD4 cell count < 50 cells/mm^3 when entering care. Patients who died of AIDS had lower CD4 counts (median 100 cell/mm^3 [IQR 30-310] when entering care compared to patients who died of another cause (median 250 cells/mm^3 [IQR 97-450]). Among patients who entered care with more than 300 CD4 cells/mm^3 and who died of AIDS, the cause of death was relatively more often an AIDS-related malignancy (33%) compared to patients who entered care with less than 50 CD4 cells/mm^3 (16%). The time between entry into care and death was significantly shorter in patients who died of AIDS (median 3 years [IQR 0.7-8.0]) compared to patients who died of a non-AIDS cause (median 7 years [IQR 4-12], p<0.001). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time *(Figure 4.1)*, partly as a consequence of the increasing average age of the Dutch HIV-infected population.

Figure 4.1: *Relative changes in causes of death in HIV-1-infected patients in different periods of time since the introduction of combination antiretroviral therapy (cART) in the Netherlands.*



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

Data collection on adverse events of anti-HIV drugs (D:A:D) study

The D:A:D study investigated trends over time in all-cause mortality and for specific causes of death between 1999 and 2011 in individuals with HIV. This study included 49,731 individuals from 212 different HIV clinics in Europe, including the Netherlands. During follow up, there were 3,909 deaths. The most common causes of death were AIDS-related (29%), non-AIDS-defining cancers (15%), and cardiovascular disease (11%). Overall mortality decreased from 17.5 deaths in 1999-2000 to 9.1 deaths in 2009-2011 per 1,000 person years of follow up. A similar decrease in AIDS-related deaths was observed in the same time period, but death from non-AIDS cancers increased slightly. However, after adjustments for different factors including time-updated CD4 cell counts, the decrease in AIDS-related death was no longer observed, although all-cause mortality, death from liver disease, and cardiovascular disease still decreased over time. The reduction in AIDS-related death is linked to continued improvements in CD4 cell counts. Within the D:A:D study population, death from non-AIDS cancer is now the leading cause of death [99].

We used Poisson regression analysis to examine factors associated with death in individuals from the time of entering care. After correction for all variables listed in *Appendix Table 4.3*, including time-updated age, and time-updated lagged CD4 cell counts, the odds ratios for a number of possible risk factors are presented in *Appendix Table 4.3*. In general, men were more likely to die than women, and patients survived for a shorter time after HIV-1 diagnosis if they were older, had a current CD4 cell count less than 200 cells/mm^3, were underweight, or had spent more time with an HIV RNA level above 1,000 copies/ml. Although a lower mortality risk was observed in patients of non-Dutch origin, this is likely due to the larger proportion of Sub-Saharan Africans being lost to follow up, as illustrated in *Appendix Table 4.4*. Furthermore, the incidence of loss to follow up in Sub-Saharan African and South-East Asian individuals was higher with lower time-updated CD4 cell counts, whereas in individuals born in the Netherlands incidence of loss to follow up did not depend on time-updated CD4 cell count. This suggests that loss to follow up in Sub-Saharan African and South-East Asian individuals is associated with mortality, at least to a higher degree than in individuals born in the Netherlands.

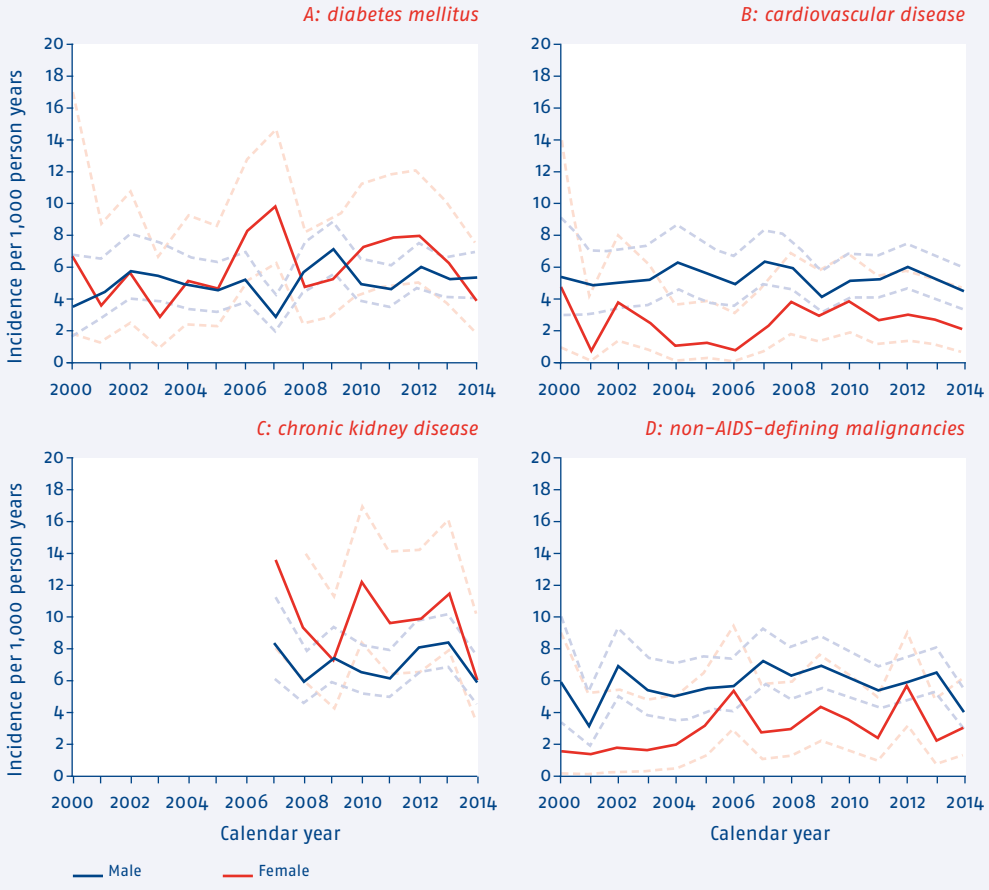
The incidence of the first occurrence of any AIDS-defining event after entering in care was 29 events per 1,000 person years of follow up. *Appendix Table 4.5* gives an overview of the AIDS events occurring between 1996 and 2014. The most common AIDS events occurring between 2007 and 2015 were oesophageal candidiasis (17% of all events), Kaposi's sarcoma (12%), tuberculosis (10%), AIDS dementia complex/HIV encephalopathy (4%) and cytomegalovirus-associated end organ disease (3%). Risk factors for AIDS-defining events are

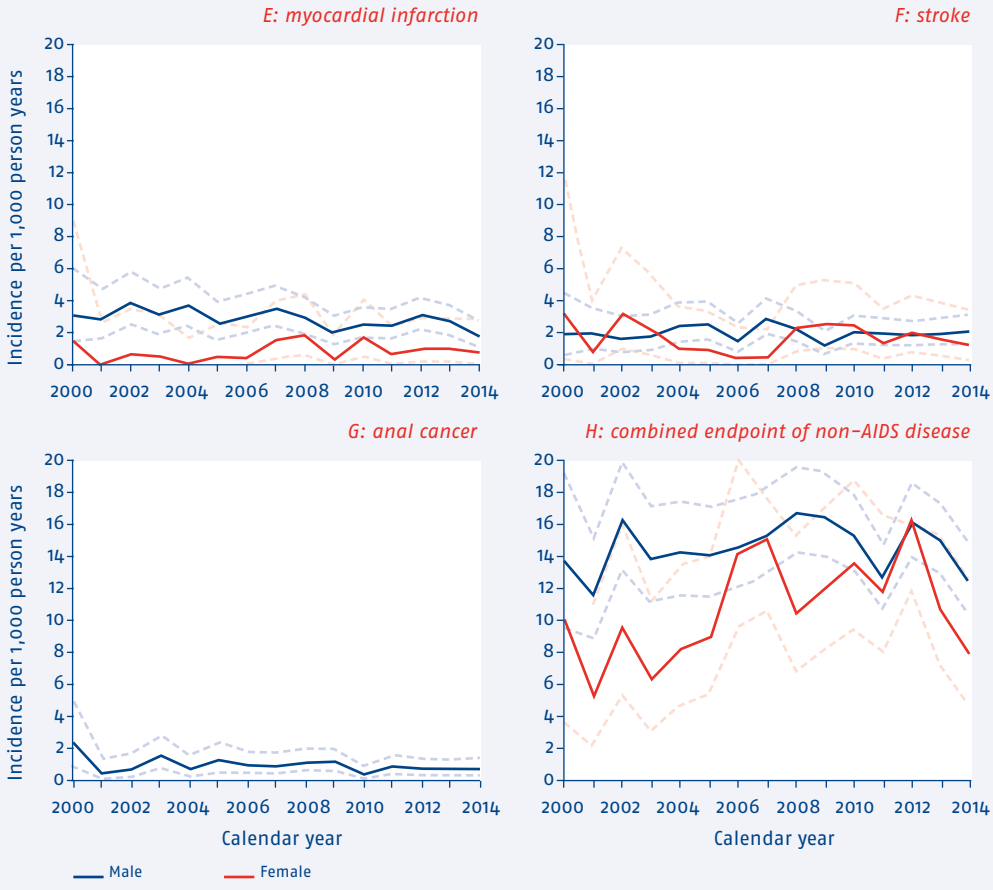
shown in *Appendix Table 4.3*. In the present analyses, we concentrate on the first occurrence of any AIDS-defining event after entry in care. The results of these analyses show that patients were more likely to experience their first AIDS-defining event if they were men, had become HIV-1 positive through injecting drug use, had a current CD4 cell count below 200 cells/mm^3, or had more than 1000 HIV RNA copies/ml for a longer period of time.

Non-AIDS-defining events

Of the 22,883 HIV-1-infected adults and children ever entered in the Dutch national HIV registration and monitoring database, 21,885 were aged 18 years or older at HIV-1 diagnosis and in follow up in or after July 2000. For these treated and untreated individuals, we report incidence figures and risk factors for diabetes mellitus, a composite cardiovascular disease endpoint (and separately for myocardial infarction and stroke), non-AIDS malignancies (separately for anal cancer), and CKD. We also present the incidence of the first occurrence of either diabetes mellitus, cardiovascular disease, or non-AIDS malignancies as a combined non-AIDS disease endpoint (*Figure 4.2; Appendix Table 4.6*).

Figure 4.2: Crude incidence rates per 1,000 person years of follow up and 95% confidence intervals (dotted lines) of diabetes mellitus (A), cardiovascular disease (B), chronic kidney disease (C), non-AIDS-defining malignancies (D), myocardial infarction (E), stroke (F), anal cancer (G), and combined endpoint of non-AIDS disease (diabetes mellitus, cardiovascular disease, and non-AIDS-defining malignancies) (H) by gender, with exception of anal cancer, which is presented for males only.





Diabetes mellitus

Of the 21,885 individuals aged 18 years or more at HIV-1 diagnosis and in follow up in or after July 2000, a total of 889 (684 men and 205 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 4.2.A*) and, in 2014, was 5.4 (95% CI 4.0-7.0) per 1,000 person years of follow up in men and 3.8 (95% CI 1.7-7.2) per 1,000 person years in women. Compared to last year's report, incidence figures are slightly higher because the definition of diabetes mellitus has been amended to better comply with the definition used in the D:A:D study[100]. In both men and women, the incidence increased with older age (*Appendix Table 4.6.A*). In men, the age-standardised

incidence ratio declined over time and was significantly higher in 2000-2005 compared to 2011-2014. In women, the age standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2014 (*Table 4.1)*.

Table 4.1: *Crude and age-standardised incidence of diabetes mellitus per 1,000 years of follow up during 2000-2005, 2006-2010 and 2011-2014 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Men		Women	
	Crude incidence (95% CI)	Standardised* incidence ratio	Crude incidence (95% CI)	Standardised* incidence ratio
2000-2005	4.9 (4.8-6.3)	1.17 (1.00-1.35)	4.5 (3.3-6.1)	0.79 (0.58-1.06)
2006-2010	5.3 (4.6-6.0)	1.10 (0.97-1.24)	7.0 (5.6-8.6)	1.14 (0.93-1.41)
2011-2014	5.3 (4.7-6.0)	1.00	6.6 (5.2-8.3)	1.00

** Standardised according to the observed age distribution between 2011-2014.*
Legend: *CI=confidence intervals.*

Demographic and clinical factors independently associated with increased risk of new-onset diabetes mellitus were being of male gender, non-Dutch origin, or older age; having a BMI either greater than 25 kg/m^2 or less than 18 kg/m^2; having hypertension; acquiring HIV through heterosexual or contaminated blood contact or injecting drug use; having a latest CD4 cell count <200 cells/mm^3; spending a longer time on stavudine, zidovudine, or didanosine; and having ever had an AIDS diagnosis (*Appendix Table 4.7*).

Cardiovascular disease

From 2000 onwards, 805 individuals (719 men and 86 women) had a fatal or non-fatal cardiovascular event (411 myocardial infarction, 329 stroke (52 haemorrhagic, 164 ischaemic and 93 unknown), 66 coronary artery bypass graft, 297 coronary angioplasty or stenting, and 7 carotid endarterectomy). The crude incidence over time remained stable and was lower in women than in men (*Figure 4.2.B*). The incidence in both men and women increased with older age (*Appendix Table 4.6.B*). The standardised incidence ratio in men declined over time, whereas in women the standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2014 (*Table 4.2*).

Table 4.2: Crude incidence of cardiovascular disease per 1,000 years of follow up between 2000-2005, 2006-2010, and 2011-2014 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Crude incidence (95% CI)	Standardised* incidence ratio	Crude incidence (95% CI)	Standardised* incidence ratio
2000-2005	5.5 (4.8-6.3)	1.56 (1.36-1.79)	2.1 (1.3-3.2)	1.18 (0.76-1.84)
2006-2010	5.3 (4.7-6.0)	1.20 (1.06-1.35)	2.8 (1.9-3.8)	1.27 (0.92-1.77)
2011-2014	5.3 (4.7-6.0)	1.00	2.6 (1.8-3.7)	1.00

** Standardised according to the observed age distribution between 2011-2014.*
***Legend:** CI=confidence intervals.*

In the analysis of risk factors, those associated with cardiovascular disease were male gender, Dutch origin, older age, infection through injecting drug use, a latest CD4 cell count <200 cells/mm^3, a prior AIDS diagnosis, use of abacavir (either currently or in the last 6 months), current smoker, and presence of hypertension. Cardiovascular risk was also higher during 2000-2005 than during 2011-2014, independent of other variables included in the analysis *(Appendix Table 4.7)*.

From 2000 onwards, 93 men and 7 women experienced a fatal or non-fatal secondary cardiovascular event (59 myocardial infarction, 42 stroke). The crude incidence per 1,000 years of follow up over the whole period between 2000 and 2014 in men and women with a prior cardiovascular event was 24.7 (95% CI 20.0-30.3) and 15.9 (95% CI 6.4-32.9), respectively.

Trends in cardiovascular risk factors

The percentage of men with a cholesterol level of 6.2 mmol/l or higher has decreased over time from 25% with an available cholesterol measurement in 2000 (regardless of whether statins were used) to 13% in 2014 (*Figure 4.3*). In women, this figure was lowest in 2005 at 11% and increased to 15% in 2014. *Appendix Figure 4.2* gives an overview of the absolute numbers of individuals in each cholesterol category over time.

Figure 4.3: Distribution of cholesterol levels (mmol/l) at the end of each calendar year in men (A) and women (B) as a percentage of the total number of men and the total number of women with an available cholesterol measurement. For each individual, the last available measurement in each year was selected.

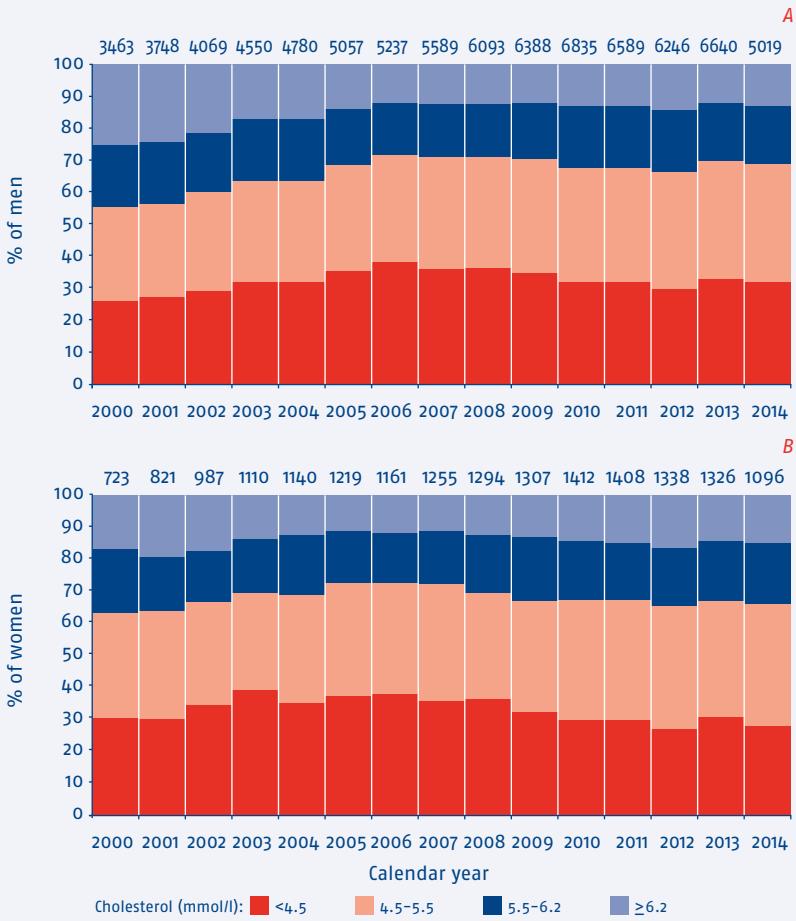


Figure 4.4 shows that the distribution of body mass index (BMI) of both men and women in the HIV-1-infected population has increased over time. In particular, in 2014, the percentage of overweight (25-30 kg/m^2) and obese (≥30 kg/m^2) men with an available BMI measurement was 31% and 7%, respectively. In women, these percentages were 31% and 25%, respectively. *Appendix Figure 4.3* gives an overview of the absolute numbers of individuals in each BMI category. Using mixed effects modelling, we investigated

whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the HIV-infected population. This revealed that the increase in BMI over time could partially be explained by adjusting for age, region of origin, transmission risk group, and time since first starting cART, and this effect was more marked in men than women.

Figure 4.4: Distribution of the body mass index (BMI) at the end of each calendar year in men (A) and women (B) as a percentage of the total number of men and women with a known BMI in each year. For each patient, the last available weight measurement in each year was selected.

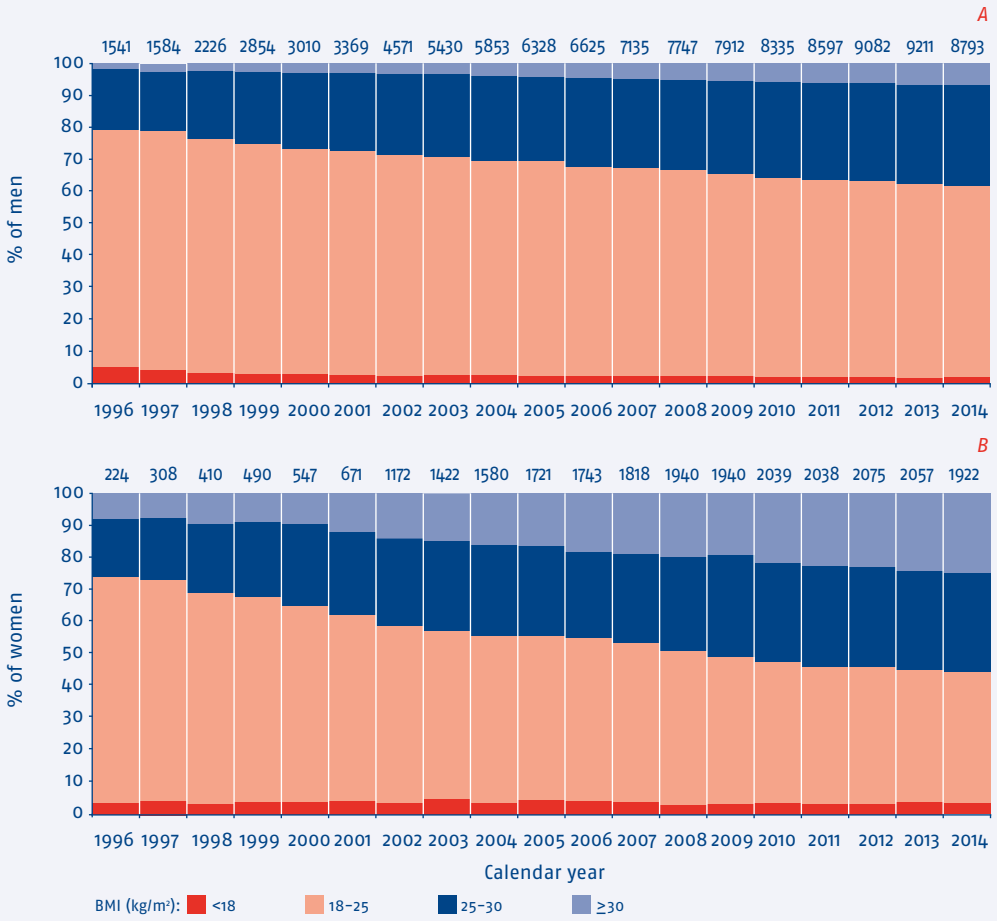
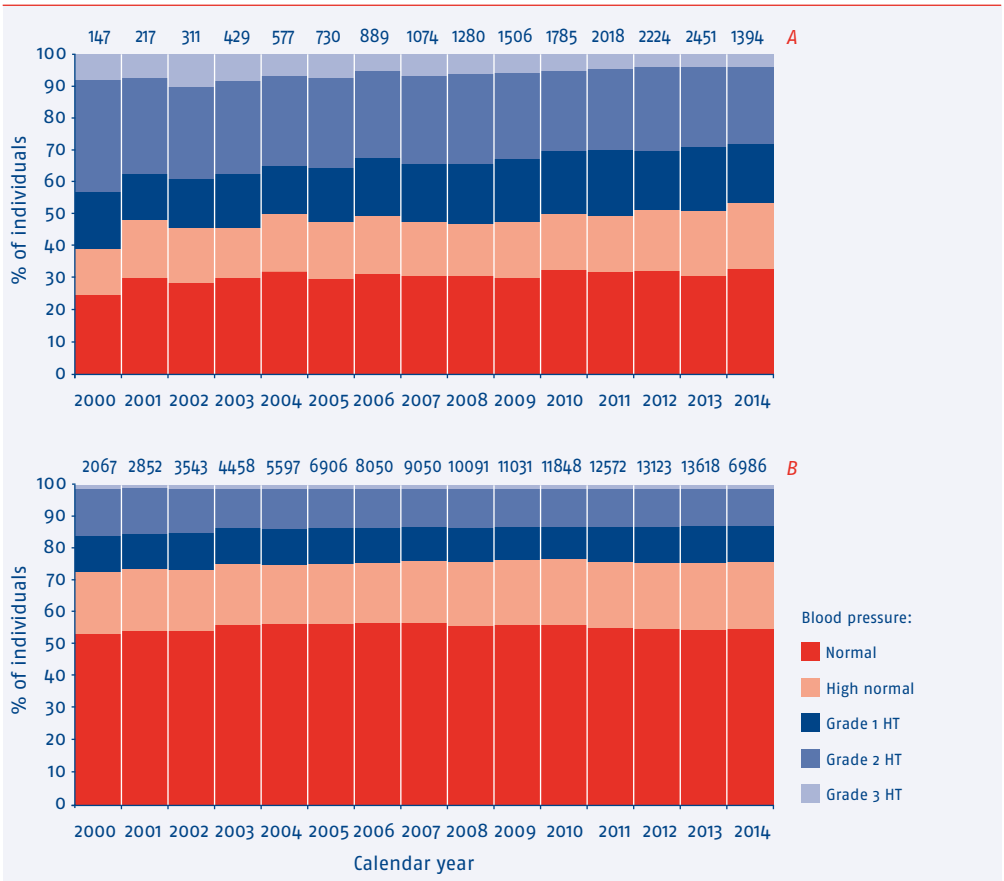


Figure 4.5: Distribution of graded blood pressure at the end of each calendar year in individuals known to be receiving antihypertensive treatment (A) and in those individuals not recorded as being treated for hypertension (B). For each individual, the last available systolic and diastolic blood pressure measurement in each year was selected. Blood pressure was graded according to the classification recommended in the guidelines for the management of arterial hypertension by the European Society of Hypertension and of the European Society of Cardiology [101]. Normal: systolic blood pressure (SBP) <130 mmHg or diastolic blood pressure (DBP) <85 mmHg, high normal: SBP 130–139 mmHg or DBP 85–89 mmHg, grade 1 hypertension SBP 140–159 mmHg or DBP 90–99 mmHg, grade 2 hypertension SBP 160–179 mmHg or DBP 100–109 mmHg, grade 3 hypertension SBP ≥ 180 mmHg or DBP ≥ 110 mmHg.



Legend: *HT=hypertension.*

Figure 4.5.A shows that, in 2014, 46% of those treated with antihypertensives still had grade 1 hypertension or higher. The figures above the bars show that over time an increasing number of patients are using antihypertensives, while *Appendix Figure 4.4.A* shows an increasing number of patients on antihypertensive therapy have normal or high normal blood pressure. In 2014, 1,687

(24%) untreated individuals had grade 1-3 hypertension (*Figure 4.5.B*). For 1,345 of these 1,687 individuals, a 5-year cardiovascular disease (CVD) risk could be calculated. Of the 1,345 individuals, 7% had a 5-year CVD risk of 10% or more; according to the European AIDS Clinical Society (EACS) guidelines, these individuals in particular should receive antihypertensive treatment[102].

Figure 4.6: *Estimated five-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D: study [103]. Calculation of risk included variables such as 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 former smokers, and if this information was not available, a value was imputed. Plot A shows the percentage of patients 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. Risk could not be estimated especially in younger individuals because of missing data. Hence, the reported absolute number of individuals is smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are overrepresented.*

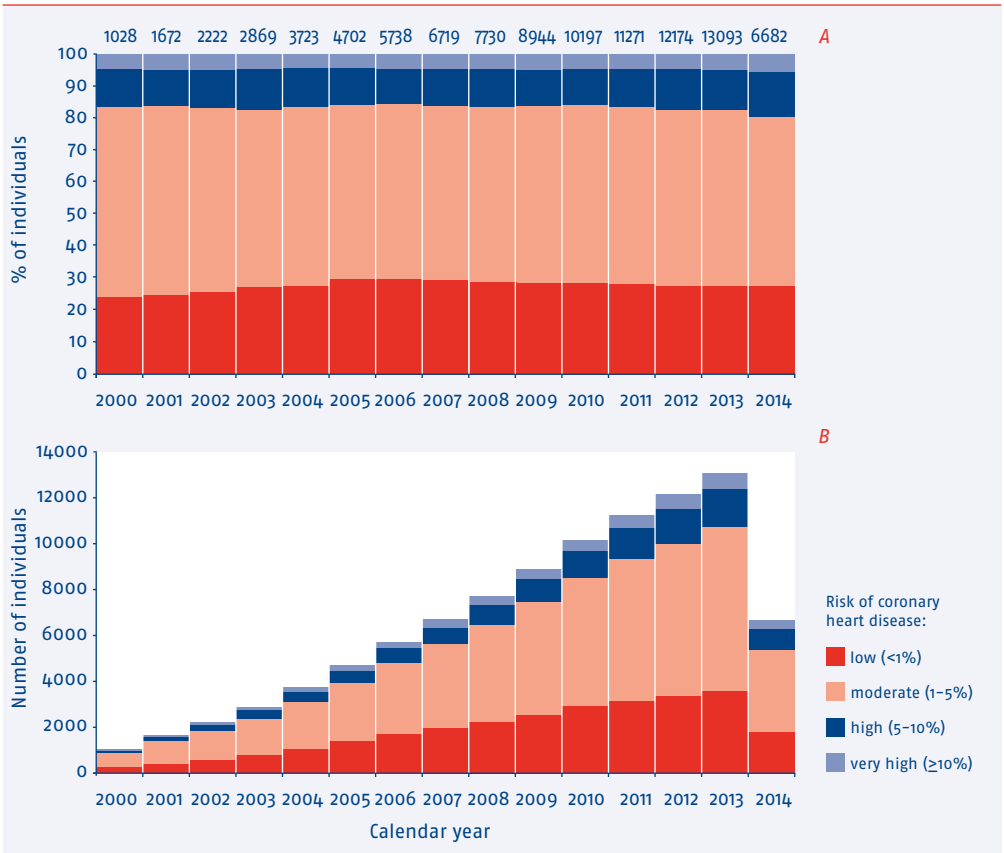


Figure 4.6 gives an overview of the cART-treated population's estimated risk of the development of CVD over time, calculated with the D:A:D study algorithm [103]. The percentage of individuals at high (5-10%) or very high risk (≥10%) increased slightly from 23% in 2007 to 29% in 2014. The slight increase in the percentage of individuals at high or very high risk may reflect the ageing of the population under study. Furthermore, based on the D:A:D algorithm, the risk of CVD increased with older age, male gender, current or previous smoking, current use of abacavir, longer cumulative exposure to indinavir and 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.

Data collection on adverse events of anti-HIV drugs (D:A:D) study

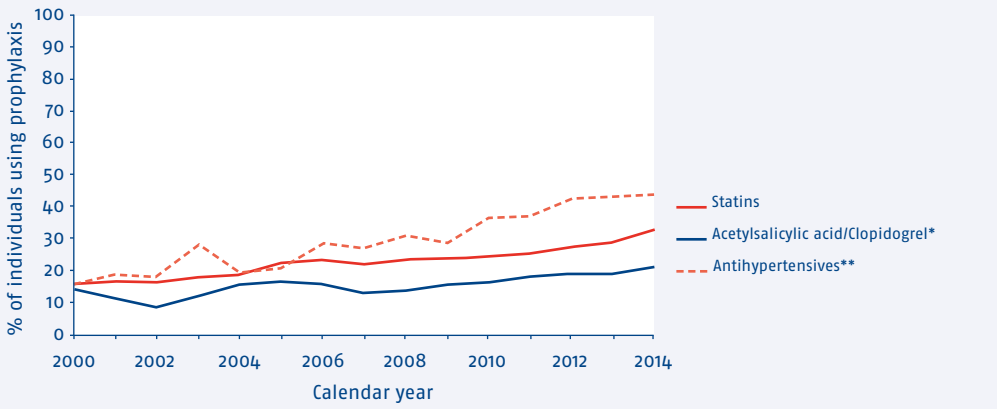
The D:A:D study assessed the impact of the observed gain in body mass index (BMI) in the first year after the start of cART on the subsequent risk of cardiovascular disease (CVD) and diabetes in individuals without prior exposure to antiretroviral therapy and no prior history of CVD or diabetes [100]. A total of 97 CVD events occurred in 43,982 person years (n=9,321) and 125 diabetes events in 43,278 person years (n=9,193). The short-term gain in BMI following ART initiation appeared to increase the longer-term risk of CVD, but only in those with pre-ART BMI in the normal range; in fully adjusted analyses for CVD, the incidence rate ratio (IRR)/unit gain in BMI (95% CI) in the first year of ART, by pre-ART BMI category, was: <18.5 kg/m², 0.90 (0.60-1.37); 18.5-25 kg/m², 1.18 (1.05-1.33); 25-30 kg/m², 0.87 (0.70-1.10), and ≥30 kg/m², 0.95 (0.71-1.28) (p-value for interaction=0.04). BMI gain was also associated with an increased risk of diabetes regardless of pre-ART BMI (incidence rate ratio/unit gain in BMI 1.11, 95% CI 1.03-1.21) [100].

Use of primary or secondary prophylaxis for myocardial infarction or stroke

Primary prophylaxis

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a 5-year CVD risk ≥ 5%; angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, diuretics, and antihypertensives (verapamil or diltiazem) should be offered to individuals with a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg and a 5-year CVD risk ≥10%; and acetylsalicylic acid should be offered to individuals aged 50 years or more with a 5-year CVD risk ≥10% [104]. *Figure 4.7* shows the trends in the use of these medications in these target populations for individuals without a prior stroke, myocardial infarction, or cardiovascular surgical procedure. There has been an increase over time in the percentage of individuals for whom primary prophylaxis using statins and the above-mentioned antihypertensive agents (referred to collectively hereafter as antihypertensives) is recommended. Similarly, there has also been an increase over time in the percentage of individuals at high risk aged 50 years or more who use acetylsalicylic acid/clopidogrel as primary prevention, although the overall level remains minimal.

Figure 4.7: Percentage of individuals without a previous myocardial infarction, stroke, or cardiovascular surgical procedure who, according to European AIDS Clinical Society (EACS) guidelines, should be offered statin therapy, acetylsalicylic acid, or antihypertensives as primary prophylaxis for myocardial infarction or stroke.



** Includes acetylsalicylic acid, carbasalate calcium, clopidogrel, dipyridamole or warfarin.*

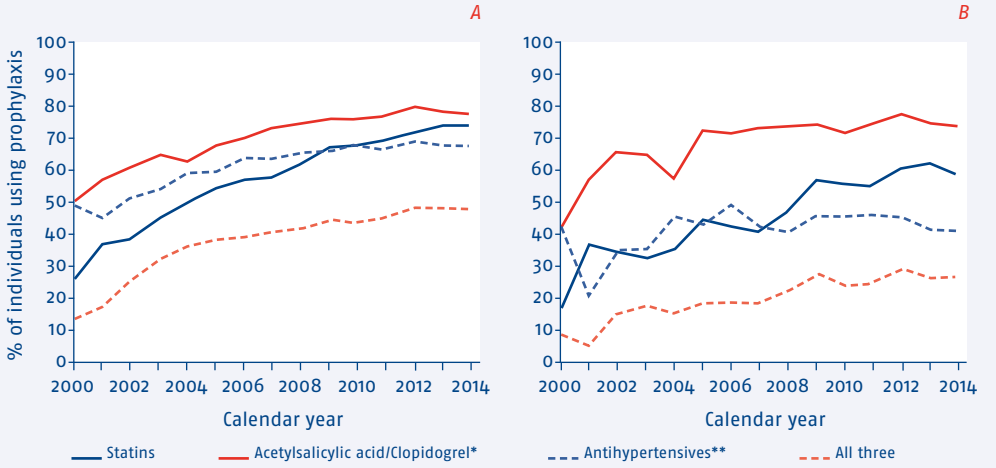
*** Includes ACE inhibitors, angiotensin receptor blockers, dihydropyridine calcium channel blockers, sulfonamides, verapamil or diltiazem.*

***Legend:** ACE= angiotensin converting enzyme.*

Secondary prophylaxis for myocardial infarction or stroke

According to all guidelines, individuals with a prior myocardial infarction or ischaemic stroke should receive lifelong treatment with statins, ACE inhibitors, or beta blockers or angiotensin receptor blockers (referred to here as antihypertensives), as well as low-dose acetylsalicylic acid/clopidogrel[105, 106]. *Figure 4.8.A* shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction has increased between 2000 and 2014: in 2014, 74% of individuals with a prior myocardial infarction used statins, 67% used antihypertensives, and 77% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also increased over time, in 2014 they were used less frequently after stroke than after a myocardial infarction (58% for statins, 73% for acetylsalicylic acid/clopidogrel, and 41% for antihypertensives) (*Figure 4.8.B*).

Figure 4.8: Percentage of individuals with a myocardial infarction (A) or ischaemic stroke (B) using statin therapy, acetylsalicylic acid, or antihypertensives**.*



** Includes acetylsalicylic acid, carbasalate calcium, clopidogrel, dipyridamole or warfarin.*

*** Includes ACE inhibitors, beta-blockers or angiotensin receptor blockers.*

Chronic kidney disease

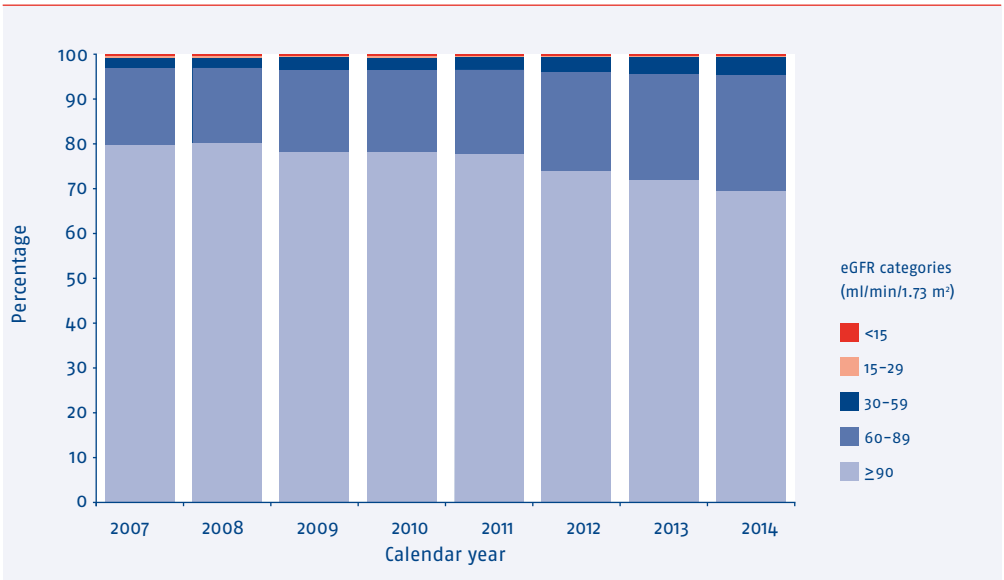
Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely, the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[107]. As all three equations used to measure estimated GFR (eGFR) are based on serum creatinine, they may be markedly affected by rapid changes in muscle mass, as is seen in some patients with advanced HIV disease who commence cART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in HIV-infected patients[107, 108]. However, because the Cockroft Gault equation takes body weight into account, we have chosen to report eGFR values as estimated by this equation. The distribution of eGFR categories (≥90, normal kidney function; 60-89, mildly reduced; 30-59, moderately reduced; 15-29, severely reduced; and <15, very severely reduced kidney function) is shown in *Figure 4.9*. The percentage of patients with normal kidney function decreased over time from 80% in 2007 to 70% in 2014. This decrease was observed in both men and women *(Figure 4.10)*. Typically, eGFR decreases with increased age, which is shown by *Figure 4.11*, and therefore, the decrease in the proportion of patients with normal function over time is likely to partly reflect the increasing age of patients in care.

In patients with an eGFR >60ml/min/1.73m² at inclusion in the analyses and without previously confirmed CKD, the crude incidence of CKD, defined as eGFR <60ml/min/1.73m² confirmed by a second test at least three months later, varied over time *(Figure 4.2.C)*. From 2007 onwards, 1,045 cases of CKD were identified. In men, the incidence changed from 6.9 cases per 1,000 person years in the period 2007-2010 to 7.3 in 2008-2014, and in women the incidence went from 11.1 to 10.2 cases per 1,000 person years during the same periods *(Table 4.3.A)*. The standardised incidence ratio in men and women declined over time (*Table 4.3.A*).

Since creatinine levels were not collected in a standardised manner until 2007, eGFR could not be calculated before 2007. For this reason, the crude incidence of CKD and the standardised incidence ratios were recalculated for patients who were diagnosed with HIV in or after 2007 (*Table 4.3.B*). No statistically significant decline in the standardised incidence ratio was seen.

Risk factors for CKD included female gender, non-Dutch origin, low current CD4 cell count, heterosexual or IDU HIV transmission risk group, older age, lower body mass index, diabetes mellitus, cardiovascular disease, and HCV co-infection *(Appendix Table 4.7)*. An earlier publication from the D:A:D study has previously shown that traditional risk factors such as diabetes or hypertension and current CD4 count were the strongest predictors for CKD[109]. Moreover, a recent study among HIV-infected patients in the Netherlands showed that patients who originated from Sub-Saharan Africa had a higher CKD prevalence at entry into the cohort, but that being from Sub-Saharan Africa had no impact on newly developing CKD over time[110].

Figure 4.9: Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year as a percentage of the total number of individuals with an available creatinine measurement. For each patient, the last measurement in each year was selected.



Legend: *≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.*

Figure 4.10: Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year in men (A) and women (B). For each patient the last available measurement in each year was selected.

Legend: ≥90 ml/min/1.73m²: normal kidney function; 60–89 ml/min/1.73m²: mildly reduced; 30–59 ml/min/1.73m²: moderately reduced; 15–29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severely reduced kidney function.

Table 4.3.A: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2007-2010, and 2011-2014 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Crude incidence	Standardised* incidence ratio (95% CI)	Crude incidence	Standardised* incidence ratio (95% CI)
2007-2010	6.9 (6.1-7.8)	1.16 (1.03-1.31)	10.1 (8.1-12.3)	1.40 (1.14-1.72)
2011-2014	7.3 (6.5-8.1)	1.00	9.3 (7.6-11.3)	1.00

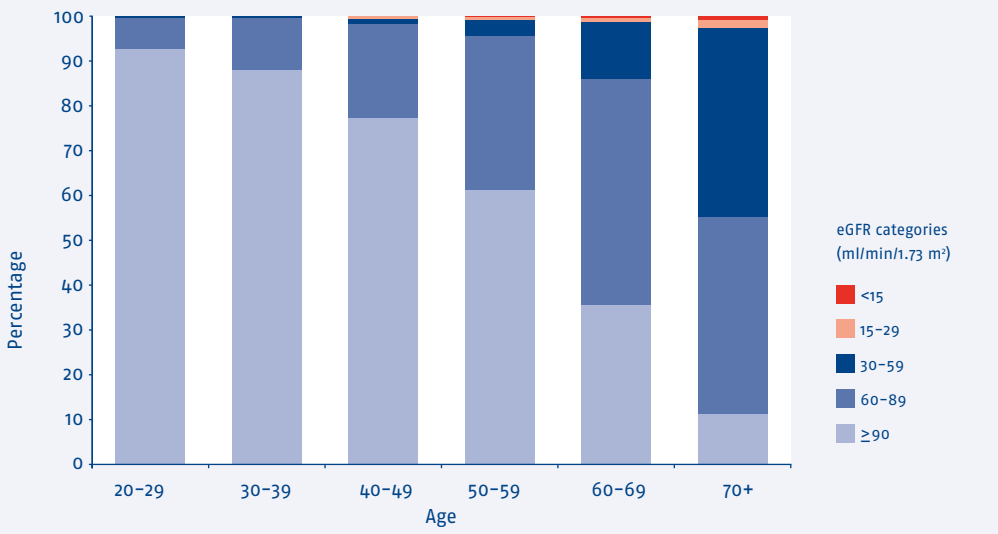
** Standardised according to the observed age distribution between 2011-2014.*
***Legend:** CI=confidence interval.*

Table 4.3.B: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2007-2010, and 2011-2014 and age-standardised incidence ratio with 95% confidence intervals in men and women with an HIV-1 diagnosis in or after July 2007.

Calendar year	Men		Women	
	Crude incidence	Standardised* incidence ratio (95% CI)	Crude incidence	Standardised* incidence ratio (95% CI)
2007-2010	6.2 (4.4-8.5)	1.37 (1.00-1.88)	11.1 (5.9-18.9)	1.37 (0.80-2.36)
2011-2014	5.5 (4.5-6.7)	1.00	10.2 (7.0-14.5)	1.00

** Standardised according to the observed age distribution between 2011-2014.*
***Legend:** CI=confidence interval.*

Figure 4.11: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2014 for different age categories. For each patient, the last available measurement in 2014 was selected.



Legend: ≥90 ml/min/1.73m²: normal kidney function; 60-89 ml/min/1.73m²: mildly reduced; 30-59 ml/min/1.73m²: moderately reduced; 15-29 ml/min/1.73m²: severely reduced; <15 ml/min/1.73m² very severe reduced kidney function.

Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study

Within the D:A:D cohort study, a long-term risk score model for chronic kidney disease (CKD) in HIV-positive individuals has been developed[111] with data from 17,954 HIV-infected individuals with three or more eGFR values. During 103,185 person years of follow up, 641 patients developed CKD. CKD was predicted by older age, injecting drug use, hepatitis C virus co-infection, lower baseline eGFR, female gender, lower nadir CD4 count, hypertension, diabetes mellitus, and cardiovascular disease. The adjusted incidence rate ratios of these nine predictors were scaled and summed to create a risk score. External validation of this risk score in two HIV cohorts showed that the risk score had a high predictive value in these cohorts.

Non-AIDS-defining malignancies

Since 2000, 942 patients in SHM's database have been recorded with a diagnosis of non-AIDS-defining malignancy. The most common types of non-AIDS-defining cancer were lung cancer (17%), invasive anal cancer (14%), Hodgkin's lymphoma (8%), and head and neck cancers (7%). *Figure 4.12* shows the relative changes in type of non-AIDS cancers over time. The proportion of patients with non-AIDS cancer other than lung, anal, Hodgkin's lymphoma

or head and neck cancer has increased over time. However, this increase is not caused by an increase in any one specific type of cancer, but instead reflects the increasing age of the study population. This is illustrated in *Figure 4.13*, which shows the relative changes in non-AIDS malignancies with increasing age at cancer diagnosis. The proportion of patients who were diagnosed with a non-AIDS-defining malignancy other than Hodgkin's lymphoma, anal cancer, lung cancer, or head and neck cancer rose with increasing age.

Figure 4.12: *Relative changes in non-AIDS-defining malignancies between 2000 and 2014 in HIV-1 infected patients in the Netherlands.*

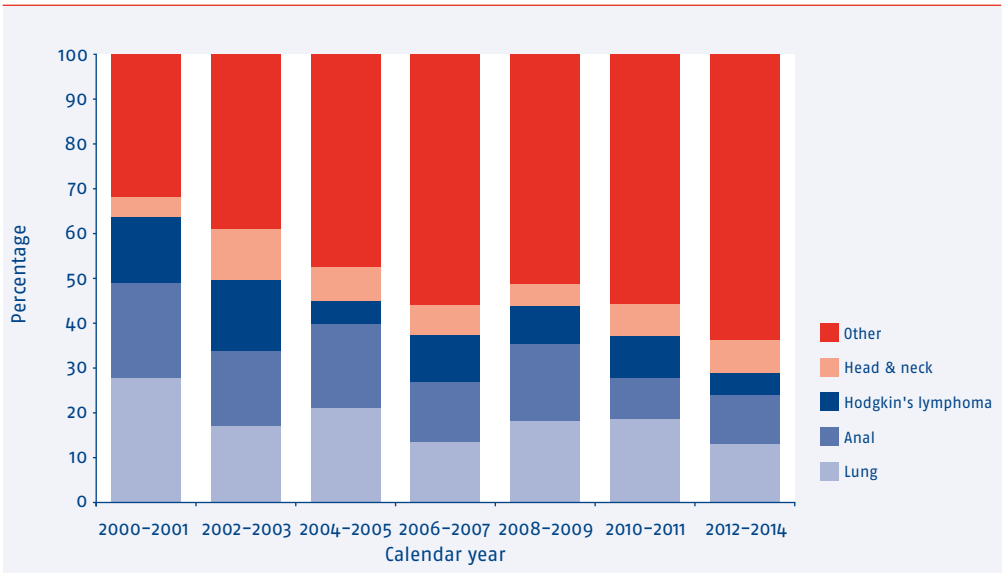
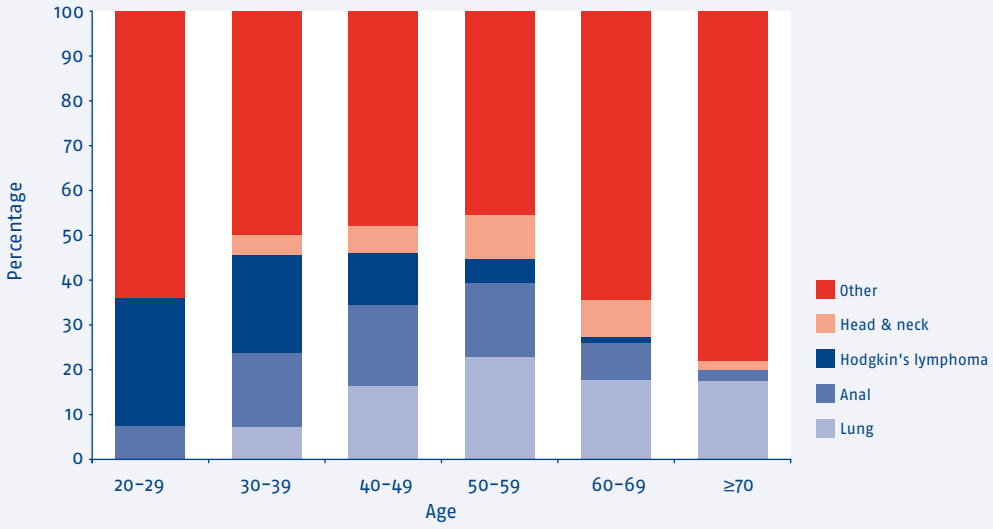


Figure 4.13: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1 infected patients in the Netherlands.



The crude incidence of non-AIDS-defining malignancies gradually increased from 7.0 cases per 1,000 person years in 2000-2005 to 8.3 cases per 1,000 person years in 2011-2014 in men and from 2.1 in 2000-2005 to 3.4 cases per 1,000 person years in 2011-2014 in women *(Figure 4.2.D; Appendix Table 4.6.D)*. In men, the age-standardised incidence was lower in the period 2011-2014 than in 2000-2005 and 2006-2010, as illustrated by a standardised incidence ratio significantly higher than 1.00 in the period 2000-2005 and 2006-2010 *(Table 4.4)*. Changes in risk factors such as smoking over time and a higher proportion of individuals with high CD4 cell counts in later years may have contributed to the lower standardised incidence in men.

Table 4.4: Crude non-AIDS-defining malignancy incidence per 1,000 years of follow up between 2000-2005, 2006-2010, and 2011-2014, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Men		Women	
	Crude incidence	Standardised* incidence ratio (95% CI)	Crude incidence	Standardised* incidence ratio (95% CI)
2000-2005	7.0 (6.2-8.0)	1.17 (1.03-1.32)	2.1 (1.3-3.2)	1.19 (0.82-1.74)
2006-2010	9.1 (8.3-10.0)	1.26 (1.15-1.38)	3.8 (2.8-5.0)	1.55 (1.21-1.99)
2011-2014	8.3 (7.5-9.2)	1.00	3.4 (2.4-4.6)	1.00

** Standardised according to the observed age distribution between 2011-2014.*
***Legend:** CI=confidence intervals.*

Demographic and clinical factors significantly associated with an increased risk of a first non-AIDS-defining malignancy were older age, lower current CD4 cell count, no treatment received for HIV, low body mass index, prior AIDS, chronic HBV co-infection, and current smoker (*Appendix Table 4.7*).

In total, 3 HIV-infected women and 119 HIV-infected men were diagnosed with anal cancer. Among HIV-infected men, the incidence of anal cancer slowly decreased over time from 1.3 cases per 1,000 person years in 2000 to 0.7 cases per 1,000 person years in 2011-2014 *(Figure 4.2 G)*. This decreasing trend in the incidence of anal cancer might be due to the trend over calendar time to start cART at higher CD4 counts, which in turn might lead to a decrease in anal cancer incidence, as low nadir CD4 cell count and lower current CD4 cell count have both been associated with an increased risk of anal cancer[112]. On the other hand, screening for both anal cancer (and pre-cancerous stages of anal cancer) and treatment of anal intraepithelial neoplasia may also have contributed to the decrease in anal cancer. A recent study exploring the incidence of anal cancer among HIV-1-infected patients in the Netherlands showed a significantly higher incidence of anal cancer in MSM compared to heterosexual men[113]. However, in this chapter, we will not report on the trend in anal cancer among heterosexual men over time, as the number of heterosexual men with anal cancer is too small (n=19) to observe a decreasing trend in anal cancer in this group.

Data Collection on Adverse Events of Anti-HIV Drugs (D:A:D) Study

The association between cART and cancer was studied within the D:A:D study[114]. The incidence of any type of cancer and the most frequently occurring AIDS-defining (Kaposi's sarcoma, non-Hodgkin's lymphoma) and non-AIDS-defining malignancies (lung, invasive anal cancer, head/neck cancers and Hodgkin's lymphoma) was estimated in patients who were in follow up between 2004 and 2012; 41,762 patients were included and contributed 241,556 person years of follow up. In total, 1,832 cancers were observed, 718 AIDS-defining cancers (incidence rate 0.30/100 person years, 95% CI 0.28-0.32) and 1,114 non-AIDS-defining cancers (0.46/100 person years, 0.43-0.49). Longer exposure to cART was associated with a lower risk of AIDS-defining cancers, with both protease inhibitor (PI)-based and non-nucleoside reverse transcriptase inhibitor (NNRTI)-based treatment associated with a lower risk of AIDS-defining cancers. In contrast, whereas PI-based cART was associated with a higher risk of the development of non-AIDS-defining malignancies, in particular invasive anal cancer, no such association was observed for the use of NNRTI-based cART. Further studies investigating biological mechanisms are needed to understand the observed association with PI use.

Immunological non-response and risk of disease progression and death three years after starting cART

In the 4,249 therapy-naïve individuals who started cART with less than 350 CD4 cells/mm^3 (described earlier in *Chapter 2*), we analysed the association between immunological non-responders (defined as those having less than 350 CD4 cells/mm^3 at 3 years after the start of cART, see *Chapter 2*) after 3 years of viral suppression on cART and the risk of the following endpoints after 3 years: death (n=107), AIDS (n=51), cardiovascular disease (n=92), diabetes mellitus (n=81) and non-AIDS-defining malignancy (n=82). After adjustment only for current age, region of origin, gender, and HBV and HCV status, immunological non-response was significantly associated with death (RR 1.57, 95% CI 1.06-2.31, p=0.02) and cardiovascular disease (RR 1.69, 95% CI 1.09-2.61, p=0.02), but not with AIDS (RR 1.61, 95% CI 0.89-2.94, p=0.12), diabetes mellitus (0.72, 95% CI 0.43-1.22, p=0.24) and non-AIDS-defining malignancy (RR 0.94, 95% CI 0.58-1.52, p=0.80). However, as the number of endpoints is small, these results should be interpreted with caution.

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[115], Denmark[116], several other European countries[117], and the USA[118]. Nonetheless, on average, mortality rates remain higher than in the general population, although they do

approach rates comparable to those in the general population in the subsets of patients on treatment with a CD4 count above 500 cells/mm^3 [119]. Although an overview of the causes of death among HIV-1-infected patients in the Netherlands indicates 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 a reflection of the high proportion of patients continuing to present late for care and who already have advanced immunodeficiency, AIDS, or both. Compared to patients who died from a non-AIDS-related cause, those who died of AIDS had substantially lower CD4 cell counts at entry into care and shorter time between entry into care and death.

Diabetes and cardiovascular disease

Whereas the crude incidence of diabetes mellitus and cardiovascular disease in men and women was found to have remained relatively stable, the age-standardised incidence for both diseases declined over time in men. The decline in age-standardised incidence in men may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus [120] and myocardial infarction [121] towards those that, to date, have not been associated with such risks), and increased attention to managing traditional risk factors for these conditions. Furthermore, the decline in trend of age-standardised incidence may also reflect an increasing proportion of individuals with high CD4 cell counts (partly because of the trend over time to start cART with higher CD4 cell counts, but also because an increasing proportion of individuals have been using cART long enough to have reached high CD4 cell counts). Finally, risk factors were mainly those traditionally known to be associated with these diseases, including age, hypertension and obesity, similar to what has been reported in other studies [120, 122, 123]. Several of these risk factors have been reported to be more prevalent among people living with HIV [94].

Cardiovascular risk factors

Despite the increasing age of the HIV-infected population, the proportion at high or very high cardiovascular risk increased only slightly over the period 2000-2014. This suggests that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives over time and the preferred use of cART regimens without known cardiovascular risk (*Chapter 2*). Significant room for further improvement remains, however, given the suboptimal use of statin therapy, antihypertensive therapy, and low-dose acetylsalicylic acid as secondary prevention following a myocardial infarction or ischaemic stroke, and the low, albeit improving, uptake of these medications in the prevention of primary cardiovascular disease. The clinical significance of the increase in BMI over time, especially in women, requires further study. Recent results suggest weight gain after starting cART is associated with lower mortality for normal-weight individuals, but no clear benefit for overweight or obese individuals was observed [124]. However, another study found that weight gain after starting cART is associated with an increased risk of diabetes, and, in those with a pre-ART BMI in the normal range, with an increased risk of cardiovascular disease [100]. Prospective longitudinal monitoring of lipid levels, smoking

status, blood pressure, weight, and other risk factors will be important to further optimise the assessment of cardiovascular risk in our increasingly ageing HIV-1-infected population and to study the impact of interventions, such as the use of statin and antihypertensive therapy, in modifying disease risk.

Renal insufficiency

As expected, older individuals and those with traditional risk factors such as hypertension were found to be at increased risk for CKD, as were patients with advanced immunodeficiency. Other studies have reported hepatitis B and C virus co-infection [125, 126] and the use of tenofovir, atazanavir/ritonavir, and lopinavir/ritonavir to be additional independent predictors of chronic renal impairment [127].

Non-AIDS-defining malignancies

The most common non-AIDS-defining malignancies in the Netherlands are lung, anal, and head and neck cancer, as well as Hodgkin's lymphoma. The crude incidence of non-AIDS-defining malignancies in the Netherlands has remained stable over time, and we observed a decline in age-standardised incidence of non-AIDS-defining malignancies in men. Our analyses also show that patients diagnosed with non-AIDS-defining malignancies were more likely to be older and more likely to have lower CD4 counts. Several cohorts, including the Swiss HIV cohort study, have previously reported an increased incidence of non-AIDS-defining malignancies with increasing age [128-131]. Moreover, the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies [132].

Our analyses found no association between duration of cART and the incidence of non-AIDS-defining malignancies. On the other hand, a recent paper from the D:A:D study looking at the association between non-AIDS-defining malignancies and cumulative cART use in a large study population found an overall increase in the risk of non-AIDS-defining malignancies with longer exposure to a PI-based cART regimen. This association was observed particularly for anal cancer [114]. As we did not examine individual cART regimens, no conclusion can as yet be drawn from the D:A:D study in terms of the situation in the Netherlands.

Recommendations

Although the proportion of patients dying of AIDS in the Netherlands has markedly declined throughout the cART era, it remains unacceptably high. Late presentation continues to drive most of these deaths. 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 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-defining malignancies, for which advanced immunodeficiency is a contributing risk factor. In addition, screening for pre-cancerous stages of anal cancer and prevention, identification, and appropriate treatment of viral hepatitis co-infections may also contribute to lowering

of such co-morbidities. Studies such as the AGE$_h$iV cohort study are needed to provide further insights into the independent contribution of HIV and HIV-associated factors such as innate and adaptive immune and coagulation activation and inflammation, which will guide the development of interventions that target relevant pathophysiologic mechanisms[84, 133]. 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 note that the risk of many, if not each, of the co-morbidities that are frequently identified in people living with HIV is determined by multiple factors. Besides immunodeficiency, additional key contributors for consideration include both well-known traditional unmodifiable risk factors, such as age and genetic predisposition, and modifiable lifestyle-related factors, as well as known and as yet unknown effects of antiretroviral treatment and co-infection. Development of antiretroviral agents 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 density loss, and possibly cancer[134].

Ageing, 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 average age of individuals with HIV, it will be imperative to ensure the continued collection of good quality information regarding comorbidities and their risk factors.

Awareness on the part of both physicians and patients concerning the role of modifiable, lifestyle-related risk factors, particularly in those who are older or otherwise at high risk of certain co-morbidities, and the appropriate management of these risk factors offer considerable hope for lowering the co-morbidity burden and ensuring healthy ageing in persons living with HIV.

5. Viral hepatitis

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Background

Infections with hepatitis C virus (HCV) and hepatitis B virus (HBV) are generally 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% has ever been exposed to HBV[135]. In contrast, HCV and HBV co-infections are far more prevalent in HIV-infected individuals due to shared routes of transmission[136].

Individuals with chronic HCV and HBV infection are at risk of developing liver fibrosis, which in time may lead to cirrhosis and can ultimately result in end-stage liver disease and hepatocellular carcinoma (HCC)[137, 138]. HBV infection can also directly lead to HCC without cirrhosis. Progression to severe liver disease takes, on average, 20 to 25 years in HCV or HBV mono-infected patients[139, 140]. HIV co-infection decreases the likelihood of spontaneous HCV clearance and, when chronic HCV infection is established, may accelerate the progression to liver fibrosis and cirrhosis[141-144].

In the era when treatment for HIV infection was either unavailable or insufficiently effective to achieve sustained suppression of viral replication, patients mostly progressed to AIDS and death before the effects of co-infection with HCV or HBV were able to clinically manifest as severe chronic liver disease. However, 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 an increasingly frequent cause of morbidity and mortality in persons living with HIV[145].

A working group on hepatitis, which was set up jointly by the Dutch association of HIV-treating physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) and SHM, has developed a standardised protocol for the collection of data related to liver disease and hepatitis for inclusion in the SHM database. Retrospective collection of extensive, additional data according to this protocol was implemented in July 2012. These detailed data span the entire spectrum of both HBV and HCV infection and range 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 diseases.

This chapter summarises current information regarding the demographic and clinical characteristics, progression to severe chronic liver disease and mortality, and the responses to treatment in this population with HIV and HCV and/or HBV co-infection. Importantly, it also describes the first results of treatment of HCV co-infected patients with the new direct-acting antivirals sofosbuvir, simeprevir and daclatasvir.

HCV

Demographic and clinical characteristics

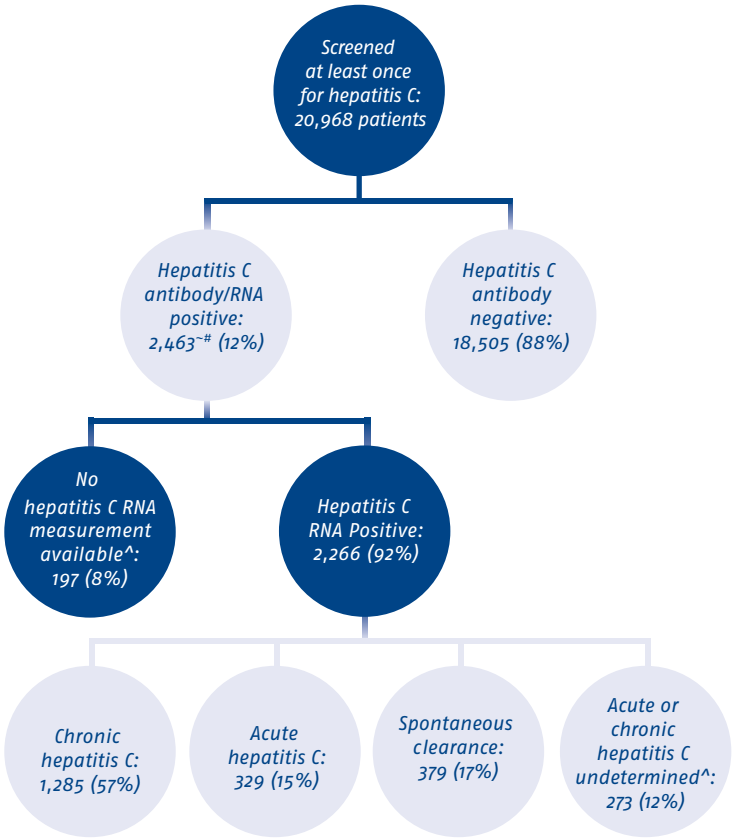
In total, 2,463 (12%) of the 20,968 HIV-1-infected adults (≥18 years of age at time of HIV-1 diagnosis) in care who were ever screened for HCV co-infection had a positive result with an HCV antibody test or HCV RNA test, confirming a far higher prevalence of HCV in the HIV-infected population than estimated for the general population in the Netherlands *(Figure 5.1)*. In 197 of the 2,463 patients (8%), HCV RNA data were not documented. Of the remaining 2,266 patients with positive HCV RNA test results, 1,285 (57%) were classified as being chronically infected (HCV RNA test result documented to have remained positive for more than six months after the first positive result), and 329 (15%) were diagnosed with acute HCV infection (documented anti-HCV IgG seroconversion or HCV RNA conversion within 12 months). Another 379 (18%) patients spontaneously cleared the HCV infection (documented positive test result for HCV antibody or HCV RNA followed by a subsequent negative HCV RNA test result, without having received treatment); demographic characteristics of the patients with spontaneous clearance of HCV are shown in *Table 5.1*. The remaining 273 patients of the 2,266 patients with available HCV RNA data had one positive test result, but no registered follow-up results. This makes it impossible to determine whether the HCV infection was acute or chronic at time of diagnosis, and, therefore, this particular group of patients was excluded from further analysis.

The analyses described in the remainder of this section on HCV are limited to patients who could be definitively classified as having either chronic (n=1,285) or acute (n=329) HCV infection.

The majority of patients who could be classified as having chronic or acute HCV infection were male (83% and 98%, respectively). Most patients originated from the Netherlands (chronic 808/1,285 [63%], acute 264/329 [80%]) *(Table 5.1)*. Fifty-nine percent of the patients ever registered and infected with HIV through injecting drug use (IDU) or former IDU had chronic HCV infection (417 of the total 705 (former) IDU), while 5% of men who have sex with men (MSM) had chronic HCV infection (599 of the total of 12,662 MSM) and 2% of MSM had an acute HCV infection (306 of the total of 12,662 MSM). For 1,120 of the 1,295 patients (86%) with a chronic HCV infection, the HCV genotype had been determined and documented in the clinical records. Most of these patients (63%) were infected with HCV genotype 1, 5% with genotype 2, 15% with genotype 3, and 15% with genotype 4.

Three percent of the patients were either infected with genotype 5 or 6 or the genotype could not be determined. In 301 of the 329 patients (91%) with an acute HCV infection, an HCV genotype was available. In the majority of cases, patients with an acute HCV infection were infected with genotype 1 (68%) or genotype 4 (21%).

Figure 5.1: Flowchart of HIV-infected patients tested at least once for hepatitis C virus (HCV).



~ *Including patients who are HCV RNA positive but with no known HCV antibody data*
\# *Including documented seroconversion*
^ *Excluded from further analyses*

Table 5.1: Demographic characteristics of hepatitis C virus (HCV) co-infected patients registered in the SHM database, 1998-2015.

	Total	Chronic HCV	Acute HCV	Spontaneous clearance
Total number of patients screened for HCV	20,968	1,285	329	379
Male gender, n (%)	17,138 (82)	1,066 (83)	322 (98)	286 (75)
Region, n (%)				
Netherlands	12,082 (58)	808 (63)	264 (80)	193 (51)
Europe	1,388 (7)	193 (15)	18 (5)	49 (13)
Sub-Saharan Africa	2,973 (14)	48 (4)	6 (2)	46 (12)
Caribbean/South America	2,400 (11)	80 (6)	18 (5)	46 (12)
South East Asia	710 (3)	33 (3)	9 (4)	13 (3)
Other	1,415 (7)	123 (10)	14 (4)	32 (8)
HIV transmission route, n (%)				
Men who have sex with men	12,662 (60)	599 (46)	306 (93)	162 (43)
Heterosexual	6,255 (30)	130 (10)	11 (4)	83 (22)
Current and former injecting drug users	705 (3)	417 (32)	4 (1)	82 (22)
Other	1,346 (6)	139 (11)	8 (2)	51 (13)
cART, n (%)	19,227 (92)	1231 (96)	318 (97)	349 (92)
HCV genotype, n (%*)				
Total determined		1,120	301	
1		704 (63)	204 (68)	
2		57 (5)	18 (6)	
3		163 (15)	5 (2)	
4		168 (15)	63 (21)	
Other		28 (3)	10 (21)	
Not determined		165	28	
Deaths, n (%)	1,989 (9)	236 (18)	8 (2)	55 (15)

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

***Legend:** n=total for each category; (%)=percentage of the total for each column; HCV=hepatitis C virus; cART=combination antiretroviral therapy.*

Changes over time

Testing for HCV over time

Screening for HCV infection among HIV-infected patients in care increased over calendar time. In 1998, 39% of the HIV-infected patients in care had not been screened for the presence of HCV infection in that specific calendar year. However, with time, a strong and steady increase in the proportion of patients with known HCV status has been observed. In 2012, only 3% of the patients in care had not been screened for HCV co-infection, and this total declined further to 0.2% in 2014 *(Figure 5.2)*.

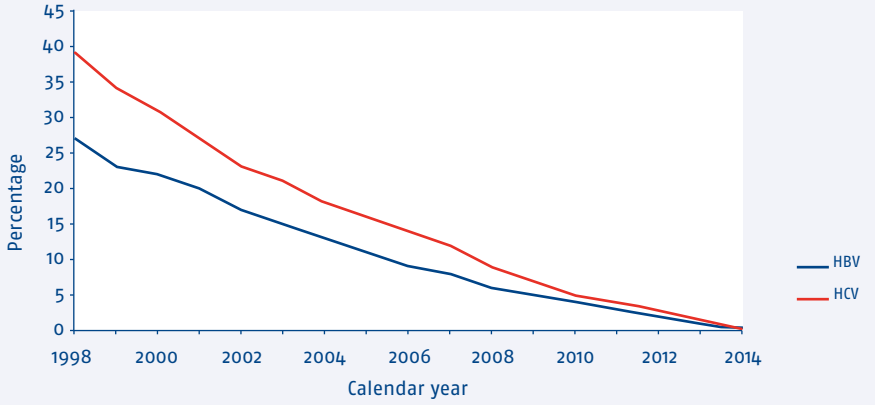
Prevalence of chronic HCV co-infected patients per calendar year

The overall prevalence of chronic HCV co-infection (defined as the proportion of patients who tested positive for HCV RNA for at least six months) among HIV-infected patients in care decreased from 13% in 1998 to 6% in 2014, but was not equally distributed among HIV transmission categories. The highest prevalence was found among patients infected with HIV by IDU or former IDU, and this number varied between 65% and 72% (*Figure 5.3)*.

Incidence of acute HCV infection over time

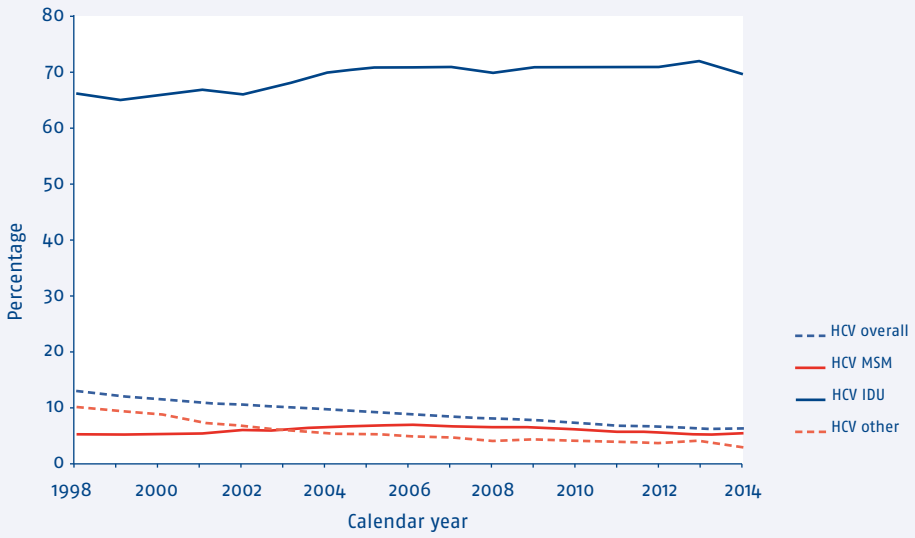
The incidence of acute HCV infection differed importantly between HIV transmission categories. The majority of acute HCV infections occurred in MSM (306/329 (93%)). For IDU or former IDU, the overall incidence was low (1.3/1,000 person years, 95% confidence interval [CI] 0.4-3.4), probably explained by the already large background prevalence of infection in former IDU together with injecting drug use having become very uncommon in the Netherlands. Among patients heterosexually infected with HIV, the overall incidence of acute HCV was 0.2 (0.09-0.35). *Figure 5.4* shows the incidence of acute HCV infection amongst MSM over time. The overall rate of acute HCV infection in this group was 2.9 per 1,000 person years of follow up (95% CI 2.6-3.3). This incidence increased from 0,4 diagnoses per 1,000 person years in 1998 to 3.7 diagnoses per 1,000 person years in 2014, with a peak in 2008 of 6.6 acute HCV infections per 1,000 person years.

Figure 5.2: Percentage of patients in care with an unknown hepatitis B or hepatitis C status per calendar year of care.



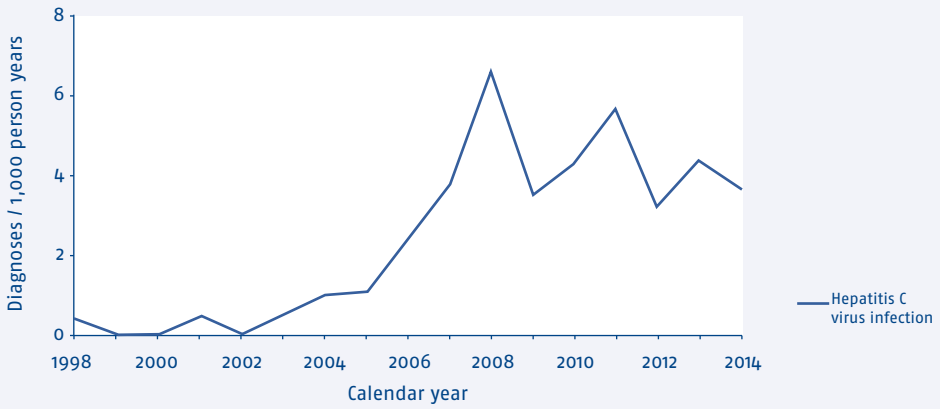
Legend: HBV=hepatitis B virus; HCV=hepatitis C virus.

Figure 5.3: Prevalence of chronic hepatitis C co-infection per calendar year.



Legend: HCV=hepatitis C virus; MSM=men who have sex with men; IDU=injecting drug users.

Figure 5.4: Incidence of acute hepatitis C infection among men who have sex with men, per calendar year.



Treatment for HCV infection

The primary aim of treatment for HCV is to achieve a sustained virological response (SVR)[102]. The treatment originally consisted of interferon alpha (IFN alpha) and subsequently pegylated interferon alpha (PEG-IFN alpha), in combination with (weight-based) ribavirin (RBV). The usual duration of treatment was 24 or 48 weeks, depending on HCV genotype. In April 2012, the first generation HCV NS3/4a protease inhibitors (PI) boceprevir and telaprevir, two direct-acting antiviral agents (DAAs) active against HCV genotype 1, became available in the Netherlands[146, 147]. These agents were used as part of triple therapy that includes one of these two agents, together with PEG-IFN alpha and RBV. In 2014, the HCV NS5B polymerase inhibitor sofosbuvir was introduced in the Netherlands. Currently, as a consequence of government restrictions, sofosbuvir is only reimbursed for HCV-infected individuals with severe liver fibrosis or cirrhosis (metavir score F3-F4 or Fibroscan stiffness ≥9.5), those patients on the waiting list for, or having undergone, a liver transplant, or those patients with extra-hepatic manifestations such as porphyria cutanea tarda, leukocytoclastic vasculitis or vasculitis and/or renal insufficiency secondary to cryoglobulinaemia.

The introduction of sofosbuvir was followed in early 2015 by the availability of two additional novel DAAs, the HCV NS3/4A protease inhibitor (PI) simeprevir and the NS5A inhibitor daclatasvir. Simeprevir is active against HCV genotypes 1 and 4, while daclatasvir is active against all HCV genotypes, but only registered by EMA for genotypes 1, 2, 3 and 4. All three agents can be used as part of a PEG-IFN-free combination regimen. *Table 5.2* gives an overview of all currently-available DAA-containing HCV treatment combinations[148].

Table 5.2: Overview of currently-available treatment regimens, including direct-acting agents active against hepatitis C in the Netherlands.

DAA/HCV treatment combination	Available since	HCV genotypes covered	Treatment duration
Boceprevir+ RBV+PEG-IFN	2012	1	24-48 weeks
Sofosbuvir+RBV+PEG-IFN	2014	All	12 weeks
Sofosbuvir+RBV	2014	All	12-24 weeks
Simeprevir+RBV+ PEG-IFN	2015	1+4	24-48 weeks
Simeprevir+sofosbuvir +/- RBV	2015	1+4	12-24 weeks
Daclatasvir+sofosbuvir+/- RBV	2015	1,2,3,4	12-24 weeks
Daclatasvir+RBV+PEG-IFN	2015	1,2,3,4	24-48 weeks

Legend: DAA=direct-acting antiviral agent; HCV=hepatitis C; RBV=ribavirin; PEG-IFN=pegylated interferon.

Figure 5.5 shows the absolute number of patients having started HCV treatment per calendar year. In total, 967 patients have received anti-HCV treatment, of whom 205 have also received second-line treatment.

Treatment with IFN/PEG-IFN plus ribavarin

The number of patients per year starting IFN alpha/PEG-IFN alpha plus ribavirin (RBV) treatment increased from 21 in 2000 to 140 in 2012, followed by a decrease from 2012 onwards to 14 in 2014 *(Figure 5.5)*.

Outcome

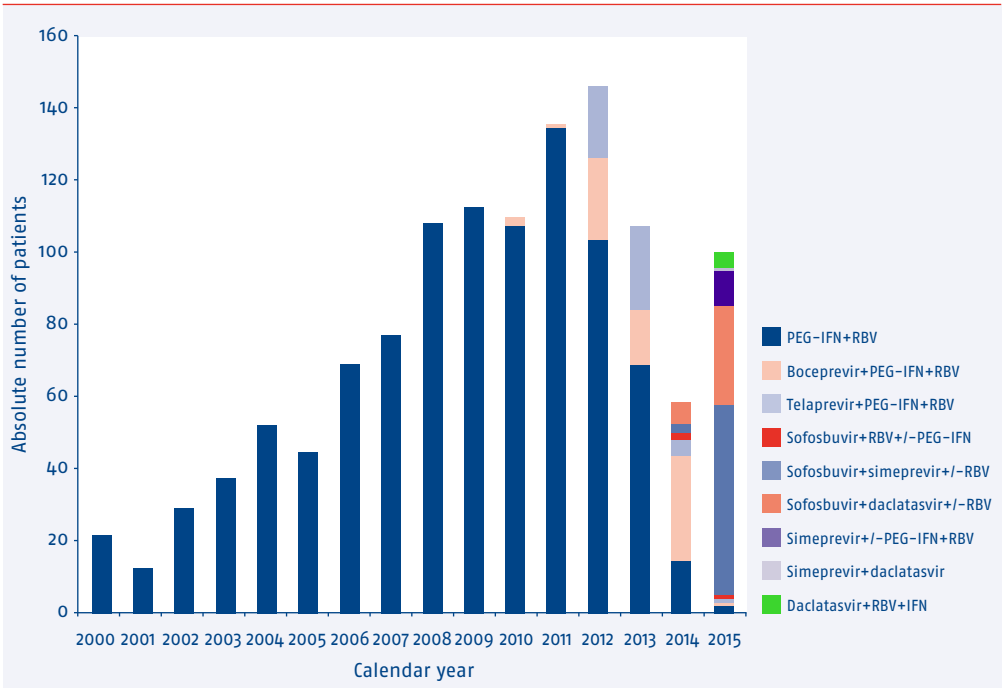
Of the 329 patients with an *acute HCV infection*, 217 initiated treatment with (PEG)-IFN alpha and RBV and, by the time of database closure, had completed a sufficient follow-up period to enable sustained virological response (SVR) calculation. The median duration of treatment in these 217 patients was 25 weeks (interquartile range [IQR] 23-47). SVR rates are shown in *Figure 5.6.A*, stratified by HCV genotype. SVR rates were as high as 73% in patients with genotype 2, but ranged from only 42% to 67% for genotypes 1, 3, and 4. It should be noted that the number of patients with genotypes 2 and 3 receiving treatment was very small, limiting conclusions about treatment response for these particular genotypes.

Of the 612 patients who had completed sufficient follow-up time to enable SVR calculation, the median duration of treatment with PEG-IFN alpha plus RBV for *chronic HCV infection* was 27 weeks (IQR 22-48). *Figure 5.6.A* shows the SVR rate stratified by HCV genotype. Forty-eight percent of the patients with genotype 3 and 47% with genotype 2 achieved SVR, with lower rates for the other genotypes (i.e., 35% for genotype 1, 45% for genotype 4, and 17% for patients with an unknown or other genotype).

Treatment with boceprevir or telaprevir

Sixty-nine patients started with boceprevir between 2010 and 2015, with treatment during the first two years provided as part of an international study[149]. From 2012 onwards, 46 patients started telaprevir treatment[147] *(Figure 5.5)*.

Figure 5.5: Number of co-infected patients starting hepatitis C treatment per calendar year.

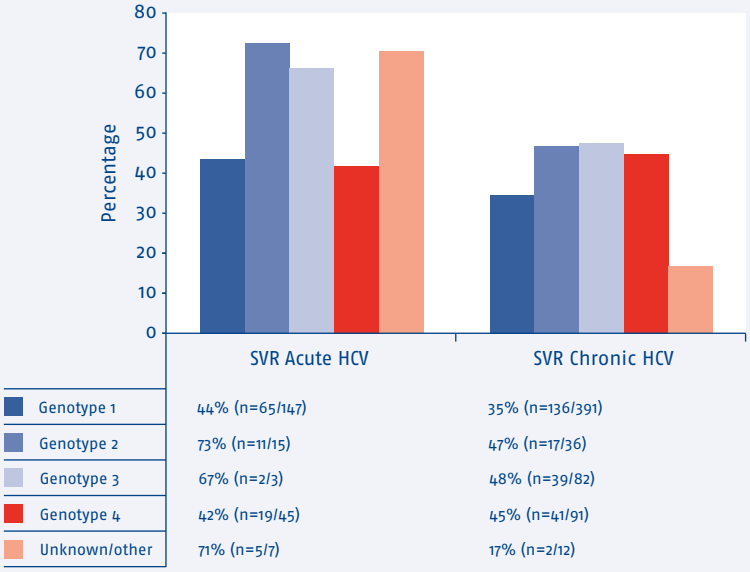


Legend: RBV=ribavirin; PEG-IFN=pegylated interferon.

Outcome

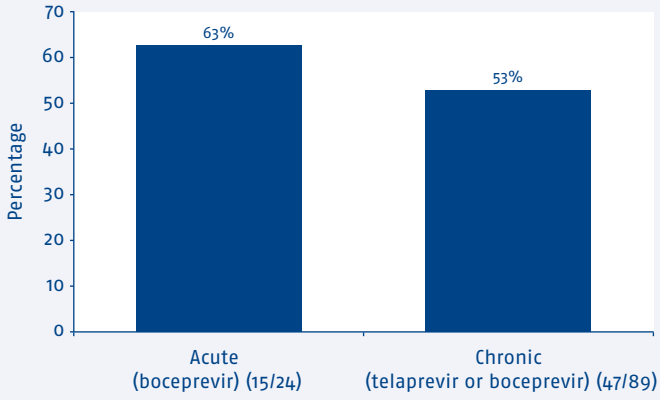
A total of 113 of these 115 patients completed treatment with boceprevir (n=67) or telaprevir (n=46) and had enough follow-up time to enable SVR calculation. The median duration of treatment was 28 weeks (IQR 12-48 weeks) with boceprevir and 26 weeks (IQR 19-48) with telaprevir. SVR was achieved in 63% (15/24) of patients with acute HCV who received boceprevir. Among patients with chronic HCV infection, 53% (47/89) of those treated with telaprevir or boceprevir achieved an SVR (*Figure 5.6.B*).

Figure 5.6.A: Sustained virological response (SVR) achieved by PEG-IFN+RBV or IFN+RBV treatment in acute and chronic hepatitis C (HCV)-infected patients, stratified by HCV genotype.



Legend: *SVR=sustained virological response; HCV=hepatitis C.*

Figure 5.6.B: Sustained virological response achieved by boceprevir or telaprevir treatment in acute and chronic hepatitis C-infected patients.



Treatment with sofosbuvir, simeprevir and/or daclatasvir

To report on the treatment with newly available DAAs, SHM made an effort to obtain updated data up to 15 September 2015, i.e. after the general database lock of 1 May 2015.

In total, 104 HIV co-infected patients have been treated with a regimen containing either sofosbuvir, simeprevir, or daclatasvir. Of these 104 patients, 11 started their treatment in 2014 and the remaining 93 patients started in 2015 *(Table 5.3)*. Fifty of these 104 patients had been pre-treated with PEG-IFN plus RBV before being treated with one of the new DAAs. The most frequently-used regimens were sofosbuvir plus daclatasvir +/- RBV (n=33) and sofosbuvir plus simeprevir +/- RBV (n=52).

One patient died of a non-natural cause and another patient died of liver decompensation after initially receiving simeprevir with sofosbuvir and subsequently switching to sofosbuvir and daclatasvir.

Outcome

In total, at the time of database closure, 104 patients were known to have started with a DAA regimen containing sofosbuvir, daclatasvir and/or simeprevir. Fifty-four patients had completed treatment with one of these regimens. For 45 out of these 54 patients, HCV RNA follow-up data was available to determine the end of treatment response after completion of the treatment: one patient had a positive HCV RNA test result after treatment discontinuation, while the remaining 44 patients had a negative HCV RNA test result *(Table 5.3)*. Twenty-two patients had enough follow up time after treatment discontinuation to calculate the SVR12 rate, and 21 out of the 22 patients achieved an SVR12 (95%).

Table 5.3: Overview of responses to new regimens containing direct-acting antivirals (DAAs) used by hepatitis C-HIV co-infected patients in care in the Netherlands, based on data available as of 15 September 2015.

Regimen	n	HCV genotype	HCV IFN+RBV pretreated	Liver fibrosis (f3f4)	Treatment completed	Treatment duration (mean, weeks)	End of treatment response* (n/total patients with available HCV RNA test results)	SVR12** (n/total patients with available HCV RNA test results)
Sofosbuvir+ PEG-IFN+RBV	2	GT 1: 1 GT 4: 1	1/2	2/2	1/2	8	1/1	1/1
Sofosbuvir+RBV	1	GT: 4	1/1	1/1	1/1	12	1/1	1/1
Sofosbuvir+ daclatasvir+RBV	8	GT 1: 4 GT 3: 2 GT 4: 1 Unknown: 1	7/8	8/8	4/8	15	2/2	–
Sofosbuvir+ daclatasvir	25	GT 1: 16 GT 3: 4 GT 4: 3 Unknown: 1	14/25	20/25	13/25	16	10/11	6/7
Sofosbuvir+ simeprevir+RBV	11	GT 1: 9 GT 4: 1 Unknown: 1	8/11	9/11	5/11	10	3/3	2/2
Sofosbuvir+ simeprevir	41	GT 1: 30 GT 4: 8 Unknown: 3	16/40	28/40	21/41	12	20/20	10/10
Simeprevir+daclatasvir	1	GT 1: 1	1/1	0/1	1/1	12	1/1	–
Simeprevir+IFN+RBV	8	GT 1: 3 GT 4: 3 Unknown: 2	1/8	1/8	7/8	13	5/5	1/1
Simeprevir+RBV	1	Unknown: 1	0/1	1/1	0/1		–	–
Daclatasvir+RBV+IFN	4	Unknown: 4	1/4	0/4	1/4	9	1/1	–
Trial with additional new DAA	2	GT 1: 2	0/2	0/2	0/2		–	–
Total	**104**		**50/104**	**70/104**	**54**		**44/45**	**21/22**

** End of treatment response=negative HCV NRA test result at time of treatment discontinuation.*

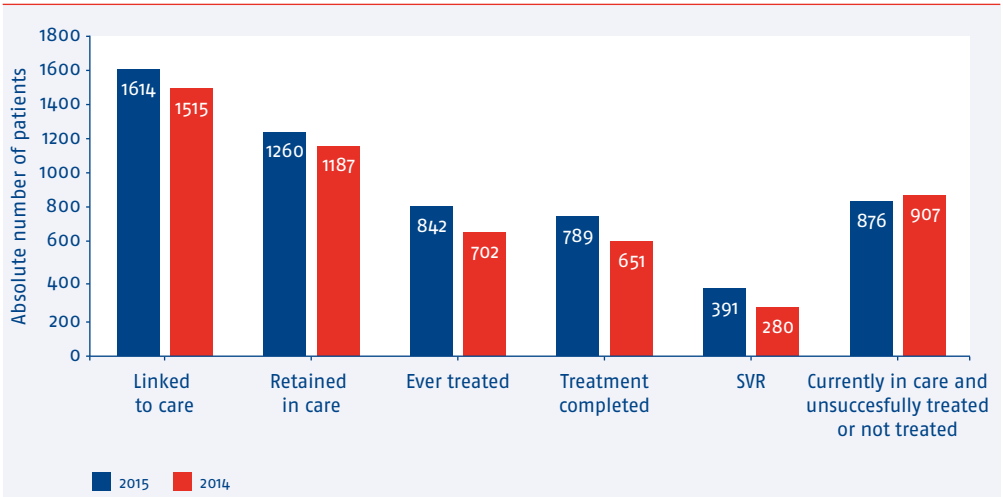
*** SVR12=sustained virological response defined as a negative HCV RNA test result 12 weeks after treatment discontinuation.*

***Legend:** PEG-IFN=pegylated interferon; RBV=ribavirin; GT=HCV genotype; DAA=direct-acting antiviral agent; SVR=sustained virological response.*

HCV treatment continuum of care

Figure 5.7 shows the continuum of care for patients with an HCV co-infection, based on the number known to be in care and on available data as of 15 September 2015, with data from last year's 2014 report (data cut-off 1 June 2014) shown for comparison. Out of a total of 1,614 patients linked to HIV care and diagnosed with HCV, 1,260 patients (78%) were retained in care, and 842 (67%) of the 1,260 had ever received treatment for HCV. Of the 842 patients treated for HCV, 789 (94%) had completed HCV treatment and had data available to calculate their HCV treatment response. Overall, 384 of the 789 (49%) patients who completed treatment achieved an SVR. As a result, 876 of the 1,260 patients (69%) who were alive and in care as of 15 September 2015 in one of the Dutch HIV treatment centres remained either untreated (n=418), not successfully treated (n=405), or were still being treated or did not have enough time after treatment discontinuation to calculate the SVR (n=53) for an active HCV infection. When compared with the figures for 1 June 2014, the continuum of care shows that an additional 140 patients have started HCV treatment and an additional 104 patients have documented evidence of a cure. In addition, in spite of the fact that the total number of patients retained in care with an acute of chronic HCV infection has increased by 73 patients, the total number of patients who remain in need of HCV treatment has decreased from 907 to 876.

Figure 5.7: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

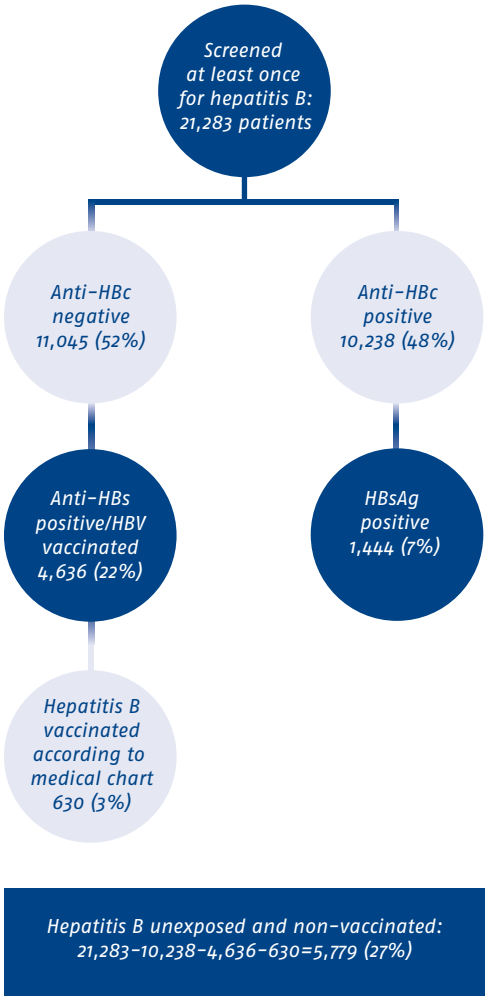
HBV

Forty-eight percent of the 21,283[1] HIV-infected patients ever registered in the SHM database and ever screened for hepatitis B core antibody (anti-HBc) tested positive during screening and thus have been exposed to HBV.

In total, 11,045 (52%) HIV-infected patients tested negative for anti-HBc. Of those patients, 4,636 (22%) were anti-HBc-negative and anti-hepatitis B surface antigen-positive (HBsAg+), indicating that they had been successfully vaccinated against HBV *(Figure 5.8)*. This proportion was 25% for MSM, 15% for heterosexuals and far lower (6%) for IDU and former IDU. For 630 patients (3%) who had not been tested for both anti-HBs and anti-HBc, the HIV-treating physician had noted HBV vaccination in their medical record; 469 of these patients were MSM.

[1] *The total number of patients screened for HBV differs from the total number of patients screened for HCV, as not all patients screened for HBV are also screened for HCV.*

Figure 5.8: Flowchart of HIV-infected patients tested at least once for hepatitis B.



Legend: *Anti-HBc=hepatitis B core antibody; anti-HBs=hepatitis B surface antibody.*

Therefore, overall, approximately 27% of the HIV-infected patients remained at risk of HBV infection because they had not been exposed to HBV, had not been vaccinated, or had been unsuccessfully vaccinated (100%-48% exposed-22% serological evidence of successful vaccination-3% former successful vaccination otherwise documented=27%). Furthermore, 21% of MSM remained at risk (100%-50% exposed-25% serological evidence of successful vaccination-4% former successful vaccination otherwise documented=21%).

Patients in these categories should be offered HBV vaccination, although they may be protected from acquiring HBV infection by the use of tenofovir as part of their cART regimen, as suggested by findings reported by one of the Dutch HIV treatment centres and an international study by Quirck *et al.*[150, 151]. Among the patients with no exposure to HBV infection, 73% are currently being treated with a cART regimen that includes tenofovir.

HBV co-infection (defined as two or more consecutive positive test results for HBsAg over a consecutive period of at least 6 months) was found in 1,444 of the 21,283 (7%) 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 (1,237/1,444, 86%), in line with those co-infected with HCV (*Table 5.4).* However, compared to patients co-infected with HCV, those co-infected with HBV were more likely to have been born in Sub-Saharan Africa and to have acquired HIV through heterosexual contact. HBV co-infection was less common than HCV co-infection amongst IDUs and former IDUs.

Table 5.4: *Demographic characteristics of HIV-infected patients with an active chronic hepatitis B virus (HBV) infection registered in the SHM database, 1998-2015.*

	Total	Hepatitis B surface antigen (HBsAg) positive
Total number of patients screened for HBV, n (%)	21,283	1,444 (7)
Male gender, n (%)	17,265 (81)	1,237 (86)
Age at HIV diagnosis (years, median IQR)		
Region, n (%)		
Netherlands	12,198 (57)	720 (50)
Europe	1,390 (7)	90 (6)
Sub-Saharan Africa	3,117 (15)	322 (22)
Caribbean/South America	2,434 (11)	150 (10)
Southeast Asia	725 (3)	59 (4)
Other	1,419 (7)	103 (7)
HIV transmission group, n (%)		
Homosexual	12,683 (60)	845 (59)
Heterosexual	6,517 (31)	417 (29)
Injecting drug user	704 (3)	76 (5)
Other	1,379 (6)	106 (7)
cART, n (%)	19,382 (91)	1,327 (92)
Deaths, n (%)	2,124 (10)	230 (16)

Legend: *n=total for each category; (%)=percentage of the total for each column; HBV=hepatitis B virus; cART=combination antiretroviral therapy.*

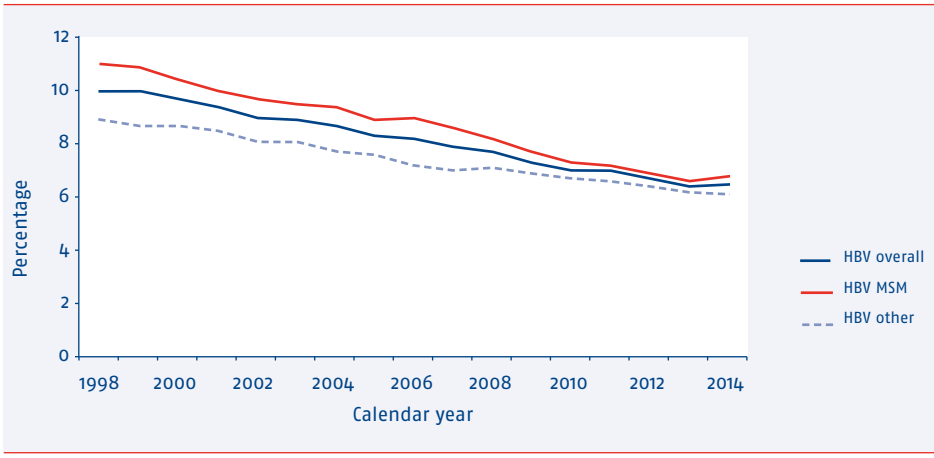
Testing for HBV infection over time

Screening for HBV infection amongst HIV-infected patients in care improved over calendar time. In 1998, 27% of the patients were not screened for the presence of HBV infection (*Figure 5.2)*. A strong decrease was subsequently observed for the proportion of HIV-infected patients with an unknown HBV status. In 2014, 0.3% of all patients in care had an unknown HBV status *(Figure 5.2)*.

Prevalence

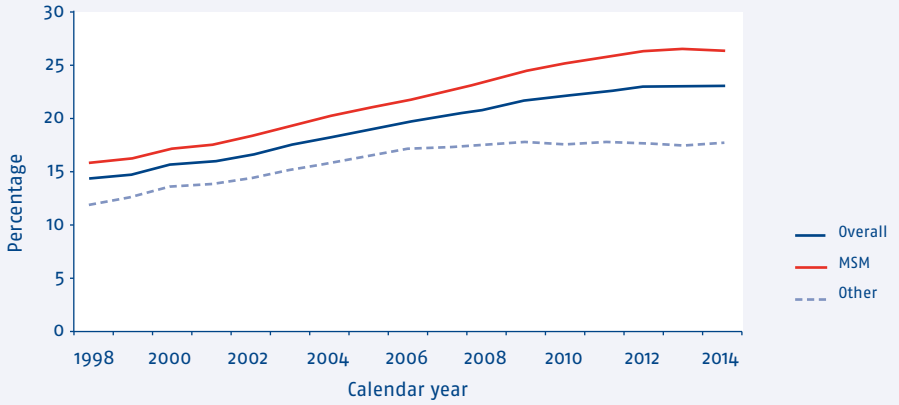
The overall prevalence of chronic HBV infection among patients in care decreased from 10% in 1998 to 6.5% in 2014. The highest prevalence was found amongst MSM. In 1998, 11% of the MSM had chronic HBV infection, decreasing to 6.8% in 2014 *(Figure 5.9)*. This decreasing prevalence of chronic HBV infection might be the result of increasing HBV vaccination rates among patients, together with the preventive effect of treatment with a cART regimen that includes tenofovir *(Figure 5.10)*.

Figure 5.9: *Prevalence of chronic active hepatitis B co-infection per calendar year.*



Legend: *HBV=hepatitis B; MSM=men who have sex with men.*

Figure 5.10: Prevalence of patients vaccinated for hepatitis B per calendar year.



Legend: HBV=hepatitis B; MSM=men who have sex with men.

Treatment for chronic HBV infection

Since chronic HBV infection is defined by the presence of HBsAg (HBsAg+), therapy is aimed at lowering the level of HBsAg to achieve HBsAg negativity in a subgroup of patients. Persistent HBsAg negativity, together with the development of antibodies against HBs, is known as HBs seroconversion. HBs seroconversion is the penultimate goal of HBV therapy. In those patients who are also e-antigen positive (HBeAg+), a similar seroconversion from HBeAg positivity to HBeAg negativity can occur, with subsequent development of anti-hepatitis B e-antigen (anti-HBe) antibodies. This so-called e-seroconversion is an important secondary treatment parameter, since studies have shown that it results in a clinically important lowering of HBV DNA and therefore lower liver fibrosis progression. Lastly, HBV DNA is the parameter most directly influenced by therapy with either nucleoside or nucleotide analogues. Therefore, HBV DNA undetectability is the best surrogate marker for treatment response, and persistent lowering of HBV DNA levels to <20 IU/ml has been shown to delay progression of liver fibrosis to cirrhosis. Several antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and particularly tenofovir, are also active against HBV.

Of the 1,444 patients with HIV in the SHM database co-infected with chronic HBV, 1,347 (93%) have ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 97 patients not having received anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=18), not receiving cART (most likely because of high CD4 counts) (n=11), lost to follow up (n=41), and unavailability of sufficient information (n=11).

Most patients (n=753/1,347, 56%) initially received lamivudine as monotherapy against HBV and the majority of these patients started with lamivudine as monotherapy before the availability of tenofovir. Of the patients treated for HBV with lamivudine only, 293 (39%) switched to a regimen containing tenofovir plus lamivudine after a median of 1.6 years (IQR 0.5-4.0), and 220 (29%) switched to a regimen containing tenofovir plus emtricitabine after a median of one year (IQR 0.3-2.7) of prior exposure to lamivudine monotherapy for HBV. For 594 of 1,347 patients (40%), the initial cART regimen included tenofovir and one additional agent with activity against HBV; for 116 of these 594 patients (20%), the additional agent was lamivudine, and for 478 patients (80%) the additional agent was emtricitabine.

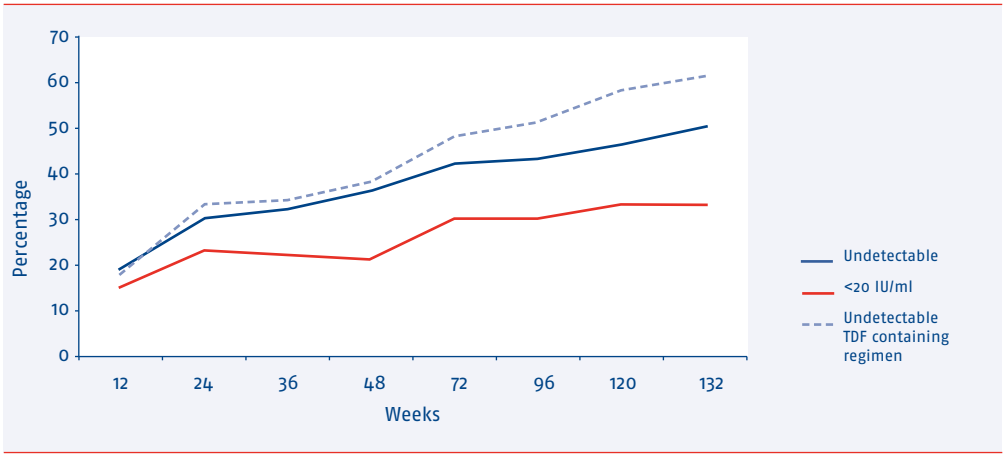
It has been shown that a persistently inactive HBV carrier state with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC in the majority of HBV mono-infected patients.

Figure 5.11 shows the proportion of patients who had an undetectable HBV DNA level below 20 IU/ml as a percentage of the total number of patients with an HBV DNA measurement. For HBV DNA measurements with a different detection limit, we used the detection limit of the specific assay (<100, <200, <400, <1000 or <2000 IU/ml). Twelve weeks after the start of HBV treatment, 19% of the patients had an undetectable HBV DNA level based on the detection limit of the assay used at that moment, and 15% had an HBV DNA level below 20 IU/ml. The percentage of patients with an undetectable HBV DNA level, based on the detection limit of the specific assays used at that moment, was 36% after the first year of treatment, with an increase to 43% two years after the start of treatment and 50% three years after the start. The percentage of patients with an HBV DNA level below 20 IU/ml was 21% one year after the start of treatment, 30% after two years, and 30% after three years. In terms of patients who were using a tenofovir-containing cART regimen, 61% of patients with HBV DNA follow-up data had an undetectable HBV DNA level after three years of receiving treatment *(Figure 5.11)*.

Among the 1,347 patients whose cART regimen ever included one or more agents with activity against HBV, 318 of the 657 patients (48%) had a documented positive test result for HBeAg. Of these 318 patients, 183 (57%) were retested, with 99 (54%) converting from HBeAg positivity to negativity and HBe antibodies developing in 51 (28%).

HBsAg clearance during HBV treatment could be assessed in 1,020/1,347 patients, and HBs seroconversion in 821/1,347 with an available repeat test result. The HBsAg clearance rate was 26% (267/1,020) and anti-HBs seroconversion rate was 9% (72/821).

Figure 5.11: Percentage of all patients and those on a tenofovir-containing regimen with undetectable hepatitis B virus (HBV) DNA levels (<100, <200, <2000 IU/ml) and percentage of all patients with an HBV DNA level <20 IU/ml, since the start of treatment.



Legend: TDF=tenofovir.

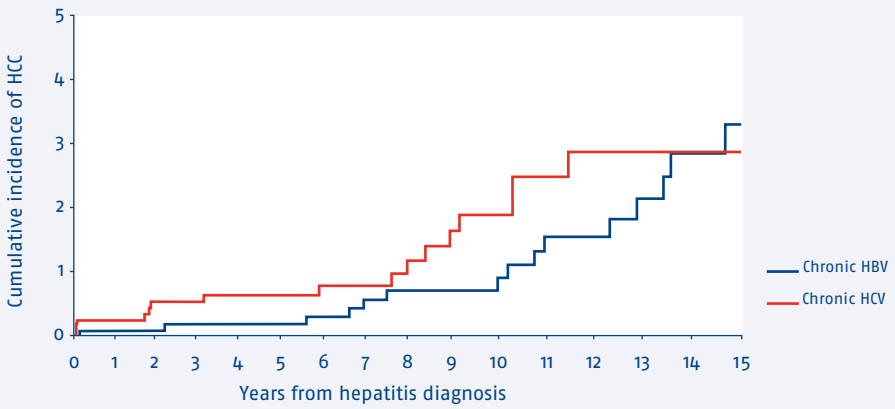
Morbidity and mortality in HCV and/or HBV co-infected patients

Liver-related morbidity

Additional data on pathology reports from liver biopsy, transient elastography (FibroScan) or both, were available for 1,312 of the 1,614 patients with chronic or acute HCV infection, and for 1,000 of the 1,444 patients with an HBV infection. Review of these additional data showed that severe chronic liver disease by our definition was considered present (presumptive and definitive categories combined) in 542 of the 1,312 patients (41%) with HCV infection and in 345 of the 1,000 HBV co-infected patients (35%). Definitive severe chronic liver disease was documented for 116 patients with an HCV infection and 50 with HBV infection.

HCC was diagnosed in 18 out of 1,285 patients (1.4%) with a chronic HCV infection, of whom 13 were born in the Netherlands. HCC was found in 21 patients (1.4%) with a chronic HBV infection, 12 of whom were born in the Netherlands, 5 in Sub-Saharan Africa, and 1 each in South America, Asia, the United States, and Australia. *Figure 5.12* shows the cumulative incidence of HCC. It should be noted, however, that the time between diagnosis of hepatitis co-infection and HCC is likely to have been shorter in patients with an HCV infection. Ten years after a known diagnosis of viral hepatitis, HCC had developed in 2.9% (95% CI 1.7-4.9%) of patients with HCV infection and in 1.3% (95% CI 0.7-2.6%) of those with chronic HBV infection.

Figure 5.12: Cumulative incidence of hepatocellular carcinoma (HCC) among co-infected patients with HIV and hepatitis C (HCV) or hepatitis B (HBV). Kaplan-Meier estimate was used to determine the time to HCC. Follow-up time was measured from the date of HIV diagnosis to the date of last contact, diagnosis of HCC, or 1 January 2015.



Legend: HCV=hepatitis C virus; HBV=hepatitis B virus; HCC=hepatocellular carcinoma.

Mortality

All-cause mortality

The overall rate of death from any cause was 15% for the 1,614 patients with an HCV infection *(Table 5.5)*. The cumulative incidence of death from any cause was higher among patients who were diagnosed with HCV or HBV before 2000 compared to those who were diagnosed in later calendar years *(Figure 5.13)*. 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 HIV and HCV co-infection diagnosed before 2000. However, for patients with an 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 both before 2000 and after 2000, the overall risk of death was higher compared to that in HIV mono-infected patients *(Table 5.6)*.

Liver-related death

In total, 90 patients co-infected with hepatitis died of a liver-related cause *(Table 5.5)*. Ten years after cART initiation, 7% (95% CI 3-14) of chronic HCV co-infected patients who were diagnosed with HCV before 2000, died of a liver-related cause. This proportion was lower (3%, 95% CI 2-5) among patients with an HCV diagnosis after 2000. Among those with HBV co-infection, 6% of patients diagnosed before 2000 died of a liver-related cause (95% CI 4-9), which dropped to 1% (95% CI 0.3-2) in those diagnosed after 2000 *(Figure 5.13)*.

Table 5.5: *Morbidity and mortality in hepatitis C virus (HCV) and hepatitis B virus (HBV) co-infected patients registered at SHM.*

	HCV infection	HBV infection
Total	1,614	1,444
Severe chronic liver disease#, n (%)	542 (34)	345 (24)
HCC, n (%)	18 (1.1)	21 (1.5)
Deaths from any cause*, n (%)	244 (15)	230 (16)
Liver-related deaths, n (%)	54 (3.3)	36 (2.5)

 # Including presumptive and definitive liver disease

** Including liver-related death*

Legend: *HCV=hepatitis C virus; HBV=hepatitis B virus; HCC=hepatocellular carcinoma.*

After adjustment for demographic and clinical characteristics, HBV co-infected patients and those co-infected with HCV diagnosed both before and after 2000 remained more likely to have a liver-related cause of death than HIV mono-infected patients *(Table 5.6)*. However, the risk of death from a liver-related cause strongly decreased in HBV co-infected patients from a hazard ratio (HR) of 21.2 (95% CI 11.5-39.2) in patients diagnosed with HBV before 2000 to an HR of 5.8 (95% CI 2.33-14.8) in patients diagnosed from 2000 onwards. This marked decrease in risk of death from a liver-related cause was thus far not observed in HCV co-infected patients.

Figure 5.13: Cumulative incidence of all-cause mortality (A) and liver-related death (B), stratified by calendar year period. The Kaplan-Meier estimate was used to determine the time to death. Follow-up time was measured from the date of HIV diagnosis to the date of last contact, death or 1 January 2015.

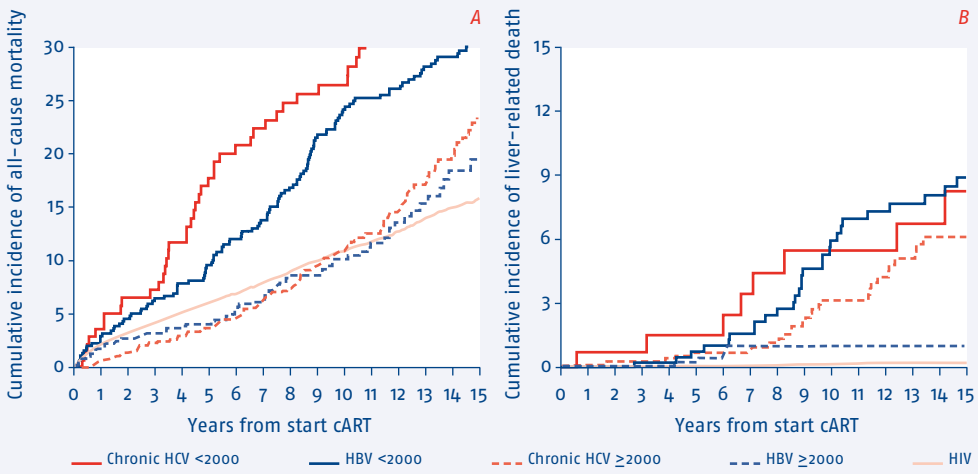


Table 5.6: Adjusted hazard ratios of time from start of combination antiretroviral therapy (cART) to all-cause mortality and liver-related death amongst HIV-infected patients with hepatitis co-infection compared to patients who are infected with HIV only. To evaluate the impact of HBV and HCV co-infection on risk of death, time on cART to death was estimated by a Cox proportional hazard model. Follow-up time was measured from the date of cART initiation until date of last contact, most recent follow-up visit, death or 1 January 2015.

	Risk of death from any cause Hazard ratio (95% CI)	p-value	Risk of liver-related death Hazard ratio (95% CI)	p-value
HIV	1	<0.001	1	<0.0001
HIV/chronic HCV, <2000	1.00 (0.73-1.37)		11.7 (5.87-14.8)	
HIV/chronic HCV, ≥2000	1.50 (1.23-1.83)		15.63 (8.12-30.1)	
HIV/chronic HBV, <2000	1.43 (1.19-1.73)		21.2 (11.5-39.2)	
HIV/chronic HBV, ≥2000	1.31 (1.04-1.66)		5.8 (2.33-14.8)	

** 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.*
***Legend:** cART=combination antiretroviral therapy; HBV=hepatitis B virus; HCV=hepatitis C virus; CI=confidence interval.*

Conclusion

Screening for HCV and HBV co-infection in the HIV-infected population continues to improve over time. While approximately 39% of the patients in care in 1998 were not screened for co-infection with HBV or HCV, this figure decreased to less than 1% in 2014.

Six percent of HIV-infected patients registered in the SHM database were documented to be chronically infected with HCV, and 1.6% of patients were documented as having acute HCV infection. Seven percent of the HIV-infected patients ever in care had chronic HBV infection. The prevalence of HBV decreased over time, which might be a result of the increased proportion of patients of non-Dutch origin being vaccinated for HBV or could be a consequence of the use of tenofovir in cART-treated patients. Nonetheless, an estimated 27% of HIV-infected patients, overall, and 21% of MSM either have not been exposed to HBV or have not been successfully vaccinated and may remain at risk of acquiring HBV. Seventy-three percent of the patients still at risk of acquiring HBV infection receive a cART regimen that includes tenofovir and thereby may be at substantially lower risk due to sustained chemoprophylaxis.

In general, HIV-infected patients co-infected with HCV or HBV are at increased risk of progression to severe liver disease[137][138]. In our study population, thirty-four percent of the chronically 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 become significantly lower for patients with chronic HBV diagnosed after 2000, likely as a result of increasingly effective treatment through the use of tenofovir-containing cART.

Our data clearly show that, with the advent of novel DAAs in 2014 and 2015, PEG-IFN-containing regimens are rapidly being replaced in clinical practice by a variety of all-oral DAA-based regimens and more patients with HCV co-infection are being treated. Based on data available up to 15 September 2015, more than 100 patients have received or are currently receiving treatment with regimens including one or more of the currently available novel DAAs sofosbuvir, simeprevir and daclatasvir. Of note, with exception of one patient, all patients who completed their treatment with these new DAAs had a negative HCV RNA test result at the end of treatment, and 95% of all patients with sufficient follow-up data to calculate an SVR were found to have been cured. These results are markedly better than what has been achieved thus far with previous PEG-IFN alpha containing regimens. These developments have already resulted in a lower number of HCV-co-infected patients

who are still in need of effective treatment, in spite of an increase in the total number of patients with HCV co-infection currently in care compared to last year's report.

The rapidly increasing availability of novel interferon-free, highly effective combination antiviral regimens for HCV, together with optimised screening for HCV co-infection with time will hopefully limit the impact of HCV co-infection on liver-related morbidity and mortality.

Recommendations

Continued efforts must be undertaken to ensure that all patients with HIV are adequately assessed for the presence of HBV and HCV co-infection. In particular, there should be ongoing efforts to increase HBV vaccination rates among HIV-infected patients at increased risk of becoming infected with HBV, particularly those who are not receiving a tenofovir-containing antiretroviral regimen. Furthermore, there should be a focus on ensuring the availability of novel highly effective interferon-free combination regimens for all known HCV co-infected HIV-positive patients in care and still in need of treatment. Over the long term, provision of these treatments can be expected to contribute to reducing the burden of severe chronic liver disease, hepatocellular carcinoma, and liver-related mortality among persons living with HIV. In addition, they may be expected to have a beneficial impact on the risk of ongoing HCV transmission. 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 hepatitis C virus (HCV) infection: Patients who remain HCV RNA positive for longer 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 [152].

Spontaneously cleared HCV infection:

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

Chronic hepatitis B virus (HBV) infection: Two or more consecutive positive test results for hepatitis B surface antigen (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 was defined:
presumptively by clinically documented evidence of:

- Bleeding from gastric or oesophageal varices, hepatic encephalopathy or hepatorenal syndrome and/or
- 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 and/or cirrhosis,

and definitively if:

- combined with a pathology or FibroScan report documenting severe liver fibrosis or cirrhosis (metavir score F3-F4 or FibroScan stiffness ≥8kPa).

< Back to page 130

6. Distinct populations: HIV-1 infected children in the Netherlands

Colette Smit, Annemarie van Rossum and Peter Reiss

Background

Healthcare for HIV-1-infected children living in the Netherlands is provided mostly by four paediatric HIV treatment centres, although some of the older children receive care in one of the HIV treatment centres for adult care. As with adult patients, diagnosis, treatment and follow up of these children are monitored by Stichting HIV Monitoring (SHM). Overall, demographic and clinical data have been collected by SHM for 534 children aged up to 18 years at the time of their HIV-1 diagnosis, representing an increase of 22 children compared to last year's report.

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-1-infected children worldwide[153-155]. In particular, early initiation of cART in HIV-1-infected children has been proven to benefit the survival of these children[156-160]. Results from birth cohort studies of children infected vertically suggest that 70% to 80% of untreated children survive to only five years of age. Until 2010, the World Health Organization (WHO) recommended starting cART in all children less than 2 years of age, regardless of their CD4 T-cell count or clinical status[161]. However, as of June 2013, this recommendation has been extended to include all children less than 5 years old[162]. Moreover, the Paediatric European Network for Treatment of AIDS (PENTA) 2015 guidelines for the treatment of paediatric HIV-1 infection recommend treatment in all children younger than one year of age, and in children of all ages before the CD4 cell count reaches the age-specified threshold for CD4 treatment[163].

Demonstrating a relation between age at initiation of cART and clinical outcome is difficult because clinical disease progression is rare in children receiving cART. For this reason, virological and immunological outcomes are used as alternative endpoints. Given that normal CD4 cell counts in younger children are highly age-dependent, it is more appropriate to analyse time-dependent CD4 count trajectories while expressing CD4 counts as z-scores, in which counts are standardised in relation to age.

Here we report the demographics, clinical characteristics, and long-term virological and immunological response to treatment in the 534 HIV-1-infected children ever cared for in one of the paediatric and/or adult HIV treatment centres in the Netherlands.

Population

Ever in care

In this chapter we define 'children' as those diagnosed with HIV-1 before the age of 18 years. The majority of children received care in a paediatric HIV treatment centre. However, children who are diagnosed with HIV-1 at an older age, and who are predominantly infected with HIV-1 through sexual transmission, are often under clinical observation in an adult HIV treatment centre *(Table 6.1)*. All patients diagnosed with HIV-1 before the age of 18 years under clinical observation in a paediatric HIV treatment centre or in an adult HIV treatment centre are included in the analyses.

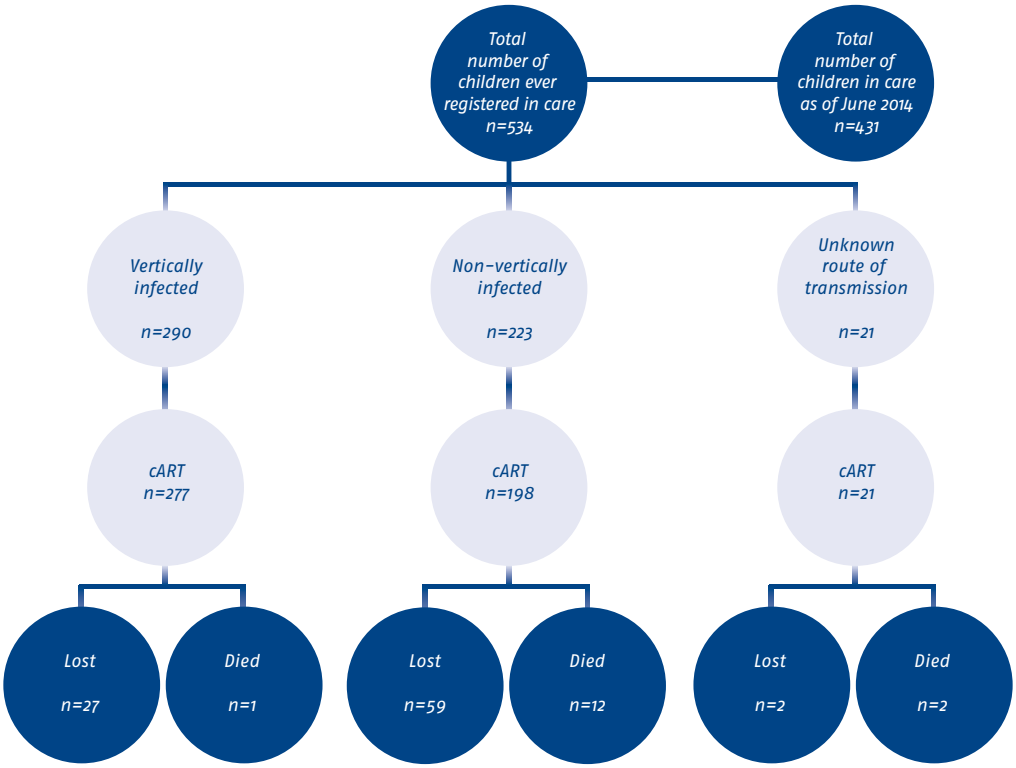
As of May 2015, 534 HIV-1-infected children have been ever registered by SHM. Of those, 290 were vertically infected with HIV-1, and 223 were non-vertically infected *(Figure 6.1)*. For a small group of children, 21 in total, the route of HIV-1 transmission was unknown.

Table 6.1: Demographics and characteristics of 534 HIV-1-infected children in care in the Netherlands.

Characteristics	Vertically acquired HIV-1 infection n (%)	Non-vertically acquired HIV-1 infection n (%)	Route of transmission unknown n (%)
Total	290 (54)	223 (42)	21 (4)
HIV-1 treatment centre			
Child care	282 (97)	27 (12)	13 (62)
Adult care	8 (3)	196 (88)	8 (38)
Gender			
Male	144 (50)	90 (40)	15 (71)
Female	146 (50)	133 (60)	6 (29)
Country of origin child			
The Netherlands	107 (37)	56 (25)	2 (10)
Sub-Saharan Africa	145 (50)	120 (54)	15 (76)
Other	38 (13)	47 (21)	4 (14)
Country of origin mother			
The Netherlands	23 (8)	5 (2)	2 (10)
Sub-Saharan Africa	174 (60)	34 (15)	7 (33)
Other/unknown	93 (32)	184 (83)	12 (57)
Age at HIV-1 diagnosis	1.52 (0.3-4.2)	16.9 (15-18)	11.7 (5-16)
CDC* event at HIV-1 diagnosis			
CDC-b	20 (7)	8 (4)	3 (14)
CDC-c	46 (16)	13 (6)	1 (5)
Current age in years	15 (8-20)	30 (26-33)	23 (18-29)
cART-treated	277 (96)	198 (89)	21 (100)
Therapy-naive at cART initiation	237 (86)	156 (79)	21 (100)
CD4 at cART initiation	490 (260-1,090)	279 (160-400)	336 (190-475)
VL (log copies/ml) at cART initiation	5.2 (4.5-5.8)	4.4 (3.7-5.1)	5.0 (4.8-5.4)
cART regimen			
NNRT+≥ 2 NRTIs	87 (31)	78 (40)	9 (43)
PI+≥ 2 NRTIs	185 (67)	106 (54)	9 (43)
NNRTI+PI+2NRTIs	4 (1)	7 (4)	1 (5)
3 NRTIs	1 (0.4)	7 (4)	2 (10)

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

Figure 6.1: Overview of HIV-infected children registered by Stichting HIV Monitoring as of May 2015.



Vertically-infected children

A total of 290 children were vertically infected with HIV-1 *(Table 6.1)*. The median age at HIV-1 diagnosis for the vertically-infected children was 1.5 years (interquartile range [IQR] 0.3-4.17 years). Although 37% of the children were born in the Netherlands, only 3% of these children (10 out of 290) had parents who both originated from the Netherlands, while 62% (179 out of 290) had at least one parent who originated from Sub-Saharan Africa. Of the 290 vertically-infected children, 97% received care in a paediatric HIV treatment centre, and 96% of these 290 children had started cART.

Non-vertically-infected children

Of the 534 HIV-1 infected children ever registered, 223 were non-vertically infected. The non-vertically-infected children were far older at the time of HIV-1 diagnosis than the vertically-infected children, with a median age at diagnosis of 17 years (IQR 15-18). The majority of the 223 non-vertically infected children received care in an adult HIV treatment centre (196/223, 88%). The main route of HIV-1 transmission was sexual contact. Of the non-vertically

infected children, 135 out of 223 (61%) were infected through heterosexual contact, 33 (15%) were infected by homosexual contact and 41 (18%) by contaminated blood or blood product. The remaining 14 children were infected by injecting drug use or accidentally through contaminated needles. Fifty-four percent of the non-vertically infected children were born in Sub-Saharan Africa. Of the 223 non-vertically infected children, 198 (89%) received cART *(Table 6.1)*.

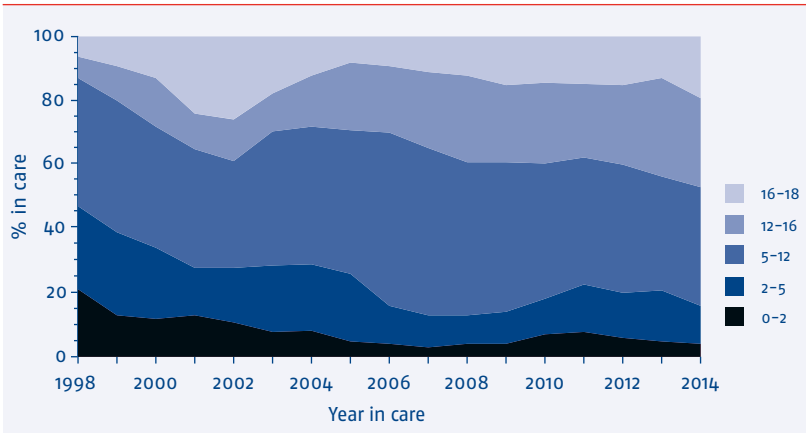
Unknown route of HV-1 transmission

For 21 of the 534 HIV-1-infected children, the route of transmission was unknown. Their median age at diagnosis was 12 years (IQR 5-16) years, and 13 of these children were in care at a paediatric HIV treatment centre. All 21 children had started cART *(Table 6.1)*.

Age distribution

The age distribution of the HIV-1-infected children ever in care over calendar time demonstrates a gradual increase in the proportion of children above 12 years of age (*Figure 6.2)*.

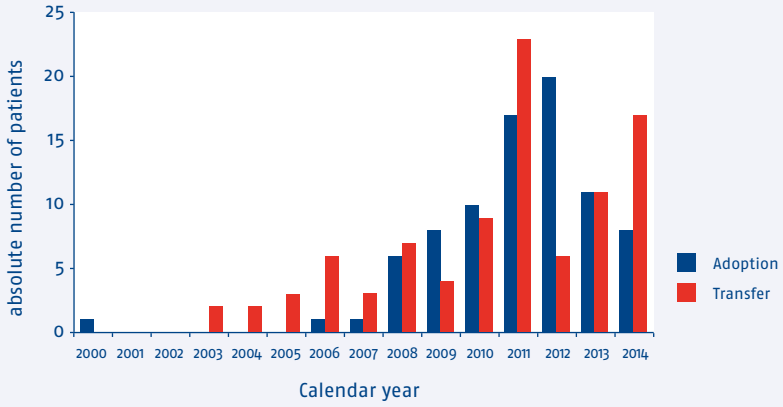
Figure 6.2: *Time-dependent age distribution of HIV-infected children in care over time.*



Adopted children

In total, 86 children in care for HIV-1 infection were adopted by Dutch parents. The majority of these children were born in Sub-Saharan Africa (87%) and diagnosed with HIV-1 before the age of 2.5 years (81%). The number of children adopted varied between 1 and 23 per calendar year *(Figure 6.3)*.

Figure 6.3: Number of HIV infected children who came into paediatric care through adoption and children who transferred to adult care by calendar year.



Children currently in clinical care

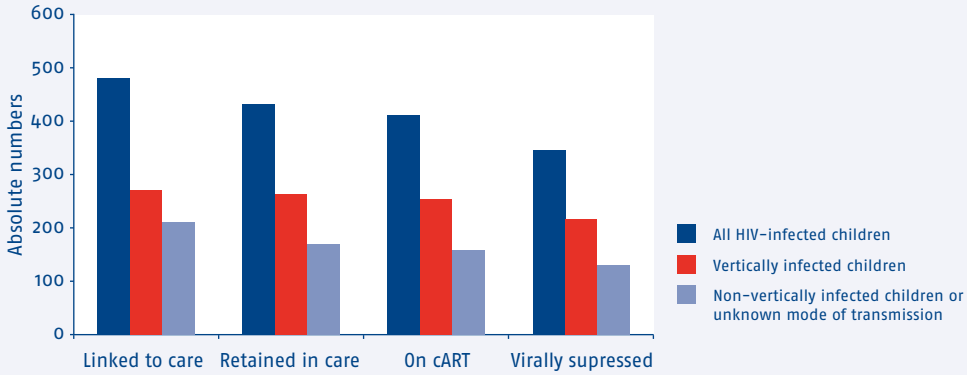
Of the 534 HIV-1-infected children ever registered by SHM, 431 (81%) are still under clinical observation *(Figure 6.1)*. Of these 431 children, 262 (61%) were vertically-infected, 152 (35%) were non-vertically infected, and 17 had an unknown mode of transmission. Of the 103 children who were no longer in clinical care, 15 (15%) had died, 12 of whom were 18 years or older at time of death, and 88 (85%) were lost to care.

Continuum of care

On the basis of the total number of HIV-1-infected children ever registered by SHM, a 'continuum of care' was constructed. This is a way of depicting engagement in HIV-1 care across a few key indicators, the last one being the number of children with a most recent HIV RNA measurement below 100 copies/ml *(Figure 6.4)*. In total, 481 children were ever linked to care, registered by SHM, still alive, and not reported as having moved abroad. Fifteen children had died and 38 children were reported as having moved abroad. Of the 90% of children who were retained in care (431/481), 96% had started cART. Overall, 84% of those starting cART had a most recent HIV RNA measurement below 100 copies/ml (345/412). In addition, a continuum of care was constructed in the same way, but stratified by mode of HIV transmission (vertically infected and non-vertically or unknown mode of transmission, combined) (*Figure 6.4*). In this group of vertically-infected children, 271 children were linked to care, 1 child had died and 18 had moved abroad. Of the 271 vertically-infected children, 262 (97%) were still in care as of 1 January 2015 (9 had been lost to follow up), 97% of those still in care (253/262) had started cART and 85% (215/253) of those starting cART had a most recent HIV RNA measurement below 100 copies/ml. Among those non-vertically infected with HIV or with

an unknown mode of transmission, 210 were linked to care, 14 had died and 20 had moved abroad. Of those linked to care, 80% (169/210) were retained in care and 41 patients were no longer in care as they had been lost to follow up. Among those who were still in care, 94% (159/169) had started cART and 82% (130/159) of those starting cART had a most recent HIV RNA measurement below 100 copies/ml.

Figure 6.4: Continuum of care for all HIV-infected children, for vertically infected children and non-vertically infected children or unknown mode of transmission.



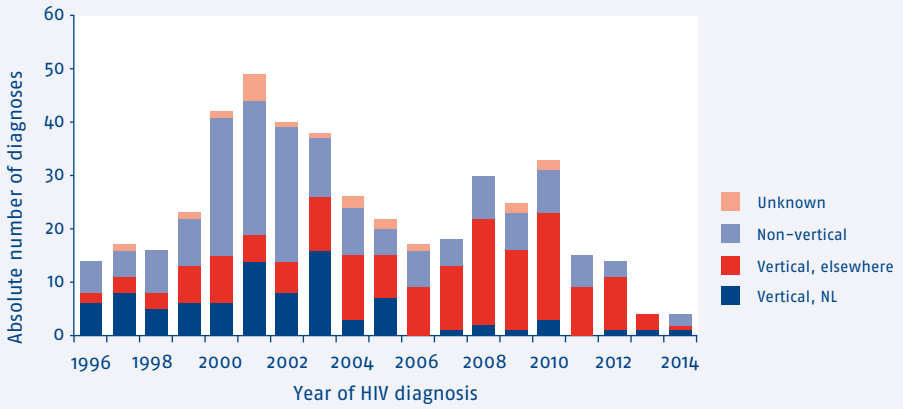
Legend: cART=combination antiretroviral therapy.

Registered HIV-1 diagnoses and vertical transmission of HIV-1 in the Netherlands

Figure 6.5 shows the number of newly registered HIV-1 diagnoses among children by year of diagnosis and according to mode of transmission. As shown in the figure, vertical transmission of HIV-1 in the Netherlands was relatively frequent prior to 2004 (16 cases in 2003), after which it markedly declined, with a single documented case of vertical transmission in the Netherlands in 2014. This newborn was diagnosed with HIV-1 infection at three months of age, having tested HIV-positive after being admitted to the hospital due to respiratory insufficiency. The mother of this newborn tested HIV-negative during the pregnancy screening, but became infected during the second or third trimester of the pregnancy. The decline of vertical transmission in the Netherlands is most likely due to compulsory HIV-1 screening among pregnant women, which was introduced in 2004 [164, 165]. Since the introduction of the screening, 11 children born with HIV-1 in the Netherlands have been reported to SHM. Two of these children were born in 2004 to women who became pregnant before 1 January 2004. Six children were born to mothers who tested positive after giving birth; the mothers of four children tested negative during the screening and became infected during the pregnancy. One child was born to a mother who was known to be

infected with HIV-1, but who was not receiving treatment during her pregnancy for an unknown reason. The remaining two children were born to a mother without a known screening or known HIV-1 status during pregnancy.

Figure 6.5: Number of registered HIV-1 diagnoses amongst children according to year of HIV diagnosis, route of transmission and region of origin.



The majority of children with a newly registered diagnosis of HIV-1 infection through vertical transmission in recent years were infected outside the Netherlands; this number fluctuates each year (e.g., 20 cases in 2010 and 3 cases in 2013).

The number of children who acquired HIV-1 infection by another mode of transmission ranged between 0 and 26 per calendar year.

Mortality

During follow up, 3 out of 534 children (0.6%) died at less than 18 years of age. These were all boys born outside the Netherlands who died at 11, 12 and 17 years of age in 2009, 1998, and 2001, respectively. The boy who was 11 years old at time of death had been infected by blood or blood products and was diagnosed with HIV-1 when he was 10 years old. He never received cART and died of multi-organ failure 1.5 years after the diagnosis. The boy who was 12 years of age at time of death had been vertically infected with HIV-1 and diagnosed when he was nine years old. He died of an AIDS-related event three years after diagnosis, having been treated with cART for 14 months. The 17-year-old boy was diagnosed when he was 16, and his route of HIV-1 transmission was unknown. He died 10 months after HIV-1 diagnosis from toxoplasmosis, having been on cART for two months.

Treatment

In total, 496 of the 534 children started cART; 384 started with a cART regimen before 2010, 85 started between 2010 and 2013, and 27 started cART from 2013 onwards.

The majority of HIV-1-infected children ever registered in the Netherlands have received cART *(Table 6.1)*. Most children (59%) were treated with a first-line regimen including a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs); 35% of the children received a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. The median time on first-line regimens was 13 months (IQR 3-32). Not taking into account weight-related dose changes, 416 children (84%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART regimens included toxicity (11%), low drug plasma concentrations (7%), simplification (11%), and parental non-adherence (3%). Virological failure accounted for 5% of the reasons. Other reasons were decisions by parents and/or child, research protocol-driven reasons, or unknown.

Median CD4 counts at time of cART initiation were higher in children who initiated cART from 2010 onwards compared to children who started before 2010 *(Table 6.2)*, reflecting the implementation of newer treatment guidelines.

Table 6.2: *Median CD4 cell counts at treatment initiation of the 496 children who initiated cART, stratified by calendar year and age categories according to World Health Organization (WHO) treatment guidelines for different calendar years (to account for the changing guidelines for treatment initiation over time).*

cART initiation	<2010 median (IQR)	≥2010 and <2013 median (IQR)	≥2013 median (IQR)
0–1 year	1132 (490–1770)		
1–3 years	695 (310–1520)		
3–5 years	630 (420–1030)		
0–2 years		1959 (1099–2218)	
2–5 years		641 (406–860)	
<5 years			1681 (474–2928)
≥5 years	267 (130–390)	340 (275–460)	390 (241–630)

Legend: *cART=combination antiretroviral therapy; IQR=interquartile range.*

Immunological response

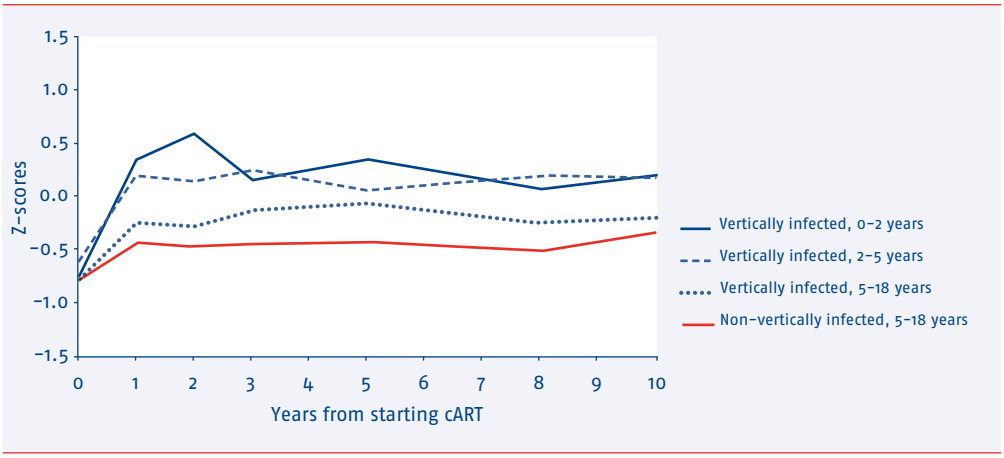
The clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers [34]. To investigate long-term CD4 cell count changes, we stratified the children who were vertically infected according to their age at the time of cART initiation. These categories were as follows: (1) vertically infected, 0-1 year; (2) vertically infected, 2-5 years; and (3) vertically infected, 5-18 years. The children who were non-vertically infected were classified

as (4) non-vertically infected or unknown mode of HIV-1 transmission, 5-18 years[166]. The number of children with an unknown route of HIV-1 transmission is too small to include as a separate category in the analysis. These children had a same age distribution as those who were non-vertically infected. For these two reasons, the children with an unknown route of HIV-1 transmission were included in the category of non-vertically infected. *Appendix Table 6.1* shows the differences in CD4 counts between younger and older HIV-1-infected children.

CD4 z-scores, which represent the standard deviation from the reference values for HIV-1-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[167] and dividing this by the age-related standard deviation. A z-score of 0 represents the age-appropriate median. A CD4 z-score of minus 1 indicated that a child's CD4 cell count is one standard deviation below the age-specific median of the HIV-1-negative population.

The youngest children (less than two years of age at cART initiation) had the highest absolute CD4 cell counts at cART initiation, but the age-adjusted CD4 z-scores did not differ significantly between groups. In the first two years after cART initiation, CD4 z-scores increased significantly in all children *(Figure 6.6)*. This increase was lower in both vertically and non-vertically infected patients aged 5-18 years at cART initiation, compared to vertically infected children less than two years of age.

***Figure 6.6:** Changes in z-scores for CD4 T-cell counts among HIV-1 infected children stratified by age at initiation of combination antiretroviral therapy (cART).*



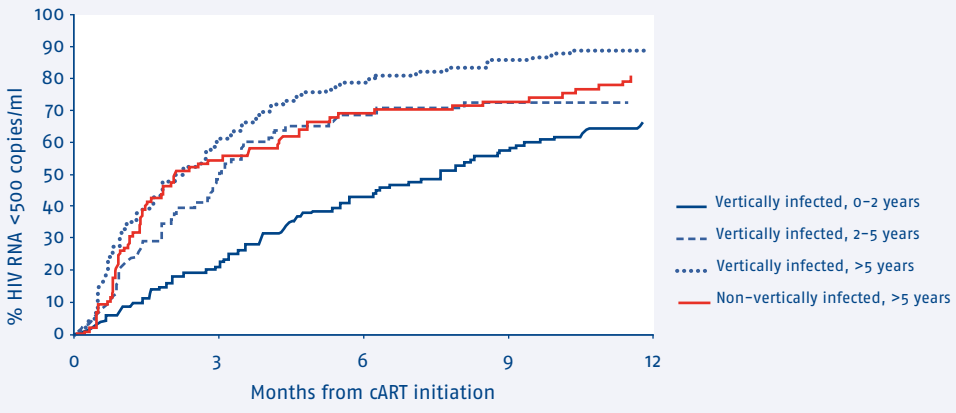
***Legend:** cART=combination antiretroviral therapy.*

Virological response to cART

At the time of cART initiation, children less than two years of age had significantly higher HIV-1 RNA levels than to older children *(Table 6.1)*. Virological response after the start of cART was analysed for the vertically and non-vertically infected children stratified by age at cART initiation (these are the same groups as those presented in the paragraph on immunological response to cART). Twelve months after starting cART, 82% of all children had a successful virological response. A successful virological response was defined as two consecutive HIV-1 RNA levels below 500 copies/ml, as the lower limit of detection of follow-up tests of HIV-1 viral load decreased from less than 1,000 copies/ml in 1996 to less than 40 copies/ml today, and a large number of tests have a lower detection limit of 500 copies/ml[168].

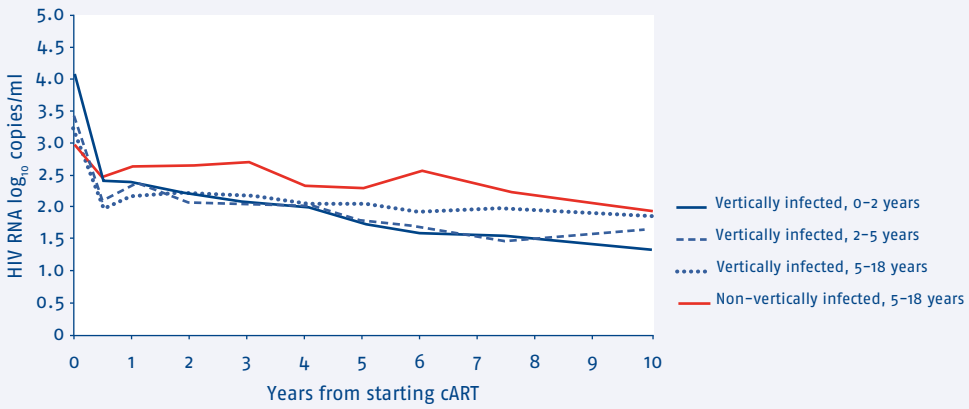
The poorest virological responses were observed among those less than two years of age (67% reached an undetectable HIV-1 RNA level 12 months after the start of cART) and those aged two to four years (86%). The best responses were among children aged five years or more who were either vertically infected (91%) or non-vertically infected (81%) *(Figure 6.7)*. *Figure 6.8* shows the longitudinally modelled long-term virological response to cART over a period of 10 years. In all groups, HIV-1 RNA levels significantly decreased during the first six months on cART (p<0.0001), with a slower decrease among children aged zero to two years. However, two years after the start of cART, the diference in virological response to cART between the different age groups was no longer statistically significant, although median HIV-1 RNA levels were somewhat higher in non-vertically infected children aged five years or more.

Figure 6.7: *Kaplan-Meier estimates of the percentages of HIV-1 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: *cART=combination antiretroviral therapy.*

Figure 6.8: Changes in HIV RNA levels among HIV-1 infected children stratified by age at initiation of combination antiretroviral therapy (cART). Virological responses were assessed in a random effects model; time is in years since start of cART.



Legend: cART=combination antiretroviral therapy.

Adopted children

Eighty-six of the 534 children were adopted by Dutch parents. Of these 86 adopted children, 83 received cART during follow up in clinical care in the Netherlands, seven of whom had been treated with monotherapy or dual therapy before the start of a cART regimen. All 86 children are currently alive and in care. All children who started cART currently remain on treatment, and 75 (87%) had an undetectable viral load at the last known time point.

Transfer to adult care

As of May 2015, 96 children who started care in a paediatric HIV treatment centre had transferred from paediatric to adult care because they had reached the age of 18 years. The number of children who transferred to an adult centre varied from two children in 2003 to 23 in 2011 *(Figure 6.3)*. The median age at transfer was 19 years (IQR 18-20). The median time in care after transfer was three years (IQR 1-5). Of the children who transferred to adult care, four were lost to follow up, three moved abroad, and two objected to further data collection. The remaining 87 were alive and in care. Seventy-eight (89%) of these 87 patients were on a cART regimen, 22 of whom (28%) had a detectable viral load (median 298, IQR 77-844) at the last known time point, with a current median CD4 count of 599 cells/mm^3 (IQR 400-780).Transferred children with a currently undetectable HIV-1 RNA level were more likely to be living with both a father and mother at the time of transferring to an adult centre (34% vs 23% of all children transferring to adult care).

Summary and conclusions

The majority of HIV-1-infected children ever in care in the Netherlands have received cART. During the first six months of treatment, a significant decline in HIV-1 RNA levels was seen in children of all ages. At cART initiation, vertically-infected children aged less than two years had higher HIV-1 RNA levels than the other age groups. Although we observed a somewhat poorer initial virological response during the first year of treatment in these children, the long-term virological response was comparable to that in older children. The slower initial virological response that has previously been described by others[169] might be explained by difficulties in performing regular dosing adjustments in young children[170], but it also could be explained by the higher pre-cART viral loads in younger children[171]. The protease inhibitors nelfinavir and (boosted) indinavir were used in the early years of cART[172] and have since been replaced by improved regimens, which include ritonavir-boosted lopinavir or efavirenz as the most frequently used NNRTI, in line with current guidelines[167, 168, 173, 174].

Younger children below five years of age had significantly higher CD4 counts at cART initiation than older children, which reflects the natural age-related difference in children's CD4 cell counts regardless of HIV-1 status. Age-adjusted CD4 z-scores at cART initiation did not differ between groups. CD4 z-scores significantly increased in the first six months after cART initiation in children of all age groups. However, after 3 to 10 years of treatment, children who were less than two years of age when starting cART had higher CD4 z-scores than children who started cART when they were five years of age or more. This underscores the importance of the recently updated guidelines that recommend earlier initiation of cART to improve immunological outcomes.

We observed low mortality rates in HIV-1-infected children in care in the Netherlands. A substantial number (30%) of the children have survived into adulthood and are now in care in one of the adult HIV treatment centres. The majority of these children are on cART, but the high rate of detectable HIV-1 viral load in these children is of concern. Children who currently have detectable viral loads were less likely to have been living with family before transferring to adult care, which may indicate barriers to successful transition to adult care. Currently, a study is being conducted within the paediatric HIV treatment centres to gain more insight into the determinants of successful transfer to adult care.

The substantial decline in vertically HIV-1-infected infants born within the Netherlands from 2004 onwards can be explained by the successful introduction of an HIV-1 screening programme in the first trimester of pregnancy[164]. However, this measure cannot completely exclude mother-to-child transmission. Screening for HIV-1 only during the first trimester does not completely rule out maternal infection, as incident primary HIV-1 infection may occur during the second or third trimester. In addition, if testing is performed shortly after primary infection of the mother, test results may still be negative. However, because

the prevalence of primary HIV-1 infection among pregnant women in the Netherlands is low, between 0.04 and 0.08%[165], a nationwide second screening during pregnancy is not likely to be cost-effective.

Recommendations

The provision of care for HIV-1-infected children living in the Netherlands has resulted in generally favourable outcomes and should be continued. A large proportion of the children have survived into adulthood and have transitioned to adult care. Although all are alive and most are receiving cART, it is striking that one-third of them currently have detectable HIV-1 viral loads. Improved insight into the determinants of successful transfer to adult care is needed and is currently the subject of ongoing research. HIV-1-infected children face lifelong treatment with cART. For these children, maintaining lifelong adherence to cART and achieving lifelong virological suppression will be particularly challenging.

7. Distinct populations: Pregnancies in HIV-1 infected women in the Netherlands

Colette Smit and Liesbeth van Leeuwen

Worldwide, the most common route of HIV transmission among children aged 0 to 15 years is transmission from an infected mother to her child[175]. Mother-to-child transmission (MTCT) can take place *in utero*, during labour and delivery, and postnatally during breastfeeding. Without intervention, the risk of MTCT varies between 15% and 20%[176]. However, with the introduction of combination antiretroviral therapy (cART) in pregnant women, this risk has dropped dramatically to less than 1%[177, 178]. To ensure timely initiation of cART and thus reduce the risk of MTCT, it is important to have information about a woman's HIV status during pregnancy. For this reason, in January 2004, voluntary HIV antibody testing of pregnant women with the possibility of opting out was introduced in the Netherlands[179].

Due to an ongoing, concerted effort by Stichting HIV Monitoring (SHM) to improve and expand the collection of pregnancy-related data, collection of these data for 2014 and 2015 has been temporarily on hold while the protocol was revised. Therefore, this year's report will not provide an update on pregnancies in HIV-1 infected women in the Netherlands. Instead, we refer readers to an overview of pregnancies in HIV-1 infected women up to January 2014, included in *Chapter 7* of the 2014 Monitoring Report.

As part of the work to expand pregnancy-related data collection, SHM has updated the protocol for the collection of pregnancy-related data. This protocol has been developed by SHM in collaboration with experts in the treatment and care of pregnant women with HIV. This revised and expanded protocol will be used to collect more extensive and additional data from the end of 2015 onwards. *Table 7.1* provides an overview of the new items that have been added to the protocol for the collection of pregnancy-related data by SHM. An analysis of the data collected with the revised protocol will be included in the 2016 Monitoring Report.

Table 7.1 New items added to pregnancy-related data collection protocol.

New items	Input
Method of conception	Spontaneous, IUI, IVF, ICI, hormone treatment, donor egg, donor sperm
Prenatal screening and testing	Specific test used and results of the screening
Recreational drug use during pregnancy	Type of drug used
Mother received ART at any time during pregnancy	Yes, no, unknown
Mother received ART at any time during labour	Yes, no, unknown
Child received antiretroviral post-exposure prophylaxis (PEP)	Yes, no, unknown and specific ARV used
Termination of pregnancy	Reason
First day of last menstrual period	Date
Time of parturition	
Start of dilation	
Start of expulsion	
Time of ruptured membranes	
Assisted vaginal delivery	Reason
Resuscitation of infant	Yes, no, unknown
Condition of infant	No complications, under observation, admission to medium or intensive care
Pathological examination of placenta	Yes, no, unknown
Congenital disorders in infant	Specification
Complications in mother after parturition	Specification

Legend: *IUI=intra-uterine insemination, IVF=in vitro fertilisation, ICI=intracervical insemination; ART=antiretroviral therapy.*

8. Quality of care

Colette Smit, Jan Prins, Kees Brinkman, Suzanne Geerlings, Frank Kroon, Ard van Sighem and Peter Reiss

Introduction

One of Stichting HIV Monitoring's (SHM) missions is to contribute to the quality of HIV care in the Netherlands. Through the collection of anonymised data from HIV patients in care in the 27 officially-acknowledged HIV treatment centres throughout the Netherlands, SHM provides a nationwide overview of the outcome of care for individuals infected with HIV. This unique overview allows SHM to facilitate the assessment of quality of HIV care in the Netherlands.

In general, guidelines are intended not only to support physicians in providing optimal health care, but also to reduce the variation in care between different treatment centres. The Dutch association of HIV-treating physicians (*Nederlandse Vereniging van HIV Behandelaren,* NVHB) has drawn up national guidelines for the treatment and monitoring of HIV-infected patients in the Netherlands[180]. Using these guidelines as a basis, we defined a set of quality indicators. We used these indicators to assess the quality of care in the Dutch treatment centres and to gain insight into potential variation between treatment centres.

Methods

The indicators selected for this analysis were derived from formal NVHB recommendations that, in general, follow the US Department of Health and Human Services (DHHS) HIV/AIDS practice guidelines[180]. These indicators were classified as outcome, process or volume indicators.

Outcome indicators

The outcome indicators included retention in care, initiation of cART and achieving viral suppression. For the purpose of the current analysis, *retention in care* was defined as the percentage of those patients who had first entered care in one of the HIV treatment centres in 2012 and were still in care on 1 June 2014.

Initiation of cART described the overall percentage of those patients who had entered care in 2012 and 2013 and who had started cART within 12 months of entry into care. This indicator was also stratified according to the CD4 cell count at entry into care: CD4 ≥500 cells/mm^3, CD4 between 350 and 500 cells/mm^3 and CD4 <350 cells/mm^3.

Viral suppression was described by two indicators. The first indicator is part of the formal certification process for centres providing HIV care in the Netherlands, which was jointly developed by the Harmonisation of Quality Assessment in Health Care (*Harmonisatie Kwaliteitsbeoordeling in de zorgsector*, HKZ) and the NVHB. Viral suppression in the HKZ certification is defined as the percentage of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at 6 months (minimum 3 months, maximum 9 months) after the start of cART (the aim being ≥90%). The second indicator regarding viral suppression was the percentage of all HIV-infected patients in care who have been on cART for at least 6 months with a plasma HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2012, 2013 and 2014.

Process indicators

The process indicators were calculated for two scenarios: prior to starting cART and following cART initiation.

For the process indicators relating to the period *prior to cART initiation*, the denominator was all patients who had entered care in 2012, and the numerator was the number of these patients for whom the following measurements were available in the 12 months following entry into care: Plasma HIV RNA, CD4 cell count, results of screening for the presence of hepatitis B (HBV) and hepatitis C (HCV) co-infection, total cholesterol, alanine aminotransaminase (ALT), creatinine.

To calculate the process indicators *following cART initiation*, we included patients who started cART in 2012 or 2013. The indicators were the percentage of patients in whom the following measurements were carried out at least once within 12 months following cART initiation: CD4 cell count, plasma HIV RNA, total cholesterol, ALT, and creatinine.

An additional indicator was derived for men who have sex with men (MSM) who entered care in 2012 and who were HCV negative at entry into care. This indicator was based on the proportion of these MSM with repeat HCV serology between 2012-2015.

A non-guidelines-based indicator regarding syphilis serology was derived for all MSM who entered care in 2012, namely the proportion of these men for whom syphilis serology was repeated between 2012 and 2015.

Volume indicator

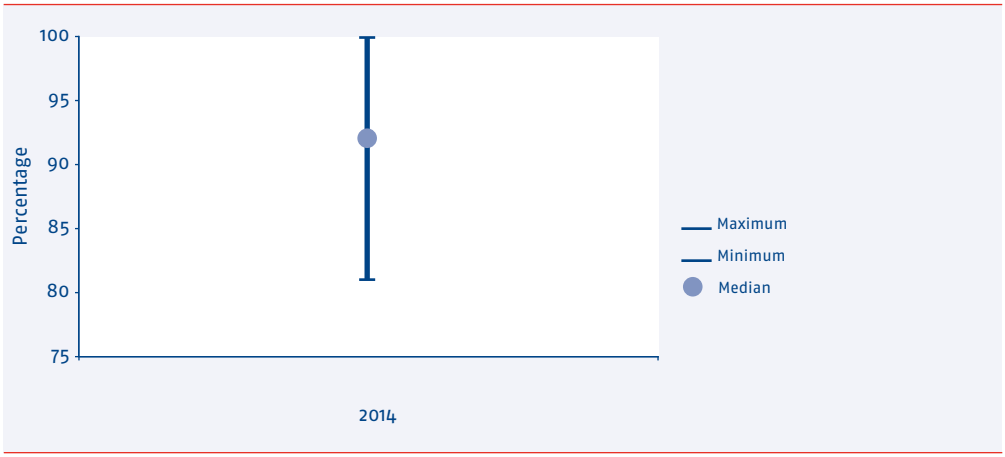
According to the national certification requirements, HIV treatment centres are expected to enrol a mean number of 20 new patients into care each year. As a volume indicator, the number of patients newly entering care for the first time in 2012, 2013 and 2014 was derived for the 27 treatment centres; the median, maximum and minimum number of patients is presented for each of these years.

Results

Retention in care

In 2012 1,117 patients newly-entered care in one of the 27 HIV treatment centres in the Netherlands. 1,017 of these 1,117 patients were still in care after 1 June 2014, providing an overall retention rate of 1,017/1,117= 91%. *Figure 8.1* shows the variation in retention rate across treatment centres. The median retention rate was 92%, with a minimum of 81% and a maximum of 100%.

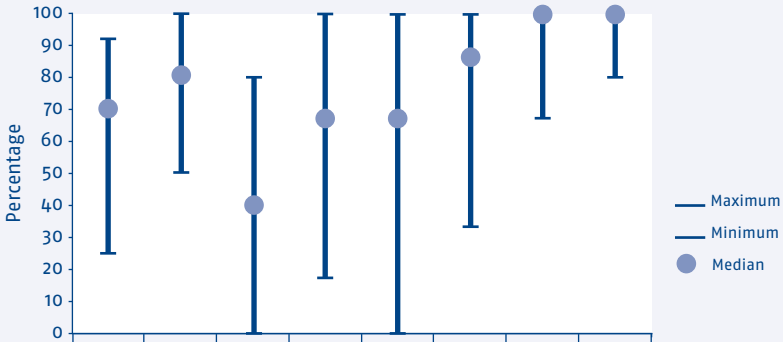
Figure 8.1: *Retention in care, defined as the percentage of patients who newly entered care in 2012, and still known to be in care after 1 June 2014. Retention rates are presented as the median, minimum and maximum retention rates across all 27 HIV treatment centres.*



Initiation of cART

Figure 8.2 shows the median, minimum and maximum percentages of patients starting cART within one year after entering care. Overall, a median of 70% of the patients who entered care in 2012 started cART within one year of entry into care, and this percentage increased to 81% among patients who entered care in 2013. In terms of variation across HIV treatment centres, the lowest percentage of patients starting cART within one year was 25% and the highest percentage was 92% for 2012, and 50% and 100%, respectively, for 2013. When stratified by CD4 cell count, the percentage of patients starting cART within one year was lower for the CD4 cell categories >500 cells/mm^3 and 350-500 cells/mm^3.

Figure 8.2: The percentage of patients who entered care in 2012 and 2013 and started combination antiretroviral therapy (cART) within one year after entry into care. Both overall percentages and percentages categorised by CD4 cell count at entry were calculated, and are presented as the median, minimum and maximum percentage of patients starting cART across all 27 HIV treatment centres.

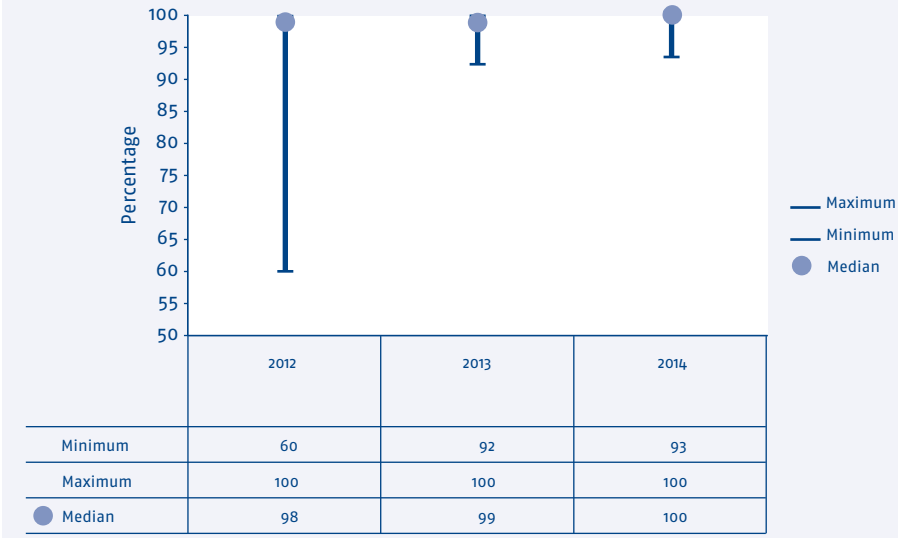


	overall 2012	overall 2013	CD4 >500 2012	CD4 >500 2013	CD4 350–500 2012	CD4 350–500 2013	CD4 ≤350 2012	CD4 ≤350 2013
Minimum	25	50	0	17	0	33	67	80
Maximum	92	100	80	100	100	100	100	100
Median	70	81	40	67	67	86	100	100

Viral suppression

Viral suppression was assessed using two indicators. The first indicator is the percentage of treatment-naive patients with an HIV RNA level <400 copies/ml at 6 months (minimum and maximum: 3-9 months) after the start of cART. The median, minimum and maximum percentages are shown for patients newly-initiating treatment in the years 2012-2014 (*Figure 8.3*). The median percentage increased from 98% in 2012 to 100% in 2014. In 2012, in two treatment centres, less than 90% of the treatment-naive patients had achieved an HIV RNA <400 copies/ml within 6 (3-9) months after the start of cART, while in 2013 and 2014 more than 90% of patients in all centres had achieved an HIV RNA <400 copies/ml within 6 (3-9) months after the start of cART.

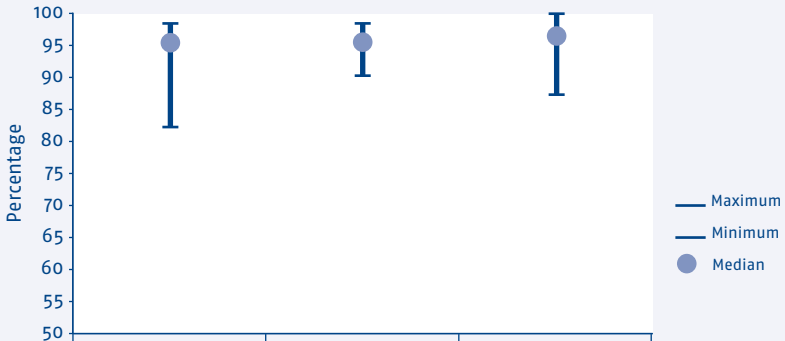
Figure 8.3: Median, maximum and minimum percentages of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at 6 months (minimum and maximum: 3-9 months) after the start of combination antiretroviral therapy (cART) across all 27 HIV treatment centres.



	2012	2013	2014
Minimum	60	92	93
Maximum	100	100	100
Median	98	99	100

The second viral suppression indicator is the percentage of all HIV-infected patients in care who had received cART for at least 6 months and had an HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2012, 2013 and 2014 *(Figure 8.4)*. In all calendar years the median percentage was above 90%.

Figure 8.4: The percentage of all HIV-infected patients in care who had received combination antiretroviral therapy (cART) for at least 6 months and had an HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2012, 2013 and 2014 and presented as the median, minimum and maximum percentage across all HIV treatment centres.



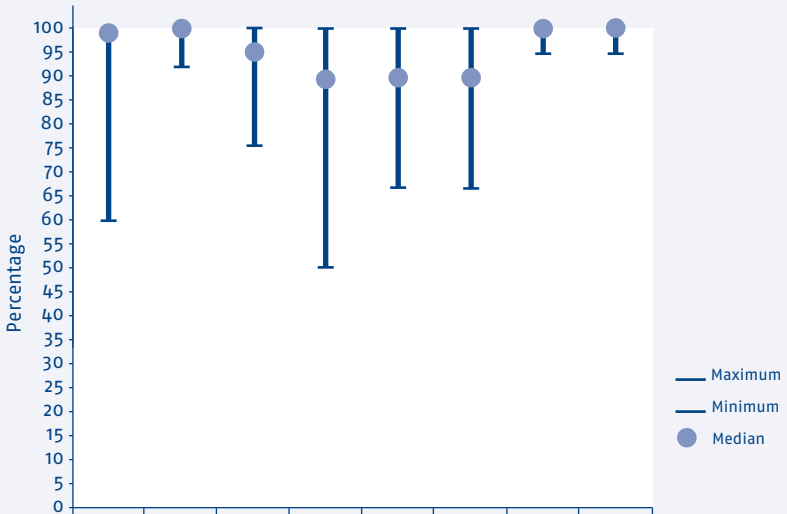
	2012	2013	2014
Minimum	82	90	87
Maximum	98	98	100
Median	95	95	96

Process indicators

Prior to starting cART

Figure 8.5 shows the variation in assessing plasma HIV RNA, CD4 cell count, total cholesterol, ALT and creatinine, as well as in screening for syphilis, hepatitis B and hepatitis C across the 27 HIV treatment centres in the Netherlands among patients who newly entered care in 2012. The median percentage of patients tested for plasma HIV RNA, CD4 cell count, syphilis, ALT and creatinine was greater than 95%. The percentage of patients screened for the presence of syphilis, hepatitis B and hepatitis C co-infection varied considerably between HIV treatment centres. The maximum percentage of patients screened for hepatitis B and hepatitis C was 100%, whereas the minimum percentage was 67% and 50%, respectively. Likewise, there was marked variation in the assessment of total cholesterol, with a maximum rate of 95% and a minimum rate of 67%.

Figure 8.5: Median, maximum and minimum percentages of patients who newly entered care in 2012 in the 27 HIV treatment centres in the Netherlands, and in whom plasma HIV RNA, CD4 cell count, total cholesterol, alanine transaminase, and creatinine had been assessed and screening for syphilis, hepatitis B and hepatitis C has been carried out.



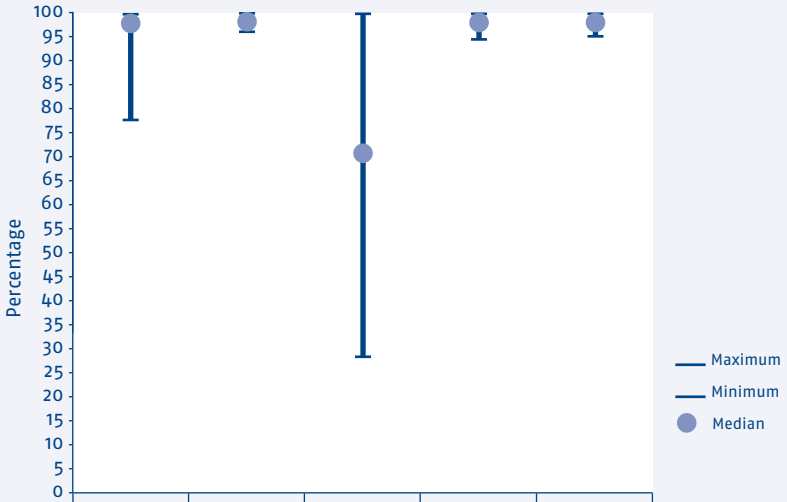
	RNA	CD4	Syphillis	HCV	HBV	Total Choles-terol	ALT	Creatinine
Maximum	100	100	100	100	100	100	100	100
Minimum	60	92	75	50	67	67	95	95
Median	98	100	95	88	90	91	100	100

Legend: cART=combination antiretroviral therapy; HBV=hepatitis B; HCV=hepatitis C; ALT=alanine transaminase.

Following the start of cART

Figure 8.6 shows the variation between the 27 HIV treatment centres in the Netherlands in terms of assessing plasma HIV RNA, CD4 cell count, total cholesterol, ALT, and creatinine levels at least once within 12 months after cART initiation for all patients who initiated cART in 2012 and 2013 and who were still in care 12 months after starting cART. HIV RNA, ALT and creatinine were assessed within 12 months after the start of cART in the majority of patients. However, for CD4 count, there was a minimum assessment rate of 77% in one HIV treatment centre. Unlike the assessment of HIV RNA, ALT and creatinine, the assessment of total cholesterol following treatment initiation showed a large variation between treatment centres. The median proportion of patients in whom total cholesterol had been assessed was 69%, with a maximum of 100% and a minimum of 27%.

Figure 8.6: *Median, maximum and minimum percentages of patients in the 27 HIV treatment centres in the Netherlands who initiated combination antiretroviral therapy (cART) in 2012 and 2013 and in whom plasma HIV RNA, CD4 cell count, total cholesterol, alanine transaminase, and creatinine was assessed within 12 months after start of cART.*



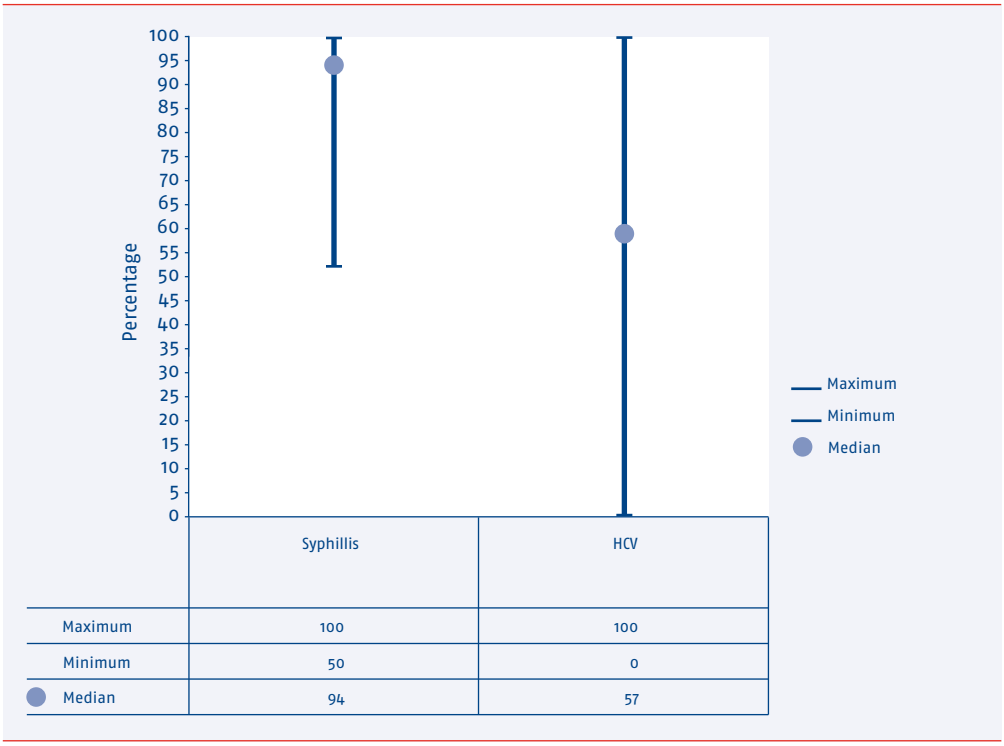
	CD4	HIV RNA	Total Cholesterol	ALT	Creatinine
Maximum	100	100	100	100	100
Minimum	77	96	27	94	95
Median	98	98	69	98	98

Legend: *cART=combination antiretroviral therapy; ALT=alanine transaminase.*

Repeat screening for hepatitis C and syphilis

In 2012, 624 HCV-negative MSM newly entered HIV care. *Figure 8.7* depicts the rate of repeat screening for HCV among MSM who were HCV-negative at entry into care. This figure shows that there is considerable variation in the rate of repeat HCV screening. The median percentage of these MSM who had at least one repeated HCV antibody or HCV RNA test during follow up in 2013 and 2014 was 57%. The maximum percentage was 100%, while one centre carried out no repeat HCV tests in MSM who were HCV-negative at entry into care. Similarly, there was also a large degree of variation between HIV treatment centres in terms of repeat screening for syphilis among MSM during follow up. The maximum proportion of patients undergoing repeat syphilis screening was 100% and the minimum was 50%, with a median of 94%.

Figure 8.7: *Median, maximum and minimum percentages of repeat screening for hepatitis C (HCV) among men who have sex with men (MSM) who were HCV negative at entry in care, and of repeat screening for syphilis among all MSM who entered care in 2012.*



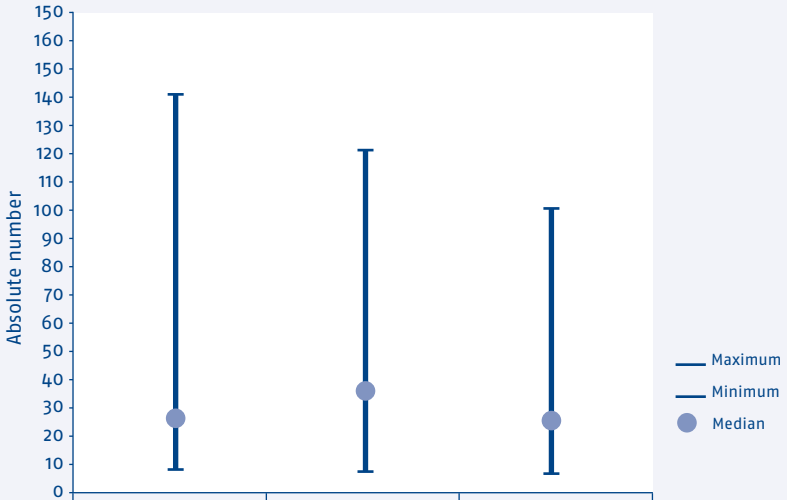
	Syphillis	HCV
Maximum	100	100
Minimum	50	0
Median	94	57

Legend: *cART=combination antiretroviral therapy; HCV=hepatitis C.*

Volume indicators

The median, minimum and maximum numbers of patients who newly entered care in 2012, 2013 and 2014 across the 27 HIV treatment centres are shown in *Figure 8.8*. The median number of patients entering care varied between 26 in 2012 and 33 in 2013. The minimum number ranged from 6 to 8 patients.

Figure 8.8: The median, maximum and minimum numbers of patients entering care per HIV treatment centre in the Netherlands in 2012, 2013, 2014.



	2012	2013	2014
Maximum	142	121	100
Minimum	8	7	6
Median	26	33	25

Key findings

The most important findings of this comparison of quality indicators in the 27 HIV treatment centres in the Netherland are as follows:

- The overall and HIV treatment centre-specific retention in care rates are high.
- Large variation is observed in the percentage of patients starting cART within one year after entering care. This variation is smallest for the group of patients who enter care with less than 350 cells/mm^3. Against the background of current guidelines recommending treatment for all patients regardless of CD4 count, it is also worth noting that, in some

HIV treatment centres, none of the patients who entered care with a CD4 cell count >500 CD4 cells/mm^3 or between 350 and 500 cells/mm^3 started cART within one year of their first clinical visit. However, compared to 2012, in 2013 the proportion of patients initiating cART increased slightly and there was a small decrease in the variation between HIV treatment centres.

- Viral suppression rates within 6 months after the start of cART were high; in 2013 and 2014, more than 90% of patients in all HIV treatment centres had achieved an HIV RNA level <400 copies/ml within 6 months after starting treatment.
- Among all patients who had been using cART for 6 months or longer, viral suppression rates were greater than 80% in all HIV treatment centres, with a median of 95% in 2012 and 2013 and 96% in 2014.
- Large variation is observed in screening for HBV and HCV, syphilis and total cholesterol before the start of cART, ranging from 67% to 100% for HBV and from 50% to 100% for HCV. The assessment of total cholesterol in the first twelve months following cART initiation ranged from 27% to 100%.
- The rate of repeat HCV co-infection screening in MSM who entered care in 2012 and who were HCV-negative at entry into care varied widely, from 0% to 100%. Likewise the proportion of all MSM repeatedly screened for syphilis varied from 50% to 100%.

Conclusion

Retention in care and viral suppression rates in the first 6 months on cART, as well as during long-term use of cART, were high across all HIV treatment centres in the Netherlands. The percentage of patients starting cART within one year after entry into care was higher among patients who entered care in 2013 than in those who entered in 2012. Although the proportion of patients starting cART within one year after entering care increased, the rate of starting treatment among patients who entered care with CD4 cell counts above 350 cells/mm^3 may be improved in some of the centres. Finally, the variation in repeated screening for HCV may, to some extent, be explained by centres/physicians applying a policy of targeted screening guided by the presence of incident transaminase elevations.

Special reports

9. The Amsterdam Cohort Studies on HIV infection: annual report 2014

Ineke Stolte and 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 2014, the cohorts reached 30 years of follow up. The initial aim of the ACS was to investigate the prevalence and incidence of HIV-1 infection and AIDS, the associated risk factors, the natural history and pathogenesis of HIV-1 infection, and the effects of interventions. During the past 30 years, these aims have remained primarily the same, although the emphasis of the studies has changed. Early on, the primary focus was to elucidate the epidemiology of HIV-1 infection, whereas later more in-depth studies were performed 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 2014, 2,649 MSM and 1,680 injecting and non-injecting drug users were included in the ACS. Every three to six months, participants complete a standardised questionnaire designed to obtain information regarding medical history, sexual and drug use behaviour, underlying psychosocial determinants, healthcare use, depression, psychological disorders, and demographics. In addition, they undergo a medical examination (HIV-positive participants and, in the past, also HIV-negative drug users), and blood is collected 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 was approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the DU cohort) is obtained from each participant.

Of the 2,649 MSM, 606 were HIV-positive at entry into the study, and 246 seroconverted during follow up. Of the 1,680 DU, 323 were HIV-positive at entry, and 99 seroconverted during follow up. By 31 December 2014, 562 DU had died, and several other participants had been asked to leave the study or had left at their own request. In total, the Public Health Service of Amsterdam (*Gemeentelijke Gezondheidsdienst Amsterdam*; GGD Amsterdam) was visited 54,811 times by MSM and 27,777 times by DU.

Collaborating institutes and funding

Within the ACS, different institutes collaborate to bring together the data and biological sample collections and to conduct research. These include the GGD Amsterdam (Infectious Diseases Cluster, Department of Research), the Academic Medical Center (AMC) of the University of Amsterdam (Departments of Medical Microbiology, Experimental Immunology, Internal Medicine, Division of Infectious Diseases, HIV treatment centre, Emma Kinderziekenhuis), University Medical Center Utrecht (UMCU, Department of Immunology), Stichting HIV Monitoring (SHM), the Jan van Goyen Medical Centre (Department of Internal Medicine) and the HIV Focus Centre (DC Klinieken) Amsterdam. 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 at Sanquin Research. Sanquin financially supports the maintenance of the biobank of viable peripheral blood mononuclear cells (PBMC) at the Department of Experimental Immunology at the AMC. In addition, there are numerous collaborations between the ACS and other research groups both within and outside of the Netherlands. The ACS is financially supported by the Centre for Infectious Disease Control of the National Institute for Public Health and the Environment (*Centrum voor Infectieziektenbestrijding-Rijksinstituut voor Volksgezondheid en Milieu*, CIb-RIVM).

The ACS in 2014

The cohort of men having sex with men

Until 1995, HIV-negative men of all age groups were eligible to participate if they lived in or around Amsterdam and had had at least two male sexual partners in the previous six months. During the period 1995–2004, only HIV-negative men aged ≤30 years with at least one male sexual partner in the previous six months could enter the study. Since 2005, recruitment has been open to HIV-negative MSM of all ages with at least one sexual partner in the preceding six months. HIV-seroconverters within the ACS remained in the cohort until 1999, when follow up of a selection of HIV-positive MSM was transferred to the Jan van Goyen Medical Center. In 2003, the 'HIV Onderzoek onder Positieven' (HOP) protocol (HIV Research in Positive Individuals) was initiated. Individuals with a recent HIV infection at study entry at the GGD Amsterdam and HIV seroconverters within the cohort return for follow up at the GGD Amsterdam or at an HIV treatment centre. All behavioural data are collected on a six-monthly basis by questionnaires, coordinated by the GGD Amsterdam, and clinical data are provided by SHM.

In 2014, 613 HIV-negative, and 47 HIV-positive MSM were in active follow up within the ACS (6-monthly visits to the GGD Amsterdam for STI testing, including HIV, and filling in behavioural questionnaires, according to the HOP protocol for HIV-positive individuals and HIV-negative protocol for HIV-negative individuals). The median age of the MSM was 40.5 years (interquartile range [IQR] 34.9-46.5), 7.6% were non-Dutch, and 79.8% had attained a high level of education. The majority of the participants (84.8%) were residents of Amsterdam. Additional efforts to expand the HIV-negative cohort resulted in 97 newly recruited HIV-negative participants in 2014.

Apart from the HIV-positive MSM visiting the GGD Amsterdam, two groups of HIV-positive MSM are also followed outside the GGD Amsterdam:

1) The HIV-positive MSM who were transferred from the GGD Amsterdam to the Jan van Goyen Medical Centre in Amsterdam in 1999. In 2014, 17 were still being followed at the Jan van Goyen Medical Centre and 109 at the HIV Focus Centrun in Amsterdam. Behavioural questionnaires were filled in by 25 MSM.
2) HIV-positive MSM who were included into the HOP protocol, but not visiting the GGD Amsterdam. In 2014, 38 MSM were followed in an HIV treatment centre other than the Jan van Goyen Medical Centre or HIV Focus Centrum and filled in a behavioural questionnaire.

The cohort of drug users

In 2014, DU included in the ACS were divided into two groups, in line with the advice issued by the scientific advisory board in 2013. Group 1 consists of DU visiting the GGD Amsterdam once a year to complete questionnaires without testing and blood sampling. In 2014, there were 224 DU in active follow up in this group. Group 2, the focus group, consists of DU who are 1) HIV positive; 2) hepatitis C (HCV) seroconverters; 3) multiple-exposed, non-infected with HIV and HCV, and 4) a random control group. This group visited the GGD Amsterdam twice a year for testing and blood sampling and to fill out questionnaires, as in the years before. In 2014, 89 DU were in active follow up in this focus group. The cohort has been closed since January 2014. Therefore, no new participants were recruited in 2014.
The median age of the DU was 52.3 years (IQR 45.9-56.6), 12.5% were non-Dutch, and 6.5% had attained a high level of education. Two hundred and thirty-eight (96.0%) were residents of Amsterdam.

Subgroup studies and affiliated studies

AGE$_h$iV Cohort Study

The AGE$_h$iV Cohort Study, a collaboration between the AMC Department of Infectious Diseases, Department of Global Health, and Amsterdam Institute of Global Health and Development, the GGD Amsterdam, and SHM, was started in October 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 aged ≥45 years,

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.

In total, 598 HIV-1-infected participants and 550 HIV-uninfected individuals completed a baseline visit between October 2010 and September 2012. HIV-1-infected participants were included through the AMC HIV outpatient clinic and HIV-uninfected participants from the same HIV exposure groups were included through the STI clinic of the GGD Amsterdam (n=486) or the ACS (n=64). All participants were aged ≥45 years and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. By the end of 2014, the first follow up had been completed, and 498 HIV-1-infected participants and 482 HIV-uninfected individuals had returned for their second visit.

ACS biobank

The ACS visits, together with data collection from several subgroup studies and affiliated studies, have resulted in a large collection of stored samples.

The ACS biobank includes plasma and peripheral blood mononuclear cell samples collected within the context of the Primo-SHM study (a national randomised study on the effects of early temporary antiviral therapy as compared to no therapy among patients who presented with primary HIV-1 infection at the AMC outpatient clinic and ACS seroconverters). These samples are stored at the AMC. At present, the biological samples are still being collected prospectively for Primo-SHM participants visiting the AMC clinic until one year after they have recommenced therapy.

The ACS biobank also includes plasma and PBMC samples that were collected from both HIV-infected and HIV-exposed children at the Emma Kinderziekenhuis in the AMC until 2008. These are also stored at the AMC. Currently, no new samples are being collected within the ACS setting. All stored samples are available for ACS research.

The HIV epidemic

HIV incidence

6 MSM participating in the ACS seroconverted for HIV in 2014. The observed HIV incidence among MSM has remained relatively stable in recent years and was 1.07 per 100 person years in 2014. The HIV incidence in drug users has been stable since 2008, with less than one case per 100 person years. As follow up was restricted to a selection of DU in 2014 and inclusion of new DU stopped, the yearly observed incidence of DU can only be presented until 2013. *Figures 9.1* and *9.2* show the yearly observed HIV incidence rates for MSM and DU from the start of the ACS through 2014 and 2013, respectively.

Figure 9.1: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2014.

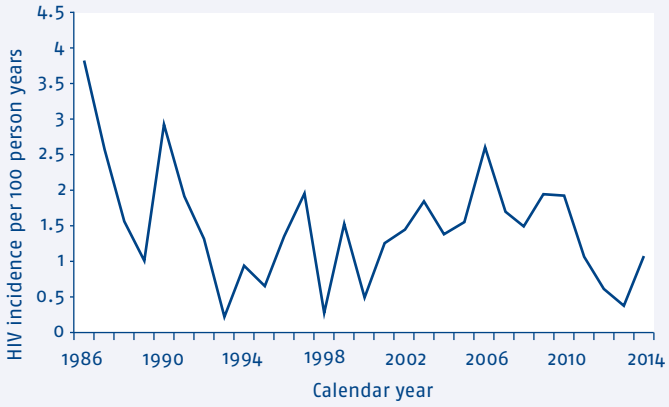
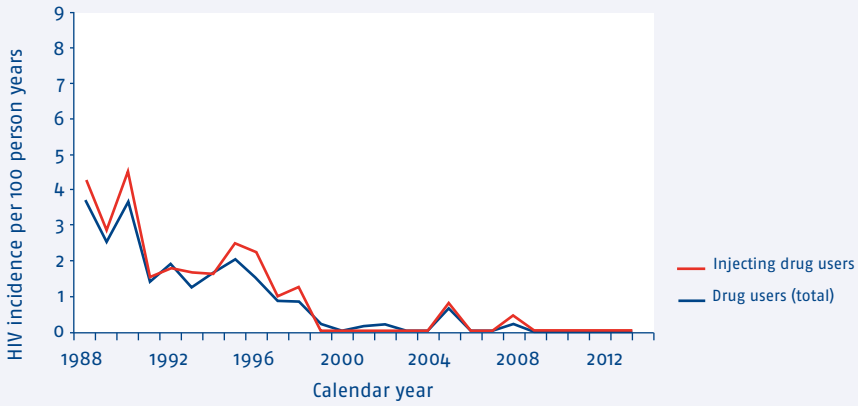


Figure 9.2: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among drug users, 1986–2013.



Transmission of therapy-resistant HIV strains

In 2014, surveillance of transmission of drug-resistant HIV-1 strains was performed for six MSM seroconverters who had their first visit after being found to be HIV-positive in 2014, and for two MSM who were seropositive at study entry. None of the individuals were infected with a virus harbouring resistance-associated mutations in the protease and reverse transcriptase genes. In all individuals, naturally occurring sequence variation

was found in the protease gene. HIV-1 subtypes were determined by phylogenetic analysis: seven individuals harboured subtype B HIV-1 strains; one had a mosaic virus containing subtype A and unknown sequences.

Highly active antiretroviral therapy (HAART) uptake

Of all 211 HIV-positive MSM from the ACS visiting the HIV Focus Centrum, the Jan van Goyen Medical Centre or one of the other HIV treatment centres in the Netherlands in 2014, treatment data were available for 205 men. Of these, 199 (97%) received some form of antiretroviral therapy. Of the 204 MSM for whom viral load results were available in 2014, 197 (87%) had a viral load of <50 copies/ml (assays M2000rt). Of the 29 HIV-positive DU who visited the GGD Amsterdam in 2014 and for whom treatment data were available, 26 (90%) received some combination of antiretroviral therapy. Of the 29 DU for whom viral load results were available, 27 (93%) had an undetectable viral load (≤150 copies/ml [assay: M2000rt]) at their latest visit.

Human papillomavirus in MSM

The H2M (HIV and HPV in MSM) study is a successful collaboration between the CIb-RIVM, the GGD Amsterdam, the Jan van Goyen Medical Centre, HIV Focus Centrum, VU University Medical Center (VUmc), and the AMC. The study aims to compare the prevalence, incidence, and clearance of high-risk (hr) human papillomavirus (HPV) infections between HIV-negative and HIV-infected MSM.

The participants were recruited from three sites: the ACS (n=520; mostly HIV-negative), the STI clinic at the GGD Amsterdam (n=120; all HIV-infected), and the Jan van Goyen Medical Centre/ HIV Focus Centrum (n=160; all HIV-infected). Recruitment was carried out in 2010 and 2011, and participants were followed for 24 months. Participants provided self-collected swabs from the anus and penile shaft, as well as oral rinse-and-gargle specimens. These were tested for the presence of HPV DNA and, if positive, HPV types were determined. Serum was tested for L1 HPV antibodies.

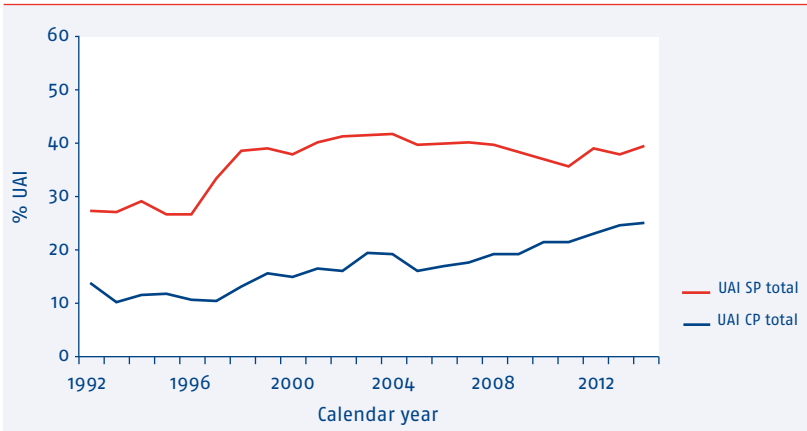
During the two-year follow-up period, a high incidence of hrHPV infections was observed, and the incidence was significantly higher in HIV-infected compared to HIV-uninfected men; this was the case for both anal and penile infections. We did not find an effect of CD4 count (curent or nadir) on incidence or clearance.

The study is now being continued in two separate studies. In the HIV-infected population, potential predictors for high-grade anal intra-epithelial neoplasia are being examined. This study, the H2M2, is an Aids Fonds-supported project, and a collaboration between the GGD Amsterdam, the CIb-RIVM, and the AMC. In the HIV-negative population, long-term incidence and clearance of anal and penile infections are being examined (H2M3 study).

Risk behaviour of MSM in ACS

Information from the questionnaires completed by 613 HIV-negative MSM during cohort visits in 2014 showed higher proportions of unprotected anal intercourse (UAI) with steady partners (39.5%) compared to casual partners (25.2%). Trends in UAI among HIV-negative MSM who are participants in the ACS, especially UAI with casual partners, continue to show a gradual increase from 1996 onwards. *(Figure 9.3)*.

Figure 9.3: Trends shown by the Amsterdam Cohort Studies (ACS) in unprotected anal intercourse (UAI) with casual and steady partners in the past six months among HIV-negative men having sex with men (MSM) with a casual and/or steady partner, 1992-2014.

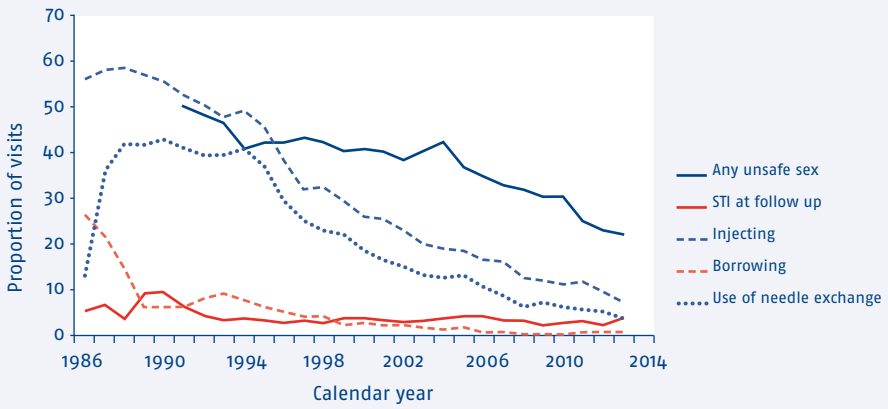


Legend: UAI=unprotected anal intercourse; SP=steady partner; CP=casual partner.

Risk behaviour of DU in ACS

As follow up was restricted to a selection of DU in 2014 and inclusion of new DU stopped, trends in risk behaviour of DU can only be presented until 2013. In HIV-negative DU, reports of both injection and borrowing needles significantly declined over the period 1985-2013. Reports of high-risk sexual behaviour at follow-up visits decreased before 1996, then remained relatively stable until 2005, and further decreased to approximately 22% in 2013. Reports of STI have remained relatively stable at approximately 1% in recent years (see *Figure 9.4*).

Figure 9.4: Proportion of visits per calendar year at which injecting and high-risk sexual behaviour was reported amongst drug users (DU) who were HIV-negative on entry to the Amsterdam Cohort Studies (ACS), 1986-2013.



Legend: STI = sexually transmitted infection

STI screening among MSM in ACS

Since October 2008, all MSM in the ACS have been routinely screened for chlamydia and gonorrhoea by polymerase chain reaction (PCR) techniques using urine samples and pharyngeal and rectal swabs. Cases of syphilis are detected by Treponema pallidum haemagglutination assay (TPHA). In 2014, a total of 668 MSM from the ACS were screened for STI. The overall prevalence of any STI was 9.2% (113/1,230).

ACS 2014 research highlights

The ability of the human immunodeficiency virus type 1 (HIV-1) to replicate in its target cells is influenced by numerous host factors that act at different steps of the viral replication cycle. On the one hand, HIV-1 exploits many host factors to successfully replicate, while on the other hand several host factors can potentially restrict viral replication. Recently, a new type of host factor was described that plays a more complex role in HIV-1 infection. These factors help HIV-1 to avoid innate recognition by limiting the production of viral nucleic acids and replication of the virus in its target cells.

The exonuclease TREX1 shields HIV-1 from recognition by innate immune receptors, thereby preventing a type I interferon response. We studied the role TREX1 in the clinical course of HIV-1 infection by analysing the effect of genetic variation in *Trex1* on HIV-1 disease progression in the ACS. The single nucleotide polymorphism (SNP) rs3135941 in *TREX1* was associated with accelerated disease progression, independent of the CCR5-Δ32 genotype and human leukocyte antigen (HLA) alleles. *In vitro,* the SNP rs3135941 in Trex1

was associated with increased HIV-1 replication in PBMCs, which might explain the association between this SNP and accelerated disease progression in HIV-1 infected individuals[181].

The innate cytosolic DNA sensor IFI16 senses incomplete viral DNA transcripts in resting CD4+ T cells, resulting in a pro-inflammatory response that ultimately leads to the death of the abortively-infected resting CD4+ T cell. We analysed whether genetic variation in the IFI16 gene affects the clinical course of HIV-1 infection in the ACS population. We observed that SNP rs1417806 in IFI16 is associated with increased CD4+ T cell counts at set point and with a delayed HIV-1 disease progression[182]. This suggests that IFI16 does affect HIV-1 pathogenesis, especially during the early phase of infection.

Despite more than 30 years of intensive research, no HIV-1 vaccine candidate is capable of establishing strong and durable protective immunity. In particular, the induction of broadly-reactive neutralising antibodies is high on the wish list for an HIV-1 vaccine. Broadly reactive neutralising antibody activity against HIV-1 generally takes 2-4 years to develop in an HIV-1-infected patient. In the ACS there are two participants, infected via injecting drug use, who are so-called elite neutralisers and who had already developed broadly reactive neutralising activity in their first year post-seroconversion. It could be that virus strains infecting these elite neutralisers have unusually immunogenic broadly neutralising antibody epitopes. The characterisation of envelope glycoproteins and the broadly neutralising antibodies from these elite neutralisers will be of great value in vaccine development to ultimately prevent HIV-1 infection[183].

Since 2010, a bivalent HPV vaccine against HPV types 16 and 18 has been offered free of charge to young girls in the Netherlands. However, boys are not routinely vaccinated. More insight into the function of naturally-induced antibodies would be helpful in designing national vaccination programmes or targeted prevention strategies. MSM, especially HIV-infected MSM, are more affected by the serious consequences of HPV infection than the general male population, notably with regard to anal cancer. Now that the survival of HIV-infected people in the era of the combination antiretroviral treatment (cART) has increased, an increased incidence of anal cancer is observed in HIV-infected MSM. Therefore, HIV-infected individuals are an important target group that should be considered when planning HPV prevention strategies. We aimed to assess whether naturally-induced HPV antibodies confer protection against subsequent type-specific anal and penile HPV infection in HIV-negative and HIV-infected MSM. HPV seropositivity at baseline was not significantly associated with subsequent type-specific HPV infection at 6 or 12 months in multivariable analyses (for anal infection, adjusted hazard ratio [aHR] 1.2; 95% confidence interval [CI] 0.9–1.6; for penile infection, aHR 0.8; 95% CI 0.6–1.2). High antibody concentrations showed no protective effect against subsequent infection either. In a population of highly sexually active, adult MSM, naturally-induced HPV antibodies may not protect MSM against subsequent anal or penile HPV infection within one year[184].

Steering committee

In 2014, the steering committee met three times. Sixteen proposals for use of data and/or samples (serum/PBMC) were submitted to the steering committee: two from the AMC Experimental Immunology department, two from the AMC Experimental Immunology and Laboratory Experimental Virology together, ten from the AMC Medical Microbiology department, and two from the GGD Amsterdam. Thirteen requests were approved, some after revision, and three requests were denied. Three of the approved proposals were collaborations with groups outside the ACS, of which two were from abroad.

Publications in 2014 that include ACS data

1. Booiman T, Kootstra NA. **Polymorphism in IFI16 affects CD4(+) T-cell counts in HIV-1 infection.** *Int J Immunogenet 2014 Dec;41(6):518-20.*

2. Booiman T, Setiawan LC, Kootstra NA. **Genetic variation in Trex1 affects HIV-1 disease progression.** *AIDS 2014 Nov 13;28(17):2517-21.*

3. de Vos AS, Prins M, Coutinho RA, van der Helm JJ, Kretzschmar ME. **Treatment as prevention among injecting drug users; extrapolating from the Amsterdam cohort study.** *AIDS 2014 Mar 27;28(6): 911-8.*

4. Engsig FN, Zangerle R, Katsarou O, Dabis F, Reiss P, Gill J, Porter K, Sabin C, Riordan A, Fätkenheuer G, Gutiérrez F, Raffi F, Kirk O, Mary-Krause M, Stephan C, de Olalla PG, Guest J, Samji H, Castagna A, d'Arminio Monforte A, Skaletz-Rorowski A, Ramos J, Lapadula G, Mussini C, Force L, Meyer L, Lampe F, Boufassa F, Bucher HC, De Wit S, Burkholder GA, Teira R, Justice AC, Sterling TR, Crane HM, Gerstoft J, Grarup J, May M, Chêne G, Ingle SM, Sterne J, Obel N; for the Antiretroviral Therapy Cohort Collaboration (ART-CC) and the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. **Long-term mortality in HIV-positive individuals virally suppressed for >3 years with incomplete CD4 recovery.** *Clin Infect Dis 2014 May;58(9):1312-21.*

5. Gijsbers EF, van Nuenen AC, de la Peña AT, Bowles EJ, Stewart-Jones GB, Schuitemaker H, Kootstra NA. **Low level of HIV-1 evolution after transmission from mother to child.** *Sci Rep 2014 May 28;4:5079.*

6. Geskus RB. **Which individuals make dropout informative?** *Stat Methods Med Res 2014 Feb;23(1):91-106*

7. Gijsbers EF, van Nuenen AC, de la Pena AT, Bowles EJ, Stewart-Jones GB, Schuitemaker H, Kootstra NA. **Low level of HIV-1 evolution after transmission from mother to child.** *Sci Rep 2014 May 28;4:5079.*

8. Grebely J, Dore GJ, Kim AY, Lloyd A, Shoukry NH, Prins M, Page K. **The genetics of spontaneous clearance of hepatitis C virus infection: A complex topic with much to learn.** *Hepatology 2014 Apr 9 [Epub ahead of print].*

9. Grebely J, Grady B, Hajarizadeh B, Page K and Dore GJ on behalf of the InC3 Study Group. **Disease progression during advanced fibrosis: IL28B genotype or HCV RNA levels?** *Hepatology 2014; 59(4):1650-51.*

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12. Kooij KW, Wit FW, Bisschop PH, Schouten J, Stolte IG, Prins M, van der Valk M, Prins JM, van Eck-Smit BL, Lips P, Reiss P; on behalf of the AGE$_h$iV Cohort Study group. **Low bone mineral density in patients with well-suppressed HIV infection: association with body weight, smoking, and prior advanced HIV disease.** *J Infect Dis. 2014 Sep 1 [Epub ahead of print].*

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27. van Santen DK, Van Der Helm JJ, Grady BP, de Vos AS, Kretzschmar ME, Stolte IG, Prins M. **Temporal trends in mortality among people who use drugs compared with the general Dutch population differ by hepatitis C virus and HIV infection status.** *AIDS. 2014 Nov 13;28(17):2589-99.*

28. Vanhommerig JW, Stolte IG, Lambers FA, Geskus RB, van de Laar TJ, Bruisten SM, Schinkel J, Prins M. **Stabilizing incidence of hepatitis C virus infection among men who have sex with men in Amsterdam.** *J Acquir Immune Defic Syndr 2014 Aug 15;66(5):e111-5.*

Theses in 2014 that include ACS data

Viviana Cobos Jiménez - 25 March 2014: **HIV-1 infection in macrophages and genes involved throughout: Big eaters versus small invaders.** Supervisor: Prof. T.B.H. Geijtenbeek (AMC); co-supervisor: Dr. N.A. Kootstra (AMC).

Jannie van der Helm - 26 September 2014: **International epidemiological studies on HIV, HCV and STI.** Supervisor: Prof. H.J.C. de Vries (AMC/GGD Amsterdam) and Prof. M. Prins (AMC/GGD Amsterdam); co-supervisor: Dr. R.B. Geskus (AMC/GGD Amsterdam).

Anneke de Vos - 28 October 2014: Heterogeneity in risk-behaviour matters; **Modelling the spread of HIV and hepatitis C virus among injecting drug users.** Supervisors: Prof. M.E.E. Kretzschmar (UMC Utrecht) and Prof. M. Prins (AMC/GGD Amsterdam).

10. Curaçao

Ard van Sighem, Ashley Duits, Gonneke Hermanides

Introduction

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

HIV-positive population

Of the total of 960 HIV-infected patients registered in Curaçao as of May 2015, 171 (18%) have died since the initial registration and 12 (1%) have moved abroad. The total follow up for the entire group of 960 patients was 7,044 person years since HIV diagnosis. Of the 777 patients who had not died or moved abroad as of May 2015, 547 (69%) were retained in clinical care and had had at least one contact with their treating physician in Curaçao since January 2014.

In total, 272 (28%) of the registered patients were diagnosed with HIV in or before 2000; 87 (32%) of these patients died before May 2015 (*Figure 10.1; Appendix Table 10.1*). Between 2001 and May 2015, 650 additional patients were diagnosed and entered care. For the remaining 38 patients, no information regarding the date of their first positive HIV test was available. Almost three-quarters of the registered population originated from the former Netherlands Antilles. The large majority of patients were infected with HIV-1, whilst two patients were infected with HIV-2, and 11 patients had antibodies against both HIV-1 and HIV-2. Approximately two-thirds of the registered patients reported being infected via heterosexual contact (*Table 10.1*).

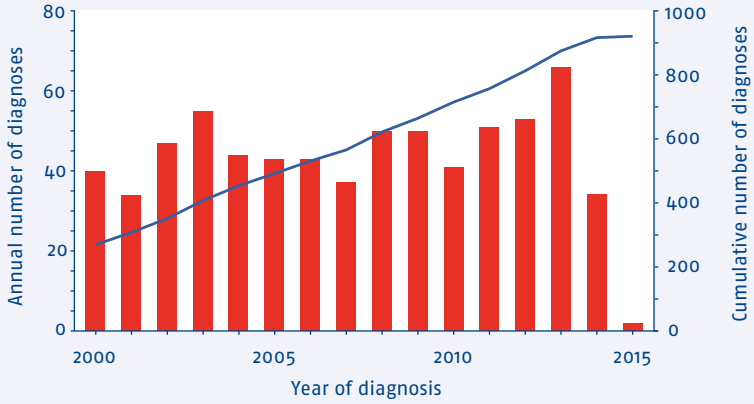
Table 10.1: Characteristics of the HIV-positive population in Curaçao registered by Stichting HIV Monitoring as of May 2015.

	Alive, n=789		Deceased, n=171		Total, n=960	
	n / median	% / IQR	n / median	% / IQR	n / median	% / IQR
Gender						
Male	484	61	119	70	603	63
Female	305	39	52	30	357	37
Transmission						
MSM	168	21	17	10	185	19
Heterosexual	522	66	107	63	629	66
Other/unknown	99	13	47	27	146	15
Country of birth						
Antilles	551	70	153	89	704	73
Haiti	93	12	6	4	100	10
Dominican Republic	67	8	7	4	73	8
Other	78	10	5	3	83	9
Treated with cART						
No	110	14	57	33	167	17
Yes	679	86	114	67	793	83
Diagnosis						
CD4 (cells/mm^3)	344	156–492	106	44–347	327	104–476
RNA (log_{10} IU/ml)	4.5	3.9–5.0	4.9	3.9–5.4	4.5	3.9–5.0
Age (years)	38	30–47	41	32–56	39	30–48
AIDS	45	6	32	19	77	8
Time to cART	1.1	0.2–4.6	0.9	0.2–4.4	1.1	0.2–4.5
Follow up (years)	6.5	2.5–12.4	2.9	0.4–7.5	5.8	2.0–11.4
Start of cART						
CD4 (cells/mm^3)	218	78–352	83	14–189	201	68–339
RNA (log_{10} IU/ml)	4.7	4.2–5.3	5.1	4.3–5.5	4.7	4.2–5.3
Age (years)	41	33–49	46	38–57	42	34–51
AIDS	82	10	54	32	136	14
Follow up (years)	4.6	1.6–9.3	2.0	0.3–5.4	4.1	1.4–8.7
Present (May 2015)[a]						
CD4 (cells/mm^3)	536	356–746	-	-	536	356–746
RNA <80 IU/ml	401	78[b]	-	-	401	78[b]
RNA <40 IU/ml	387	75[b]			387	75[b]
Age (years)	49	40–56	-	-	49	40–56

[a] for 547 patients still in clinical care; [b] percentage of 516 patients with a viral load measurement

***Legend:** IQR=interquartile range; MSM=men who have sex with men; cART=combination antiretroviral therapy.*

Figure 10.1: Annual and cumulative number of HIV diagnoses among 960 HIV-positive patients in Curaçao registered by Stichting HIV Monitoring as of May 2015. In total, 232 patients were diagnosed prior to 2000, while the year of diagnosis was unknown or not yet recorded for 38 patients.



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

Children and adolescents

Among HIV-positive patients ever registered in Curaçao, at the time of diagnosis 15 patients were younger than 13 years of age ('children'), and 19 were aged 13 to 18 years ('adolescents'). Most of the children, 12 in total, were infected by mother-to-child transmission. Adolescents were infected mainly via either heterosexual contact (n=13) or homosexual contact (n=5). In total, 10 children and one adolescent have died. Eleven adolescents, but none of the children, had a recorded contact with the treating HIV physician in 2014 or 2015.

Country of infection

For 655 patients (68%) of the registered population, the most likely country of infection was known. For 578 (88%) of these patients, the country of infection was the former Netherlands Antilles. This percentage was even higher (95%) among the 503 patients who were also born in the former Netherlands Antilles. Of the 655 patients, 28 reported that they had been infected in the Netherlands, 17 in Haiti, and 11 in the Dominican Republic. All, but 4, of the 232 patients with a known HIV-1 subtype were infected with a subtype B virus, which is the most prevalent subtype in the Caribbean and among patients of non-African origin in the Netherlands.

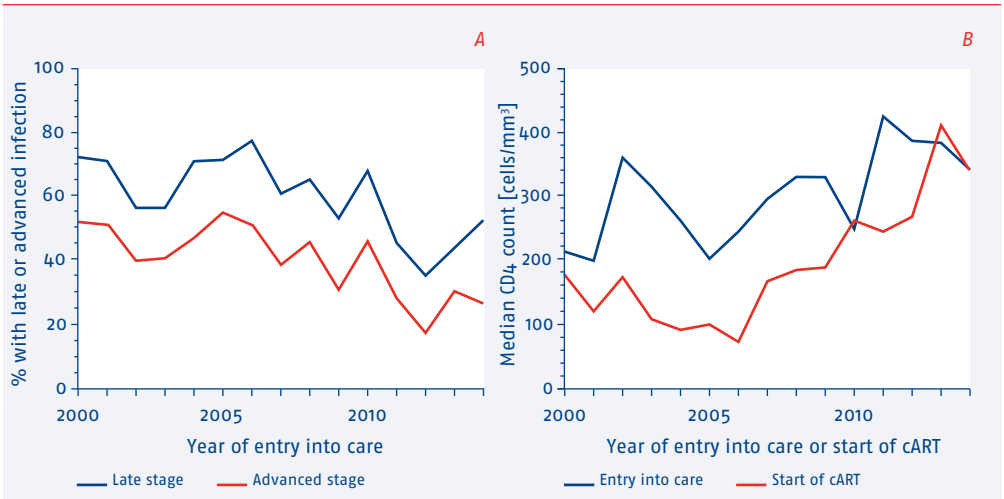
Late presentation and start of treatment

At the time of entry into care, 449 (59%) of the 759 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 10.2A*)[7]. Of these 449 patients, 306 (68%) were already in

an advanced stage of their infection, with less than 200 cells/mm³. 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, 201 cells/mm³, which is markedly below any guideline's recommended threshold to start treatment. Nevertheless, only 14% of the patients had been diagnosed with an AIDS-defining event by the time treatment was started[185]. In recent years, there has been an increase in CD4 cell counts at the start of cART (*Figure 10.2B*). Between 2011 and 2015, 29% of the patients for whom a CD4 count was available at the start of cART had less than 200 CD4 cells/mm³, whilst 27% had CD4 counts between 200 and 350 cells/mm³. During the same period, 91% of the patients entering care with less than 350 cells/mm³, 58% of those with CD4 counts between 350 and 500 cells/mm³, and 40% of patients with 500 CD4 cells/mm³ or more received treatment within six months.

Figure 10.2: *(A) From 2000 onwards, 59% of patients entered clinical care with late-stage HIV infection, while 39% 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, the median CD4 count at the time of entry was 316 cells/mm³ (interquartile range [IQR], 107–475), while the median CD4 count at the start of combination antiretroviral therapy (cART) was 212 cells/mm³ (IQR, 73–342). In recent years, CD4 counts at start of cART have clearly increased (339 cells/mm³ in 2014), indicating more timely diagnosis and start of treatment.*



Legend: *cART=combination antiretroviral therapy.*

Patient monitoring

Current guidelines recommend monitoring HIV-infected patients two to three times a year, depending on CD4 count and treatment status[15]. In most recent years, these guidelines have been generally well followed in Curaçao. Between 2009 and 2014, on average, 1.9 immunology measurements were performed annually per patient. During the same period, the viral load was monitored 1.9 times per year, while follow-up visits for each patient averaged 2.5 per year.

Combination treatment

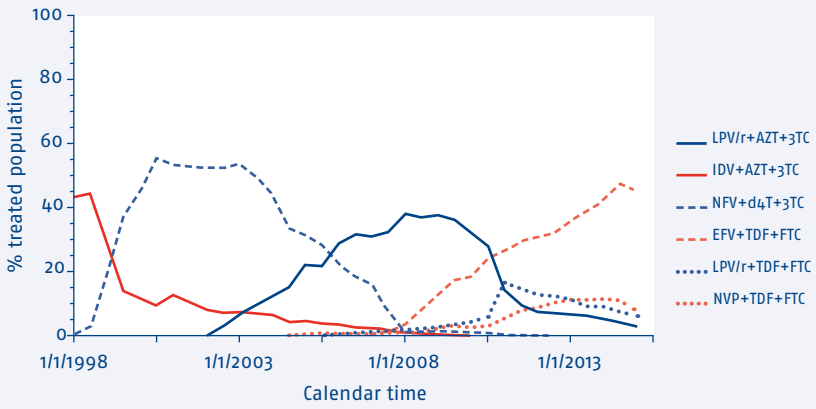
In total, 793 (83%) patients started cART, including 45 (6%) who were pre-treated with mono or dual therapy and 748 (94%) who started while being antiretroviral therapy-naive. Of the 374 who did so between 2009 and 2015, 59% started with a combination of tenofovir/emtricitabine and efavirenz and 20% started on a combination of zidovudine/lamivudine and ritonavir-boosted lopinavir. Over time, there have been clear shifts in the treatment regimens prescribed in Curaçao (*Figure 10.3*). Since 2008, a combination of tenofovir/emtricitabine with either efavirenz, nevirapine, or lopinavir has become more widely used. Of the 531 patients who started cART and were still in clinical care as of May 2015, 49% were receiving efavirenz, 19% rilpivirine, 10% elvitegravir, 7% lopinavir, and 6% nevirapine, whilst 86% were receiving tenofovir/emtricitabine and 4% zidovudine/lamivudine.

Treatment outcome

For 45% of the 731 antiretroviral therapy-naive patients who started cART in 1995 or later, CD4 counts increased by at least 150 cells/mm^3 during the first six months of treatment; after two years, this proportion increased to 77%. At the same time, 73% of the patients reached a viral load level below 80 IU/ml within six months of starting treatment.

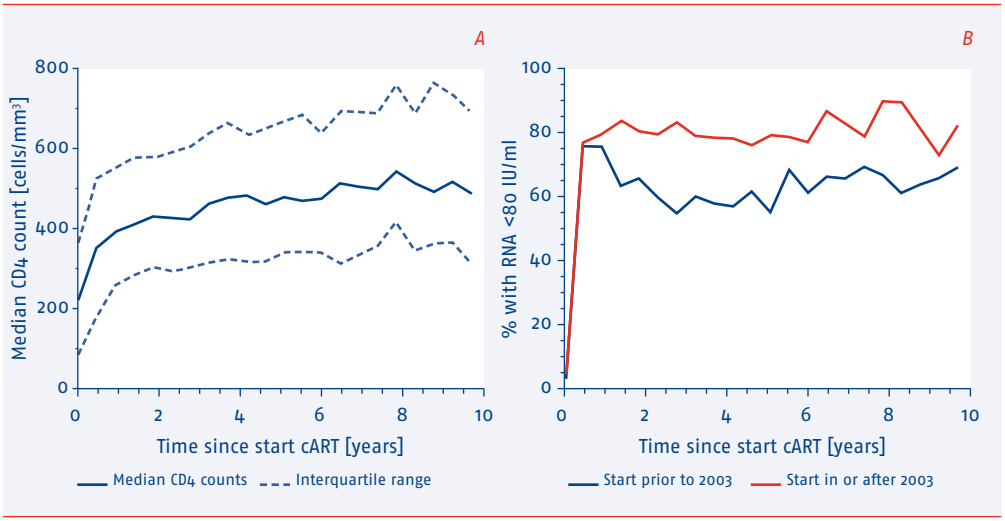
In patients who were still in clinical care as of May 2015, CD4 counts reached a plateau around 500 cells/mm^3 after five years of cART (*Figure 10.4A*). During the same period, the proportion of patients with a viral load less than 80 IU/ml was 79% after 48 weeks and 75% after five years of treatment. However, among those who started cART in 2003 or later, the proportion of patients who were able to maintain viral suppression remained approximately 80% (*Figure 10.4B*). For 78% of the patients still in clinical care, the most recent viral load result was less than 80 IU/ml, whilst 75% had a viral load less than 40 IU/ml. These proportions were the same irrespective of the period in which cART was started.

Figure 10.3: 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 43% in 1998 to almost 0% after 2008. This decrease was counterbalanced by an increase in the proportion of patients treated with NFV+d4T+3TC. From 2002 to 2010, a combination of LPV/r+AZT+3TC was increasingly common. The use of EFV+TDF+FTC and LPV/r+TDF+FTC increased from 2008 onwards, and at the beginning of 2015, 45% of the patients were receiving EFV+TDF+FTC, 8% NVP+TDF+FTC, 6% LPV/r+TDF+FTC, and 3% 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.

Figure 10.4: CD4 cell counts and viral load in 527 treated patients who were still in care as of May 2015. (A) Median CD4 counts (solid line; dotted line: interquartile range [IQR]) increased from 222 (IQR 85–365) cells/mm³ at the start of combination antiretroviral therapy (cART) to 352 (IQR 183–524) cells/mm³ after 24 weeks and reached a plateau around 500 cells/mm³ after five years. (B) The proportion of patients with HIV RNA <80 IU/ml was 79% after 48 weeks, and it remained high among those who started cART in 2003 or later. For patients starting prior to 2003, the proportion <80 IU/ml gradually declined to between 50% and 60% after five years but then increased again to between 60% and 70%.



Legend: cART=combination antiretroviral therapy.

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 defined as an HIV RNA level above 200 IU/ml despite at least four months of continuous treatment, the proportion of patients with virological failure steadily declined from approximately 35% between 2000 and 2004 to 9% in 2014.

Mortality and survival

Of the group of 880 patients who were still alive as of 1 January 2005 or who were diagnosed with HIV after that date, 91 had died by May 2015. Overall, the survival probability after seven years of follow up was 86%. All together, 537 patients started cART in or after 2005, and of this group, 45 had died, 18 of whom died within six months of starting cART. After eight years, the survival probability was 82%.

Conclusion

In recent years, HIV-positive patients in Curaçao appear to be diagnosed increasingly earlier in their infection, as the proportion of patients entering care in a late or advanced stage of their infection is decreasing. As a consequence, cART can be started earlier and, thus, in a more timely manner. The quality of monitoring and treatment offered to HIV-infected patients in Curaçao has improved considerably. However, adherence to treatment is still not optimal, and levels of retention in care are worryingly low.

Recommendations

Curacao is in a unique position in the Caribbean in that data from HIV patients in care is collected and monitored; however, it is important that the quality of these data is maintained. In particular, special attention should be paid to the collection of data of HIV-positive children. Further, adherence to treatment and retention in care need to be improved to reduce the number of patients failing on treatment[186]. Finally, HIV infections need to be detected at an even earlier stage, so that patients can start antiretroviral treatment in accordance with current recommendations.

Appendix figures and tables

Appendix figures and tables are listed by chapter

Appendix Table 1.1: *Characteristics of the 18,355 HIV-positive patients in follow up as of May 2015.*

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=11,204	n=2,344	n=3,070	n=243	n=96
Current age [years]					
0–12	0	0	0	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%
13–17	0	0	1	0	0
	0.0%	0.0%	0.0%	0.0%	0.0%
18–24	200	12	51	0	0
	1.8%	0.5%	1.7%	0.0%	0.0%
25–34	1,377	229	557	15	3
	12.3%	9.8%	18.1%	6.2%	3.1%
35–44	2,640	524	1,081	31	12
	23.6%	22.4%	35.2%	12.8%	12.5%
45–54	3,974	870	883	110	48
	35.5%	37.1%	28.8%	45.3%	50.0%
55–64	2,179	476	350	80	29
	18.5%	20.3%	11.4%	32.9%	30.2%
65–74	729	198	116	7	4
	6.4%	8.4%	3.8%	2.9%	4.2%
≥75	105	35	31	0	0
	0.9%	1.5%	1.0%	0.0%	0.0%
Current age 50 years or older					
No	6,197	1,216	2,212	88	26
	55.3%	51.9%	72.1%	36.2%	27.1%
Yes	5,007	1,128	858	155	70
	44.7%	48.1%	27.9%	63.8%	72.9%
Current age 60 years or older					
No	9,525	1,944	2,805	207	84
	85.0%	82.9%	91.4%	85.2%	87.5%
Yes	1,679	400	265	36	12
	15.0%	17.1%	8.6%	14.8%	12.5%

	Blood or blood products		Other / unknown		Total	
	Men	Women	Men	Women	Men	Women
	n=150	n=91	n=883	n=274	n=14,824	n=3,531
	0	0	60	67	60	67
	0.0%	0.0%	6.8%	24.5%	0.4%	1.9%
	1	2	43	33	43	36
	0.7%	2.2%	4.8%	12.0%	0.3%	1.0%
	2	1	49	41	263	93
	1.3%	1.1%	5.5%	15.0%	1.8%	2.6%
	19	13	110	28	1,750	601
	12.7%	14.3%	12.5%	10.2%	11.8%	17.0%
	26	27	167	37	3,388	1,157
	17.3%	29.7%	18.9%	13.5%	22.9%	32.8%
	52	25	237	39	5,243	995
	34.7%	27.5%	26.8%	14.2%	35.4%	28.2%
	27	16	138	23	2,900	418
	18.0%	17.6%	15.6%	8.4%	19.6%	11.8%
	21	6	70	5	1,025	131
	14.0%	6.6%	7.9%	1.8%	6.9%	3.7%
	2	1	10	1	152	33
	1.3%	1.1%	1.1%	0.4%	1.0%	0.9%
	74	59	557	227	8,132	2,524
	49.3%	64.8%	63.1%	82.8%	54.9%	71.5%
	76	32	326	47	6,692	1,007
	50.7%	35.2%	36.9%	17.2%	45.1%	28.5%
	118	79	748	261	12,542	3,229
	78.7%	86.8%	84.7%	95.3%	84.6%	91.4%
	32	12	135	13	2,282	302
	21.3%	13.2%	15.3%	4.7%	15.4%	8.6%

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=11,204	n=2,344	n=3,070	n=243	n=96
Region of origin					
Netherlands	8,238	1,061	863	143	49
	73.5%	45.3%	28.1%	58.8%	51.0%
Sub-Saharan Africa	144	670	1,344	4	0
	1.3%	28.6%	43.8%	1.6%	0.0%
Western Europe	709	79	75	25	30
	6.3%	3.4%	2.4%	10.3%	31.3%
South America	691	213	304	10	1
	6.2%	9.1%	9.9%	4.1%	1.0%
Caribbean	396	126	165	6	1
	3.5%	5.4%	5.4%	2.5%	1.0%
Other	984	192	315	55	15
	8.8%	8.2%	10.3%	22.6%	15.6%
Unknown	42	3	4	0	0
	0.4%	0.1%	0.1%	0.0%	0.0%
Years aware of HIV infection					
<1	466	78	82	0	0
	4.2%	3.3%	2.7%	0.0%	0.0%
1-2	1,297	228	231	4	3
	11.6%	9.7%	7.5%	1.6%	3.1%
3-4	1,397	277	278	6	1
	12.5%	11.8%	9.1%	2.5%	1.0%
5-10	3,351	653	824	24	7
	29.9%	27.9%	26.8%	9.9%	7.3%
10-20	3,224	952	1,335	91	25
	28.8%	40.6%	43.5%	37.4%	26.0%
>20	1,463	153	293	118	60
	13.1%	6.5%	9.5%	48.6%	62.5%
Unknown	6	3	27	0	0
	0.1%	0.1%	0.9%	0.0%	0.0%
Current CD4 count [cells/mm^3], median / IQR	630	548	620	508	635
	480-810	384-730	450-819	327-727	344-918
Current CD8 count [cells/mm^3], median / IQR	883	850	800	844	865
	658-1,190	610-1,160	572-1,070	570-1,190	626-1,240
Current HIV RNA <500 copies/ml	10,028	2,067	2,652	216	81
	89.5%	88.2%	86.4%	88.9%	84.4%
Current HIV RNA <100 copies/ml	9,846	1,993	2,566	209	81
	87.9%	85.0%	83.6%	86.0%	84.4%

Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women
n=150	n=91	n=883	n=274	n=14,824	n=3,531
97	18	404	115	9,943	1,045
64.7%	19.8%	45.8%	42.0%	67.1%	29.6%
28	42	233	92	1,079	1,478
18.7%	46.2%	26.4%	33.6%	7.3%	41.9%
4	2	42	24	859	131
2.7%	2.2%	4.8%	8.8%	5.8%	3.7%
2	9	50	9	966	323
1.3%	9.9%	5.7%	3.3%	6.5%	9.1%
4	4	34	2	566	172
2.7%	4.4%	3.9%	0.7%	3.8%	4.9%
15	16	111	30	1,357	376
10.0%	17.6%	12.6%	10.9%	9.2%	10.6%
0	0	9	2	54	6
0.0%	0.0%	1.0%	0.7%	0.4%	0.2%
4	1	30	7	578	90
2.7%	1.1%	3.4%	2.6%	3.9%	2.5%
17	4	62	17	1,608	255
11.3%	4.4%	7.0%	6.2%	10.8%	7.2%
13	7	91	24	1,784	310
8.7%	7.7%	10.3%	8.8%	12.0%	8.8%
13	22	229	69	4,270	922
8.7%	24.2%	25.9%	25.2%	28.8%	26.1%
50	37	284	97	4,601	1,494
33.3%	40.7%	32.2%	35.4%	31.0%	42.3%
53	20	76	45	1,863	418
35.3%	22.0%	8.6%	16.4%	12.6%	11.8%
0	0	111	15	120	42
0.0%	0.0%	12.6%	5.5%	0.8%	1.2%
560	680	550	729	610	630
340–730	461–970	365–790	471–1,060	460–800	450–840
751	921	830	780	875	800
530–1,180	650–1,190	600–1,180	560–1,086	643–1,180	576–1,080
132	78	694	227	13,137	3,038
88.0%	85.7%	78.6%	82.8%	88.6%	86.0%
129	76	667	219	12,844	2,942
86.0%	83.5%	75.5%	79.9%	86.6%	83.3%

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=11,204	n=2,344	n=3,070	n=243	n=96
Ever AIDS	2,029	716	667	88	43
	18.1%	30.5%	21.7%	36.2%	44.8%
AIDS at diagnosis	1,063	495	382	19	10
	9.5%	21.1%	12.4%	7.8%	10.4%
Current treatment					
cART	10,431	2,210	2,879	234	94
	93.1%	94.3%	93.8%	96.3%	97.9%
Non-cART	14	3	2	1	0
	0.1%	0.1%	0.1%	0.4%	0.0%
Not started	759	131	189	8	2
	6.8%	5.6%	6.2%	3.3%	2.1%

Legend: *MSM=men who have sex with men; IDU=injecting drug use; IQR=interquartile range; cART=combination antiretroviral therapy.*

	Blood or blood products		Other / unknown		Total	
	Men	Women	Men	Women	Men	Women
	n=150	n=91	n=883	n=274	n=14,824	n=3,531
	49	25	263	75	3,145	810
	32.7%	27.5%	29.8%	27.4%	21.2%	22.9%
	27	12	194	38	1798	442
	18.0%	13.2%	22.0%	13.9%	12.1%	12.5%
	141	89	742	251	13,758	3,313
	94.0%	97.8%	84.0%	91.6%	92.8%	93.8%
	0	0	2	0	20	2
	0.0%	0.0%	0.2%	0.4%	0.1%	0.1%
	9	2	139	23	1,046	216
	6.0%	2.2%	15.7%	8.4%	7.1%	6.1%

Appendix Table 1.2: *Annual number of HIV-1 diagnoses among children and among adults per transmission risk group, including men who have sex with men (MSM), patients infected via heterosexual contact, injecting drug use (IDU), contact with contaminated blood or blood products, or other or unknown modes of transmission. Note: data collection for 2013 and 2014 had not yet been finalised at the time of writing.*

	MSM	Heterosexual		IDU	
Year of diagnosis	**Men**	**Men**	**Women**	**Men**	**Women**
≤1995	2,223	266	391	287	131
1996	381	90	80	30	10
1997	441	112	127	42	10
1998	331	107	114	22	6
1999	352	107	137	19	7
2000	378	159	192	18	3
2001	445	165	215	15	5
2002	463	165	248	16	3
2003	456	179	274	22	5
2004	581	198	262	9	4
2005	635	196	259	15	2
2006	668	162	197	10	5
2007	768	154	206	10	3
2008	847	177	177	6	1
2009	767	155	180	7	0
2010	767	177	161	5	1
2011	749	145	145	4	1
2012	692	142	142	6	1
2013	703	113	115	2	2
*2013**	*724*	*116*	*118*	*2*	*2*
2014	552	100	100	0	0
*2014**	*613*	*111*	*111*	*0*	*0*
2015	90	15	16	0	0
Total	13,289	3,084	3,738	545	200

**Projected numbers*

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

	Blood or blood products		Other/unknown		Children		Total
	Men	Women	Men	Women	Men	Women	
	61	21	156	52	49	38	3,675
	3	4	36	5	11	3	653
	7	3	42	7	8	9	808
	6	5	30	8	7	9	645
	8	4	19	6	11	12	682
	3	4	34	4	13	29	837
	7	4	42	7	15	34	954
	15	7	58	3	19	21	1,018
	9	3	65	14	16	22	1,065
	4	3	70	10	14	12	1,167
	3	7	64	10	11	11	1,213
	4	7	56	4	8	9	1,130
	2	6	49	7	7	11	1,223
	4	2	55	6	14	16	1,305
	1	1	49	9	12	13	1,194
	6	3	40	7	17	16	1,200
	8	6	56	4	9	6	1,133
	4	3	33	9	5	9	1,046
	11	1	40	4	2	2	995
	11	*1*	*41*	*4*	*2*	*2*	*1023*
	6	2	39	6	1	3	809
	7	*2*	*43*	*7*	*1*	*3*	*898*
	2	0	7	1	0	0	131
	174	96	1,040	183	249	285	22,883

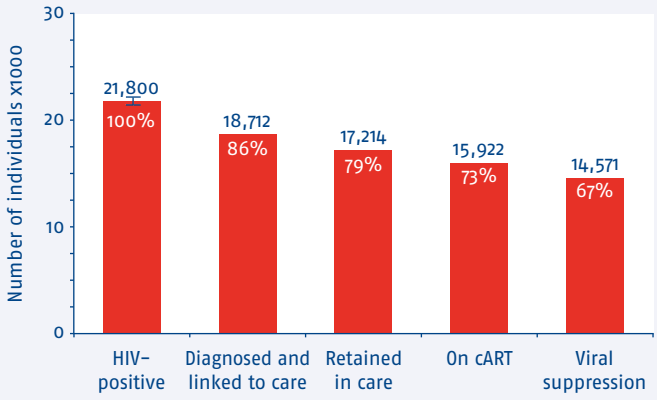
Appendix Table 1.3: *Region of origin of the 22,883 adult HIV-1-positive patients with a recorded date of diagnosis. For men who have sex with men (MSM) and for heterosexual men and women, numbers are stratified according to year of HIV diagnosis.*

	MSM			Heterosexual men		
	<2012	**≥2012**	**Total**	**<2012**	**≥2012**	**Total**
The Netherlands	7,981	1,504	9,485	1,091	189	1,280
	70.9%	73.8%	71.4%	40.2%	51.1%	41.5%
Sub-Saharan Africa	164	24	188	892	72	964
	1.6%	1.2%	1.4%	32.9%	19.5%	31.3%
Western Europe	923	91	1,014	100	14	114
	8.2%	4.5%	7.6%	3.7%	3.8%	3.7%
Central Europe	205	76	281	74	15	89
	1.8%	3.7%	2.1%	2.7%	4.1%	2.9%
Eastern Europe	62	17	79	10	3	13
	0.6%	0.8%	0.6%	0.4%	0.8%	0.4%
South America	763	103	866	274	29	303
	6.8%	5.1%	6.5%	10.1%	7.8%	9.8%
Caribbean	362	85	447	140	20	160
	3.2%	4.2%	3.4%	5.2%	5.4%	5.2%
South and Southeast Asia	323	59	382	48	9	57
	2.9%	2.9%	2.9%	1.8%	2.4%	1.8%
Other/unknown	469	78	547	85	19	104
	4.2%	3.8%	4.1%	3.1%	5.1%	3.4%

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

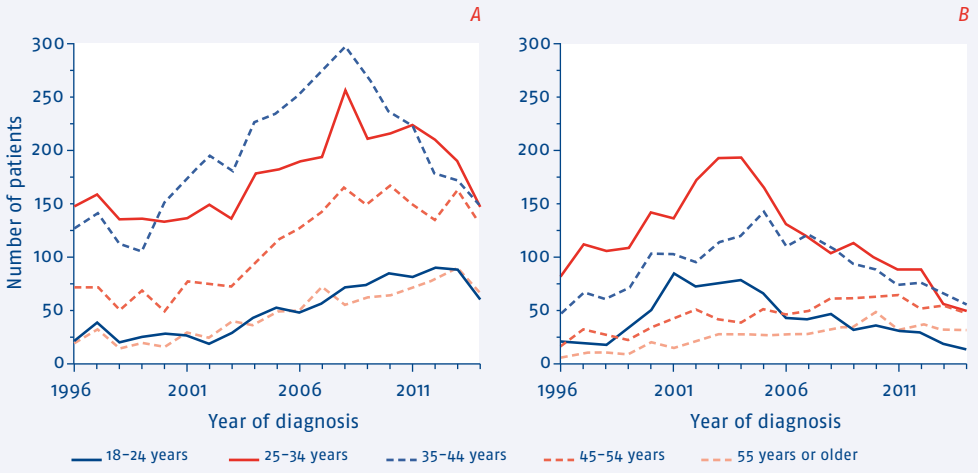
	Heterosexual women			IDU	Other
	<2012	≥2012	Total	Total	Total
	811	126	937	444	652
	24.1%	33.8%	25.1%	59.6%	43.7%
	1,605	138	1,743	8	367
	47.7%	37.0%	46.6%	1.1%	24.6%
	93	9	102	141	118
	2.8%	2.4%	2.7%	18.9%	7.9%
	47	11	58	27	53
	1.4%	2.9%	1.6%	3.6%	3.5%
	25	5	30	30	24
	0.7%	1.3%	0.8%	4.0%	1.6%
	328	42	370	25	87
	9.7%	11.3%	9.9%	3.4%	5.8%
	199	11	210	13	41
	5.9%	2.9%	5.6%	1.7%	2.7%
	205	25	230	22	61
	6.1%	6.7%	6.2%	3.0%	4.1%
	52	6	58	35	90
	1.5%	1.6%	1.6%	4.7%	6.0%

Appendix Figure 1.1: *Continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2013. According to a recently developed method, 21,800 people were living with HIV in the Netherlands. In total, 18,712 of these individuals were diagnosed, linked to care, and registered by SHM. Of these patients, 17,214 were still in care in 2013, 15,922 had started combination antiretroviral treatment (cART), and 14,571 patients had a most recent RNA measurement below 100 copies/ml. Percentages were calculated relative to the 21,800 individuals living with HIV.*

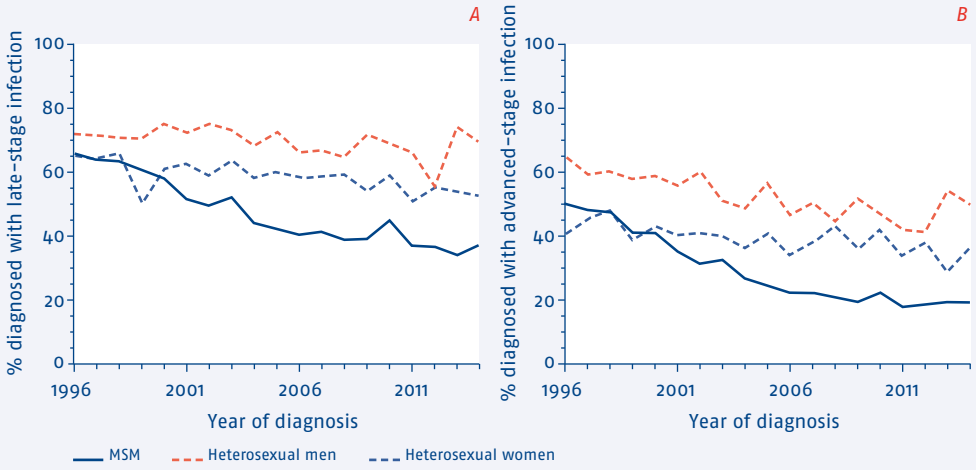


Legend: *cART=combination antiretroviral treatment.*

Appendix Figure 1.2: *Age distribution at the time of diagnosis among HIV-1-infected adult men who have sex with men (A) and heterosexual men and women (B). Note: data collection for 2013 and 2014 had not yet been finalised at the time of writing.*

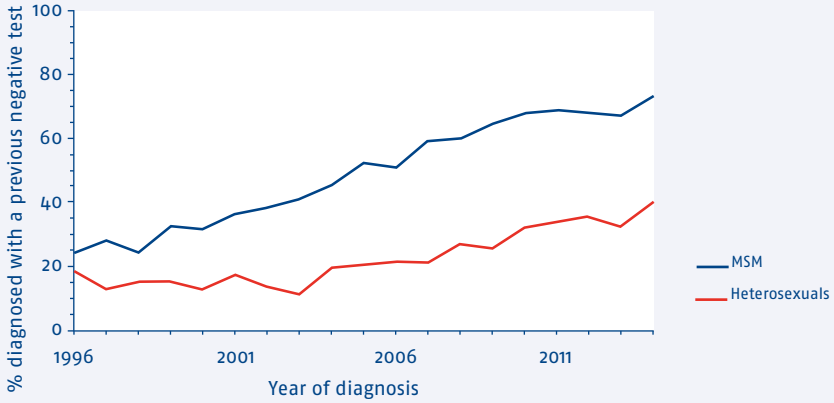


Appendix Figure 1.3: *Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection at the time of HIV diagnosis. From 1996 onwards, 53% (44% from 2012) were diagnosed with late-stage HIV: men who have sex with men (MSM) 44% (36% from 2012), heterosexual men 70% (66% from 2012), and heterosexual women 58% (53% from 2012). Overall, 35% (28% from 2012) were advanced presenters: MSM 26% (18% from 2012), heterosexual men 52% (48% from 2012), and heterosexual women 39% (34% from 2012). Late stage infection: CD4 counts below 350 cells/mm³ or having AIDS, regardless of CD4 count. Advanced stage infection: CD4 counts below 200 cells/mm³ or having AIDS.*



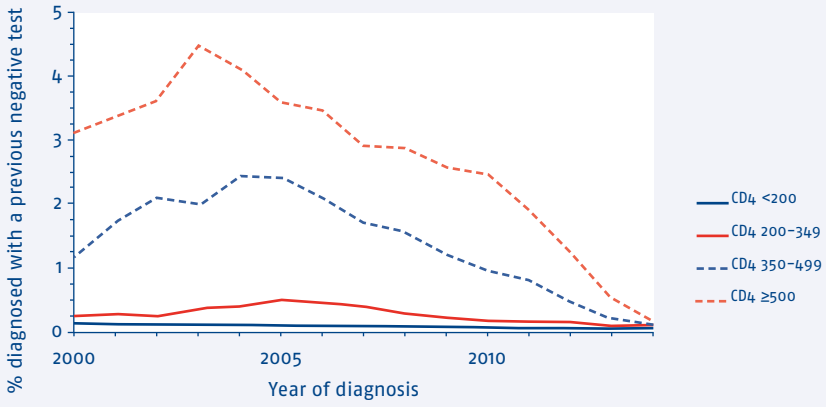
Legend: *MSM=men who have sex with men.*

Appendix Figure 1.4: *Proportion of patients diagnosed after a previously negative HIV test. All together, 73% of men who have sex with men (MSM) and 40% of heterosexuals (men 26%, women 54%) diagnosed in 2014 had a previously negative HIV test.*



Legend: *MSM=men who have sex with men.*

Appendix Figure 1.5: *Median time to start of combination antiretroviral treatment (cART) by year of diagnosis stratified by CD4 count at the time of diagnosis.*



Legend: *cART=combination antiretroviral therapy.*

Appendix Table 2.1: *Adjusted risk ratios (95% confidence intervals) of a toxicity-driven therapy change during the first three years in therapy-naive individuals starting combination antiretroviral therapy (cART) in, or after, 2009 by Poisson regression analysis. The probability of a toxicity-driven therapy change is higher compared to the reference group when the risk ratio is higher than 1.00.*

	Risk ratio	95% CI	(overall) p-value
Gender			
Male	1.00		
Female	1.23	1.09-1.40	0.001
Region of origin			(0.02)
Netherlands	1.00		
Caribbean/South America	0.94	0.82-1.08	0.40
Sub-Saharan Africa	1.07	0.93-1.23	0.32
Western Europe / North America	0.74	0.61-0.91	0.004
CD4 cell count (cells/mm^3)			(<0.0001)
<200	0.84	0.74-0.96	0.01
200-350	0.85	0.76-0.95	0.004
350-500	1.00		
≥500	1.28	1.13-1.46	0.0002

	Risk ratio	95% CI	(overall) p-value
HIV RNA (log_{10} copies/ml)			(<0.0001)
<4	1.00	0.87–1.14	0.99
4–5	1.00		
≥5	1.18	1.08–1.30	0.0005
Year of starting cART			(0.002)
2009	1.00		
2010	1.11	0.98–1.25	0.10
2011	1.12	0.99–1.27	0.06
2012	1.12	0.99–1.28	0.08
2013	0.91	0.78–1.05	0.19
2014	0.73	0.59–0.90	0.003
Time after starting cART (months)			(<0.0001)
0–3	1.00		
3–6	0.45	0.39–0.51	<0.0001
6–12	0.36	0.32–0.40	<0.0001
12–24	0.26	0.23–0.29	<0.0001
24–36	0.22	0.19–0.25	<0.0001
Number of previous toxicity-driven therapy changes			(<0.0001)
0	1.00		
1	1.61	1.44–1.79	<0.0001
2	2.39	1.97–2.91	<0.0001
≥3	3.08	2.28–4.17	<0.0001
AIDS diagnosis at start of cART	1.23	1.09–1.38	0.0005
Start during primary infection	1.25	1.09–1.42	0.001
Start during pregnancy	1.19	0.90–1.57	0.22

Legend: *CI=confidence interval; cART=combination antiretroviral therapy.*

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Appendix Table 2.2: *Overview of the most frequently-recorded adverse events leading to a toxicity-driven therapy stop from 2009-2014. Multiple adverse events in a patient during the same year are counted once. For every toxicity-driven therapy stop, up to three adverse events could be recorded; therefore, percentages do not add up to 100%.*

	2009		2010	
	n	%	n	%
Individuals with at least 1 toxicity-driven therapy stop	1,001	100.0	1,066	100.0
Body composition and serum lipids				
Lipodystrophy, any	108	10.8	81	7.6
Lipoatrophy, peripheral fat loss	81	8.1	58	5.4
Lipohypertrophy – central fat accumulation	22	2.2	20	1.9
Lipodystrophy unspecified	3	0.3	4	0.4
Elevated cholesterol	11	1.1	14	1.3
Elevated triglycerides	17	1.7	17	1.6
Liver				
Icterus	8	0.8	24	2.3
Elevated gamma-glutamyl transpeptidase	25	2.5	22	2.1
Elevated aspartate aminotransferase	15	1.5	14	1.3
Elevated alanine aminotransferase	9	0.9	12	1.1
Elevated bilirubin	11	1.1	15	1.4
Hepatic steatosis	4	0.4		0.0
Elevated alkaline phosphatase	1	0.1	2	0.2
Elevated creatine phosphokinase	3	0.3	1	0.1
Renal				
Renal-related issues*	66	6.6	76	7.1
Nephrolithiasis	2	0.2	5	0.5

	2011		2012		2013		2014	
	n	%	n	%	n	%	n	%
	1,035	100.0	1,349	100.0	1,376	100.0	1,079	100.0
	51	4.9	63	4.7	44	3.2	27	2.5
	33	3.2	39	2.9	23	1.7	15	1.4
	18	1.7	19	1.4	17	1.2	11	1.0
		0.0	5	0.4	4	0.3	1	0.1
	15	1.4	16	1.2	21	1.5	14	1.3
	24	2.3	9	0.7	12	0.9	4	0.4
	25	2.4	32	2.4	44	3.2	28	2.6
	25	2.4	24	1.8	12	0.9	8	0.7
	12	1.2	13	1.0	6	0.4	9	0.8
	5	0.5	16	1.2	14	1.0	10	0.9
	13	1.3	11	0.8	10	0.7	3	0.3
	8	0.8	1	0.1		0.0		
	1	0.1	3	0.2	5	0.4		
	3	0.3		0.0	1	0.1	2	0.2
	91	8.8	160	11.9	186	13.5	163	15.1
	10	1.0	5	0.4	10	0.7	4	0.4

	2009		2010	
	n	%	n	%
Neurological / psychosocial				
Central nervous system toxicity **	142	14.2	169	15.9
Depression	46	4.6	48	4.5
Sleeplessness	29	2.9	40	3.8
Mood changes	32	3.2	44	4.1
Dizziness	45	4.5	43	4.0
Nightmares	23	2.3	33	3.1
Headache	9	0.9	27	2.5
Non-HIV-related neuropathy	14	1.4	13	1.2
Concentration disorders	10	1.0	8	0.8
Fear	9	0.9	10	0.9
Loss of libido	1	0.1	2	0.2
Erection disorders	1	0.1	7	0.7
Psychosis	4	0.4	2	0.2
Paraesthesia (transient numbness or tingling)	5	0.5	2	0.2
Loss of memory			4	0.4
Confusion	3	0.3	2	0.2
Gastrointestinal				
Diarrhoea	101	10.1	104	9.8
Nausea	42	4.2	43	4.0
Vomiting	25	2.5	28	2.6
Abdominal pain	12	1.2	18	1.7
Flatulence	9	0.9	4	0.4
Loss of appetite	3	0.3	3	0.3
Weight loss	2	0.2	1	0.1
Indigestion	2	0.2		
Change in taste	3	0.3	3	0.3
Abdominal distention	1	0.1		
Constipation	1	0.1	3	0.3
Dermatological				
Rash	70	7.0	78	7.3
Pruritus	12	1.2	12	1.1
Systemic				
Fatigue	30	3.0	41	3.8
General discomfort	10	1.0	11	1.0
Fever	3	0.3	2	0.2
Night sweats	1	0.1	2	0.2

	2011		2012		2013		2014	
	n	%	n	%	n	%	n	%
	172	16.6	252	18.7	274	19.9	214	19.8
	65	6.3	93	6.9	78	5.7	53	4.9
	62	6.0	66	4.9	82	6.0	65	6.0
	39	3.8	65	4.8	70	5.1	62	5.7
	31	3.0	50	3.7	52	3.8	32	3.0
	28	2.7	57	4.2	63	4.6	49	4.5
	25	2.4	16	1.2	31	2.3	8	0.7
	14	1.4	13	1.0	10	0.7	10	0.9
	11	1.1	16	1.2	10	0.7	6	0.6
	4	0.4	6	0.4	8	0.6	5	0.5
	3	0.3	11	0.8			6	0.6
	3	0.3	4	0.3	2	0.1	5	0.5
	7	0.7	2	0.1	2	0.1	3	0.3
	3	0.3	2	0.1	2	0.1	2	0.2
	1	0.1	5	0.4	3	0.2	1	0.1
	2	0.2			2	0.1		
	98	9.5	82	6.1	84	6.1	81	7.5
	40	3.9	40	3.0	58	4.2	34	3.2
	21	2.0	18	1.3	19	1.4	23	2.1
	15	1.4	18	1.3	19	1.4	16	1.5
	11	1.1	9	0.7	6	0.4	6	0.6
	4	0.4	4	0.3	5	0.4	3	0.3
	2	0.2	1	0.1	5	0.4	2	0.2
	3	0.3	1	0.1	2	0.1	4	0.4
	2	0.2	2	0.1	2	0.1		
			4	0.3	4	0.3	2	0.2
			2	0.1	2	0.1	3	0.3
	63	6.1	66	4.9	58	4.2	34	3.2
	15	1.4	23	1.7	18	1.3	12	1.1
	46	4.4	56	4.2	62	4.5	73	6.8
	16	1.5	20	1.5	10	0.7	5	0.5
	2	0.2	4	0.3	4	0.3	4	0.4
	2	0.2	3	0.2	5	0.4	6	0.6

	2009		2010	
	n	%	n	%
Haematological				
Anaemia	31	3.1	27	2.5
Leukopenia	7	0.7	4	0.4
Neutropenia	2	0.2	2	0.2
Thrombocytopenia	1	0.1	3	0.3
Pancytopenia	2	0.2		
Neuromuscular				
Myalgia	10	1.0	7	0.7
Arthralgia	4	0.4	11	1.0
Myopathy	1	0.1	2	0.2
Skeletal				
Osteoporosis	1	0.1	3	0.3
Osteopenia			3	0.3
Cardiovascular				
Hypertension	4	0.4	5	0.5
Arrhythmia	4	0.4	1	0.1
Myocardial infarction			3	0.3
Other				
Diabetes mellitus (both I and II)	5	0.5	7	0.7
Abacavir hypersensitivity	2	0.2	2	0.2
Cough	1	0.1	2	0.2
Pancreatitis	1	0.1		0.0

** Renal related issues includes the following adverse events in the database: elevated creatinine, renal insufficiency, proteinuria, dialysis.*

*** CNS toxicity includes the following adverse events in the database: dizziness, sleeplessness, nightmares, mood changes, concentration disorders, and confusion.*

	2011		2012		2013		2014	
	n	%	n	%	n	%	n	%
	14	1.4	30	2.2	25	1.8	14	1.3
	5	0.5	7	0.5	7	0.5	2	0.2
	4	0.4	7	0.5	9	0.7	3	0.3
	3	0.3	2	0.1	5	0.4	4	0.4
	2	0.2	6	0.4	2	0.1		
	4	0.4	8	0.6	13	0.9	9	0.8
	1	0.1	5	0.4	6	0.4	4	0.4
			3	0.2	2	0.1		
	3	0.3	4	0.3	6	0.4	2	0.2
	2	0.2	4	0.3	3	0.2	1	0.1
	4	0.4	4	0.3	4	0.3	2	0.2
	2	0.2	1	0.1				
	1	0.1	2	0.1				
	7	0.7	5	0.4	4	0.3	2	0.2
			1	0.1	1	0.1	1	0.1
	3	0.3	1	0.1	3	0.2	3	0.3
	1	0.1	2	0.1	3	0.2	1	0.1

Appendix Table 2.3. *Demographic and clinical characteristics of 16,481 individuals currently in follow up, according to treatment status at the start of combination antiretroviral therapy (cART), region of origin, gender, and transmission risk group.*

Year of starting cART	**1995–2001**	
	n	**%**
Total	4,118	100
HIV RNA <50 copies/ml		
Pre-treated	1,229	92
Naive	929	33.4
Ever AIDS diagnosis		
Pre-treated	595	44.5
Naive	929	33.4

	Median	**IQR**	
Age at 1 May 2015			
Pre-treated	55.2	50.3	61.5
Naive	53	47.5	59.2
Last CD4 cell count (cells/mm^3)			
Pre-treated	621	440	840
Naive	677	500	880
Last CD4/CD8 ratio			
Pre-treated	0.67	0.44	0.98
Naive	0.79	0.54	1.09

	n	**%**
HIV RNA <50 copies/ml		
W Europe /N America	347	90.8
Caribbean /S America	361	88.5
Netherlands	2,381	92.7
Sub-Saharan Africa	423	85.6
Ever AIDS diagnosis		
W Europe /N America	138	36.1
Caribbean /S America	153	37.5
Netherlands	952	37.1
Sub-Saharan Africa	180	36.4

2002–2007			2008–2013			2014		
n		%	n		%	n		%
4,097		100	7,210		100	1,055		100
147		87.5	83		88.3	8		88.9
1,168		29.7	1,191		16.7	118		11.3
54		32.1	18		19.1	3		33.3
1,168		29.7	1,191		16.7	118		11.3
Median	IQR		Median	IQR		Median	IQR	
52.4	46.1	58.1	49.8	42.6	57.2	49.4	36.1	49.9
48.6	42.2	55.3	45	36.8	52.4	40.7	32.3	49.3
670	470	885	551	430	690	390	330	480
620	464	800	610	460	781	550	391	724
0.73	0.5	0.93	0.64	0.41	0.83	0.49	0.4	0.6
0.73	0.5	1.01	0.7	0.5	1	0.51	0.35	0.78
n		%	n		%	n		%
221		91.7	371		91.8	38		70.4
444		84.7	673		88.0	80		71.4
1,977		92.4	4,255		92.2	469		66.3
728		86.5	646		86.1	64		73.6
61		25.3	42		10.4	6		11.1
172		32.8	138		18.0	17		15.2
599		28.0	688		14.9	73		10.3
268		31.8	184		24.5	18		20.7

Year of starting cART	1995–2001		
	Median	**IQR**	
Age at 1 May 2015			
W Europe /N America	53.3	48.9	58.6
Caribbean /S America	51.7	47.1	56.5
Netherlands	55.3	50.1	62.3
Sub-Saharan Africa	48.8	43.3	53.8
Last CD4 cell count (cells/mm^3)			
W Europe /N America	660	470	895
Caribbean /S America	670	515	920
Netherlands	660	480	870
Sub-Saharan Africa	627	440	810
Last CD4/CD8 ratio			
W Europe /N America	0.76	0.51	1.10
Caribbean /S America	0.76	0.54	1.01
Netherlands	0.73	0.50	1.03
Sub-Saharan Africa	0.76	0.50	1.09

	n	**%**
HIV RNA <50 copies/ml		
Male	3,041	92.1
Female	720	88.3
Ever AIDS diagnosis		
Male	1,262	38.2
Female	262	32.1

	Median	**IQR**	
Age at 1 May 2015			
Male	54.7	49.8	61.2
Female	49.3	44.4	54.7
Last CD4 cell count (cells/mm^3)			
Male	650	470	850
Female	710	510	950
Last CD4/CD8 ratio			
Male	0.71	0.50	1.00
Female	0.89	0.60	1.28

2002–2007			2008–2013			2014		
Median	IQR		Median	IQR		Median	IQR	
51.2	44.1	55.6	45.1	38.4	51.6	44.1	32.7	49.3
46.8	40.6	52.9	41.8	34.9	50	38.2	30.6	46
51.8	45.9	58.4	47	38.6	54.5	42.9	33.5	51.1
42.9	37.1	48.3	40	33.9	46.8	36.6	31.5	45.5
640	470	843	640	470	810	545	430	660
630	440	810	580	440	750	530	378	727
629	480	820	630	482	802	570	417	740
592	430	760	520	372	680	427	240	510
0.69	0.46	0.99	0.75	0.56	1.03	0.44	0.30	0.60
0.72	0.47	1.00	0.70	0.47	0.99	0.60	0.30	0.80
0.75	0.52	1.05	0.73	0.51	1.00	0.55	0.39	0.80
0.70	0.48	0.97	0.60	0.38	0.87	0.38	0.22	0.55
n		%	n		%	n		%
2,739		91	5,642		91.8	631		68.1
945		87	916		86.3	83		64.3
929		30.9	994		16.2	99		10.7
293		27	215		20.2	22		17.1
Median	IQR		Median	IQR		Median	IQR	
50.6	44.6	56.8	45.7	37.7	52.9	40.7	32.3	49.3
43.2	37.6	49.5	40.4	33.6	48.9	40.9	32.3	49.9
610	460	800	615	462	790	560	405	722
642	480	830	590	431	770	460	334	720
0.70	0.50	0.98	0.70	0.50	1.00	0.51	0.35	0.77
0.80	0.55	1.11	0.70	0.48	1.00	0.55	0.34	0.80

Year of starting cART	1995–2001	
	n	%
HIV RNA <50 copies/ml		
MSM	2,338	93.4
Heterosexual	1,049	88.0
IDU	146	86.4
Ever AIDS diagnosis		
MSM	910	36.3
Heterosexual	417	35.0
IDU	86	50.9

	Median	IQR	
Last CD4 cell count (cells/mm^3)			
MSM	660	500	860
Heterosexual	672	490	900
IDU	560	340	810
Last CD4/CD8 ratio			
MSM	0.71	0.50	1.00
Heterosexual	0.81	0.55	1.19
IDU	0.70	0.40	0.96

Legend: *W Europe=Western Europe; N America=North America; S America=South America; MSM=men who have sex with men; IDU=injecting drug user.*

	2002–2007			2008–2013			2014		
	n	%		n	%		n	%	
	1,932	92.7		4,574	92.8		522	68.1	
	1,432	87.0		1,626	86.6		164	66.9	
	65	81.3		60	85.7		2	100.0	
	554	26.6		635	12.9		51	6.7	
	518	31.5		434	23.1		55	22.4	
	29	36.3		23	32.9				
	Median	IQR		Median	IQR		Median	IQR	
	630	490	810	630	490	810	580	440	748
	610	450	800	560	410	736	449	280	648
	540	380	730	451	316	730	827	374	1280
	0.72	0.51	1.00	0.72	0.51	1.00	0.55	0.38	0.79
	0.78	0.5	1.05	0.71	0.43	0.99	0.49	0.3	0.73
	0.60	0.41	0.90	0.53	0.39	0.81			

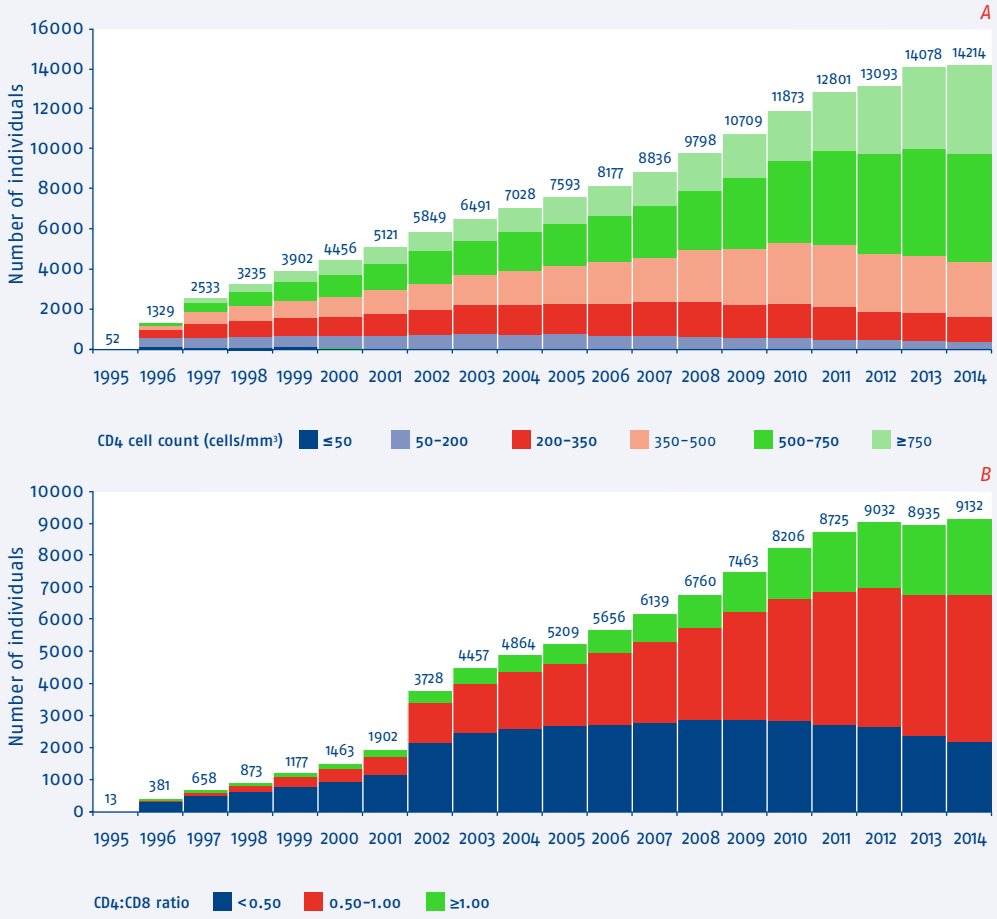
Appendix Table 2.4: *Most frequently-used initial combination antiretroviral therapy (cART) regimens in 2009-2014. Combinations are shown only if used by at least 10 individuals in at least one calendar year.*

	2009		2010	
	n	%	n	%
Number of individuals initiating cART	1,333	100.0	1,371	100.0
TDF/FTC/EVG/c				
TDF/FTC/EFV	740	55.5	744	54.3
TDF/FTC/RPV	4	0.3		
TDF/FTC/DRV/r	19	1.4	120	8.8
TDF/FTC/ATV/r	100	7.5	122	8.9
TDF/FTC/RAL	28	2.1	14	1
TDF/FTC/NVP	138	10.4	139	10.1
TDF/FTC/DTG				
ABC/3TC/DTG				
AZT/3TC/LOP/r	54	4.1	45	3.3
ABC/3TC/DRV/r			3	0.2
ABC/3TC/NVP	5	0.4	9	0.7
AZT/3TC/NVP	19	1.4	25	1.8
TDF/FTC/EFV/DRV/r				
TDF/FTC/LOP/r	73	5.5	30	2.2
ABC/3TC/EFV	11	0.8	6	0.4
TDF/FTC/EFV/RAL	4	0.3	15	1.1
AZT/3TC/EFV	12	0.9	8	0.6
TDF/FTC/EFV/LOP/r	43	3.2	24	1.8
Other	83	6.2	67	4.8

Legend: *cART=combination antiretroviral therapy; TDF=tenofovir; FTC=emtricitabine; EFV=efavirenz; DRV/r=ritonavir-boosted darunavir; RPV=rilpivirine; NVP=nevirapine; ATV/r=ritonavir-boosted atazanavir; RAL=raltegravir; 3TC=lamivudine; LOP/r=ritonavir boosted lopinavir; ABC=abacavir; EVG/c=cobicistat-boosted elvitegravir; DTG=dolutegravir; AZT=zidovudine.*

2011		2012		2013		2014	
n	%	n	%	n	%	n	%
1,235	100.0	1,257	100.0	1,428	100.0	1,063	100.0
				37	2.8	395	40.2
587	47.5	438	34.8	412	28.9	175	16.5
		142	11.3	290	20.3	144	13.5
182	14.7	190	15.1	263	18.4	129	12.1
136	11	117	9.3	102	7.1	33	3.1
32	2.6	28	2.2	42	2.9	31	2.9
119	9.6	170	13.5	130	9.1	27	2.5
						17	1.6
3	0.2			1	0.1	17	1.6
38	3.1	33	2.6	25	1.8	12	1.1
9	0.7	7	0.6	10	0.7	7	0.7
8	0.6	9	0.7	13	0.9	5	0.5
11	0.9	15	1.2	10	0.7	4	0.4
4	0.3	13	1	7	0.5	4	0.4
18	1.5	15	1.2	18	1.3	3	0.3
4	0.3	7	0.6	6	0.4		
10	0.8	5	0.4	5	0.4		
3	0.2	1	0.1	4	0.3		
19	1.5	3	0.2				
52	4.5	64	5.2	53	3.4	60	2.6

Appendix Figure 2.1: *Last available CD4 cell count (cells/mm³) (A) and CD4:CD8 ratio (B) in each calendar year after the start of combination antiretroviral therapy (cART). The absolute number of individuals with a last available CD4 cell count in each year and after the start of cART was selected for each patient. The absolute number of individuals in each CD4 cell count and CD4:CD8 ratio category is shown. CD4:CD8 ratios are not available for all centres.*



Appendix Table 3.1: *Number of patients with evidence of various levels of resistance to specific antiretroviral drugs, according to the Stanford algorithm for scoring mutations. All together, as of May 2015, out of 18,355 patients still in follow up, 2,070 (11%) with at least one major resistance-associated mutation from the July 2014 International Antiviral Society-USA (IAS-USA) list were included.*

	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	n	%	n	%	n	%	n	%	n	%
Protease inhibitors (PIs)[a]										
FPV	1,512	74	118	6	96	5	119	6	211	10
IDV	1,512	74	105	5	30	1	135	7	274	13
NFV	1,259	61	171	8	123	6	37	2	466	23
SQV	1,619	79	9	0	47	2	125	6	256	12
LPV	1,542	75	91	4	106	5	101	5	216	11
ATV	1,518	74	98	5	85	4	79	4	276	13
TPV	1,648	80	88	4	119	6	135	7	66	3
DRV	1,879	91	14	1	121	6	34	2	8	0
Any PI	1,231	60	173	8	143	7	34	2	475	23
Nucleoside RT inhibitors (NRTIs)										
ABC	545	26	144	7	524	25	308	15	549	27
AZT	1,088	53	36	2	191	9	187	9	568	27
d4T	970	47	44	2	201	10	288	14	567	27
ddI	520	25	518	25	206	10	264	13	562	27
TDF	1,063	51	149	7	228	11	245	12	385	19
Any NRTI	498	24	31	1	573	28	198	10	770	37
3TC/FTC	782	38	55	3	65	3	70	3	1,098	53
Non-nucleoside RT inhibitors (NNRTIs)										
EFV	964	47	124	6	35	2	202	10	745	36
NVP	964	47	55	3	46	2	62	3	943	46
ETR	1,114	54	329	16	161	8	384	19	82	4
RPV	1,114	54	58	3	351	17	347	17	200	10
Any NNRTI	781	38	31	1	239	12	74	4	945	46

[a] *Protease not available for 14 patients.*

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

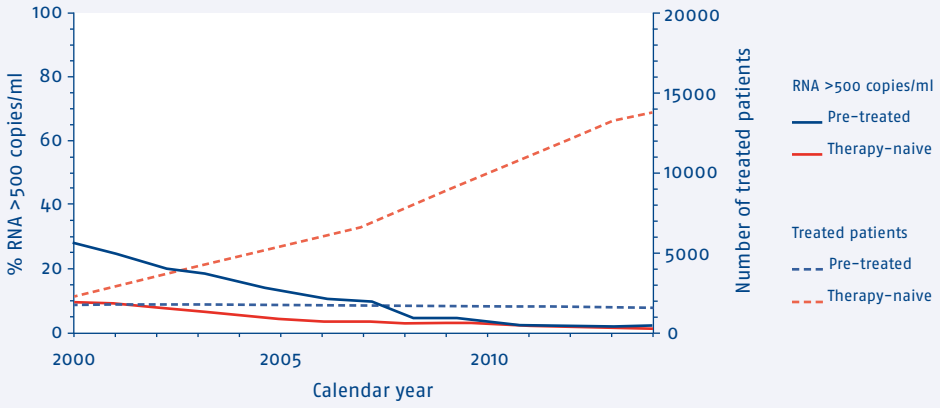
Appendix Table 3.2: *Number of patients with evidence of various levels of resistance to specific antiretroviral drugs, according to the Stanford algorithm for scoring mutations. All together, as of May 2015, out of 18,355 patients still in follow up, 7,400 (40%) with at least one genotypic sequence were included. Note that due to small differences in resistance-associated mutations between the Stanford algorithm and the International Antiviral Society-USA (IAS-USA) list, the number of patients with resistance may be different from those reported in Appendix Table 3.1.*

	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	n	%	n	%	n	%	n	%	n	%
Protease inhibitors (PIs)[a]										
FPV	6,690	92	163	2	96	1	119	2	211	3
IDV	6,710	92	128	2	32	0	135	2	274	4
NFV	5,922	81	647	9	202	3	42	1	466	6
SQV	6,838	94	9	0	51	1	125	2	256	4
LPV	6,763	93	92	1	107	1	101	1	216	3
ATV	6,732	92	103	1	89	1	79	1	276	4
TPV	6,847	94	109	1	122	2	135	2	66	1
DRV	7,102	98	14	0	121	2	34	0	8	0
Any PI	5,875	81	668	9	222	3	39	1	475	7
Nucleoside reverse transcriptase inhibitors (NRTIs)[b]										
ABC	5,721	77	289	4	524	7	309	4	549	7
AZT	6,263	85	41	1	332	4	188	3	568	8
d4T	6,130	83	63	1	342	5	290	4	567	8
ddI	5,638	76	715	10	208	3	269	4	562	8
TDF	6,380	86	154	2	228	3	245	3	385	5
Any NRTI	5,612	76	92	1	714	10	204	3	770	10
3TC/FTC	6,099	83	60	1	65	1	70	1	1098	15
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)[b]										
EFV	6,164	83	238	3	38	1	206	3	746	10
NVP	6,164	83	153	2	47	1	82	1	946	13
ETR	6,322	86	442	6	161	2	385	5	82	1
RPV	6,322	86	155	2	367	5	348	5	200	3
Any NNRTI	5,981	81	129	2	240	3	94	1	948	13

[a]Protease not available for 121 patients; [b]RT not available for 8 patients.

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

Appendix Figure 3.1: *Annual number of treated patients with a viral-load measurement while on treatment (dashed lines) and the proportion of patients with virological failure (solid lines) (i.e., a viral load above 500 copies/ml while on treatment and measured at least four months after start of cART or four months after resuming treatment following a treatment interruption). Among approximately 1,700 pre-treated patients, the proportion with failure with a threshold of 500 copies/ml decreased from 28% in 2000 to 2% in 2014. Among previously therapy-naive patients, failure was less common and decreased from 10% to 1% during the same period, while the number of therapy-naive patients increased from 2,365 to 13,730.*



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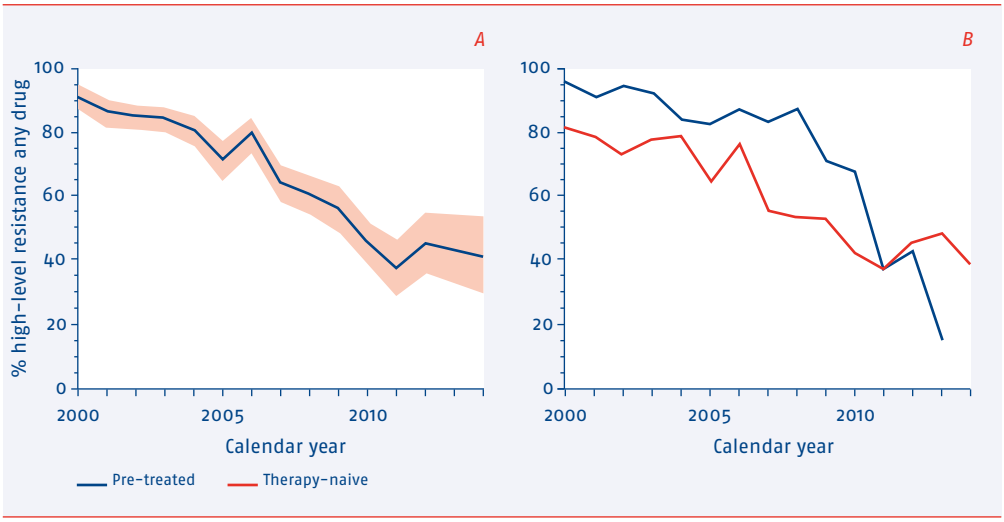
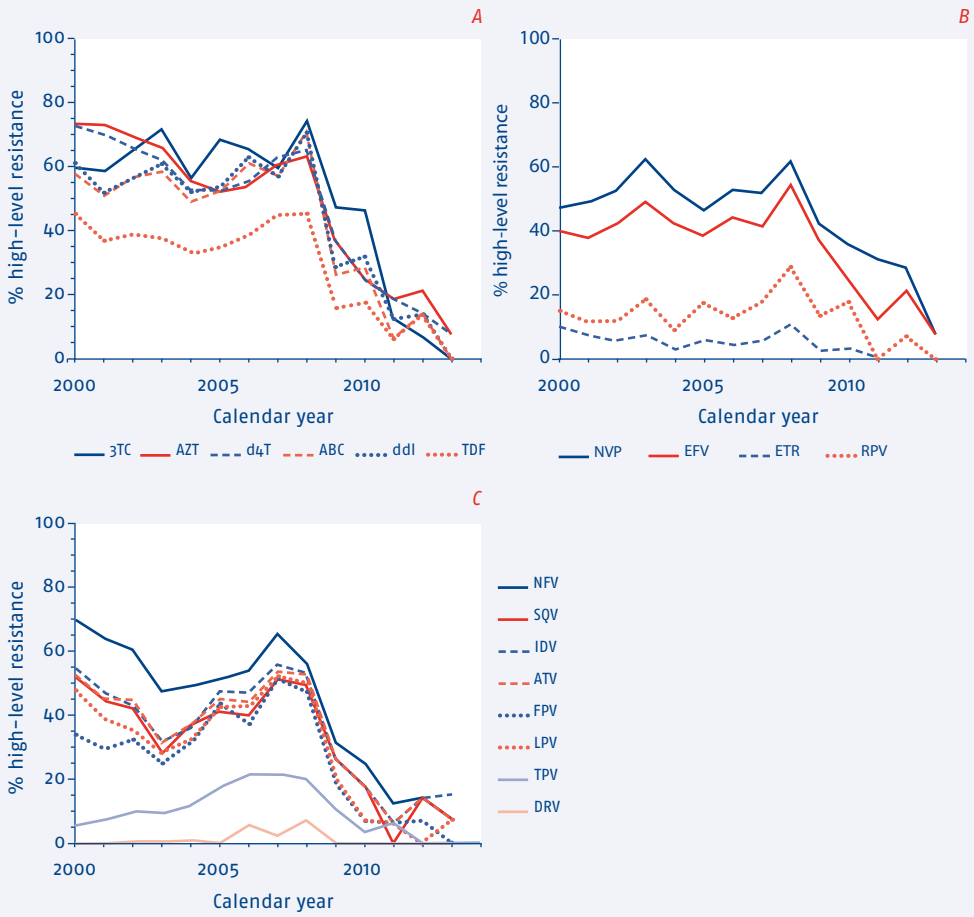
Appendix Figure 3.2: *(A) The proportion of sequences obtained at the time of virological failure with evidence of high-level resistance to any antiretroviral drug decreased from 91% in 2000 to 41% in 2014. The shaded area is the 95% confidence interval. (B) Resistance to any antiretroviral drug was found more often in patients pre-treated with monotherapy or dual therapy before commencing combination antiretroviral therapy (cART). The number of sequences in 2014 in pre-treated patients was too low to give meaningful proportions.*

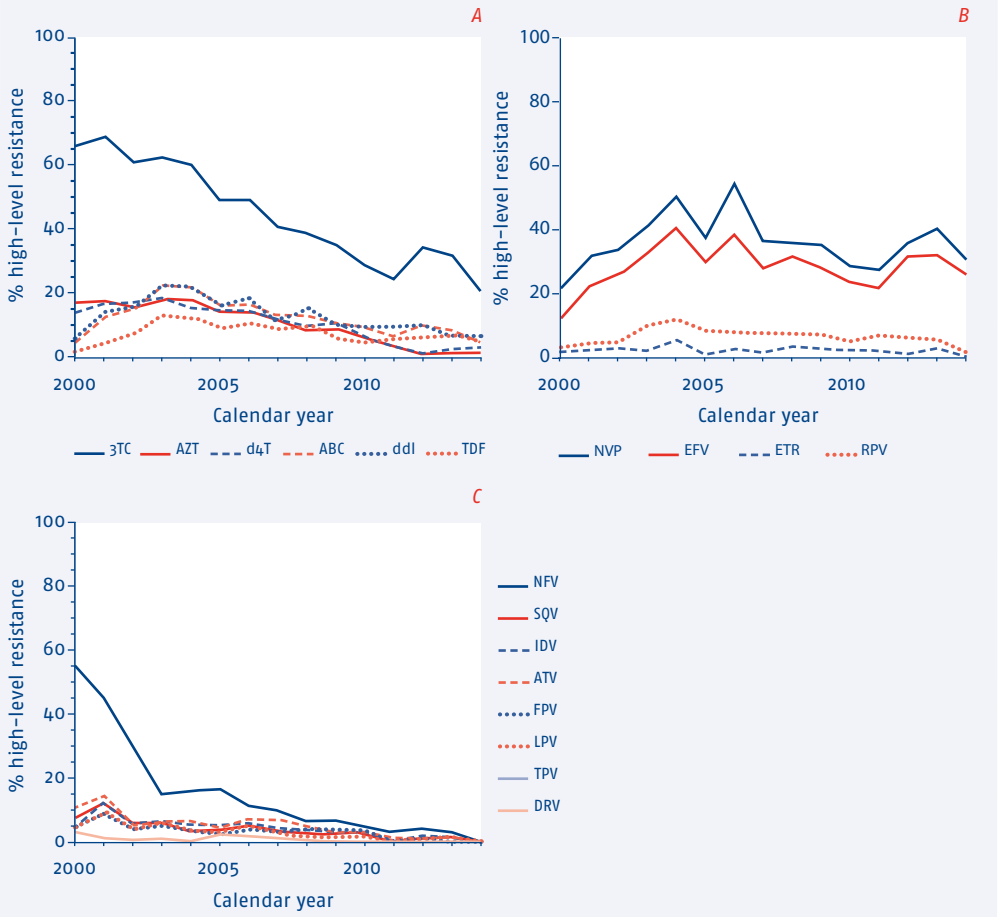


Appendix Figure 3.3: *Annual proportion of available sequences from treated patients with evidence of high-level resistance, according to the Stanford mutation interpretation algorithm, in patients who previously received treatment regimens not considered combination antiretroviral treatment (cART). Resistance to individual drugs from the three original drug classes is shown, including (A) nucleoside reverse transcriptase inhibitors and lamivudine/emtricitabine, (B) non-nucleoside reverse transcriptase inhibitors, and (C) protease inhibitors. The number of sequences in 2014 was too low to give meaningful proportions.*



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

Appendix Figure 3.4: *Annual proportion of available sequences from treated patients with evidence of high-level resistance, according to the Stanford mutation interpretation algorithm, in previously therapy-naive patients who started with combination antiretroviral treatment (cART) as their first treatment regimen. Resistance to individual drugs from the four original drug classes is shown, including (A) nucleoside reverse transcriptase inhibitors and lamivudine/emtricitabine, (B) non-nucleoside reverse transcriptase inhibitors, and (C) protease inhibitors.*



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

Appendix Table 4.1: Annual number of cases of death and first AIDS events among 22,883 HIV-1-infected patients in the Netherlands recorded up to May 2015. (Note: data collection for 2013, 2014, and 2015 had not yet been finalised at the time of writing.)

	AIDS			Death	
Year	Total	≥6 weeks after diagnosis	≥4 weeks after start of cART	Total	After start of cART
≤1995	769	489	1	34	-
1996	363	291	89	48	31
1997	306	185	117	87	68
1998	241	134	110	84	72
1999	234	133	111	89	87
2000	245	114	91	83	79
2001	262	150	100	82	79
2002	298	149	109	118	81
2003	294	144	111	141	121
2004	281	174	113	145	131
2005	354	199	134	140	123
2006	282	165	115	121	104
2007	294	171	116	148	126
2008	274	166	128	149	134
2009	269	147	106	159	145
2010	285	148	123	129	122
2011	224	134	99	148	140
2012	253	149	127	153	147
2013	219	115	97	145	140
2014	156	77	65	135	129
2015	13	1	2	16	16
Total	5,916	3,435	2,064	2,354	2,075

Legend: cART=combination antiretroviral therapy.

Appendix Table 4.2: Absolute number of causes of death among HIV-1-infected patients during the periods 1996-2001, 2002-2006, and 2007-2014.

Causes of death	1996-2001 total	2002-2006 total	2007-2014 total
All AIDS-defining causes	212	205	259
Infection	67	102	179
Malignancy	66	63	70
Not specified	79	40	10
Non-AIDS-defining malignancy	35	90	200
All cardiovascular diseases	14	29	28
Myocardial infarction	11	18	10
Stroke	3	10	9
Other ischaemic heart disease	0	1	7
Other cardiovascular diseases	0	8	2
Non-AIDS-defining infection	10	28	22
Liver failure, cirrhosis and hepatitis B or C infection at death	11	23	67
Lung-related	4	9	24
Non-natural death	26	30	21
Accident or violent death	8	11	14
Suicide	10	15	7
Euthanasia	8	4	0
Substance abuse	11	10	34
Other causes	28	46	120
Unknown	67	100	185
Total	418	570	960

Appendix Table 4.3: Adjusted risk factors for death and AIDS among HIV-1-infected patients.

	Death			Aids		
	IRR	95%CI	p-value	IRR	95%CI	p-value
Male gender	1.32	1.13-1.54	0.0004	1.29	1.17-1.43	<0.0001
Region of birth			<0.001			0.16
Region of birth	1			1		
The Netherlands	0.76	0.68-0.87		1.07	1.00-1.16	
HIV-1 transmission route			<0.0001			<0.0001
Homosexual	1			1		
Heterosexual	2.09	1.71-2.53		0.92	0.77-1.11	
IDU	1.01	0.87-1.16		1.58	1.46-1.73	
Blood contact	1.45	1.23-1.70		1.84	1.64-2.03	

	Death			Aids		
	IRR	95%CI	p-value	IRR	95%CI	p-value
Age*			<0.0001			<0.0001
Under 35 years	0.63	0.51-0.77		0.67	0.62-0.73	
35-45 years	1			1		
45-55 years	1.82	1.60-2.05		1.46	1.34-1.60	
55-65 years	3.03	2.64-3.49		1.68	1.51-1.82	
65-75 years	5.41	4.48- 6.55		1.73	1.42-2.12	
Over 75 years	10.0	7.31-13.7		2.39	1.43-3.97	
CD4 cell count**			<0.0001			<0.0001
< 50 cells/mm^3	7.89	6.62-9.39		14.88	12.4-18.0	
50-200 cells/mm^3	2.56	2.22-2.94		4.10	3.53-4.71	
200-350 cells/mm^3	1			1		
350-500 cells/mm^3	0.50	0.41-0.55		0.50	0.43-0.57	
500-750 cells/mm^3	0.34	0.29-0.40		0.48	0.42-0.56	
> 750 cells/mm^3	0.34	0.28-0.41		0.20	0.16-0.26	
Per year longer with HIV RNA load>1000 copies/ml	1.05	1.04-1.07	<0.0001	1.04	1.02-1.06	<0.0001
Treatment status			0.001			<0.0001
Not (yet) started cART	0.91	0.77-1.06		4.53	4.14-4.95	
Treatment-experienced at start cART	1.24	1.09-1.39		1.12	0.94-1.32	
Treatment-naive at start	1			1		
Prior AIDS event	2.08	1.88-2.32	<0.0001			
HBV co-infection	1.46	1.26-1.70	<0.0001	1.05	0.89-1.27	0.52
HCV co-infection	1.04	0.86-1.25	0.67	0.84	0.70-1.00	0.05
Body mass index*						
Less than 18 kg/m^2	3.03	2.61-3.56	<0.0001			
Between 18 and 25 kg/m^2	1					
Between 25 and 30 kg/m^2	0.63	0.54-0.72				
More than 30 kg/m^2	0.67	0.48-0.79				
Smoking status			<0.0001			<0.0001
Never	1			1		
Current smoker	1.48	1.22-1.77		0.77	0.69-0.87	
Past smoker	1.16	0.93-1.43		1.38	1.21-1.55	
Unknown	2.10	1.75-2.51		1.14	1.03-1.27	

** Time-updated*

*** Time-updated and lagged by three months*

p-values are overall p-values

Legend: *IRR= incidence rate ratio; IDU= injecting drug use; cART=combination antiretroviral therapy; HBV=hepatitis B; HCV=hepatitis C, CI=confidence interval; BMI: <18 kg/m^2=underweight; 18-25 kg/m^2= normal; 25-30 kg/m^2=overweight; >30 kg/m^2=severely overweight.*

Appendix Table 4.4: *Lost to follow up (no follow up after 31 December 2013) by region of origin and time-updated CD4 cell count.*

	Total				Netherlands				Western Europe / North America			
Last CD4	**n**	**PY**	**Inc**	**95% CI**	**n**	**PY**	**Inc**	**95% CI**	**n**	**PY**	**Inc**	**95% CI**
<50	72	1,427	50.5	39.5-63.6	6	572	10.5	3.9-22.8	14	123	113.4	62.0-190.3
50-200	243	9,796	24.8	21.8-28.1	24	4,971	4.8	3.1-7.2	42	892	47.1	33.9-63.6
200-350	444	25,934	17.1	15.6-18.8	70	14,459	4.8	3.8-6.1	82	2,340	35.0	27.9-43.5
350-500	565	40,301	14.0	12.9-15.2	94	23,566	4.0	3.2-4.9	127	3,685	34.5	28.7-41.0
500-750	604	54,423	11.1	10.2-12.0	153	33,210	4.6	3.9-5.4	157	4,990	31.5	26.7-36.8
≥750	354	33,691	10.5	9.4-11.7	87	21,644	4.0	3.2-5.0	107	3,468	30.9	25.3-37.3

Legend: *n=number; PY=person years of follow up; Inc=incidence; CI=confidence interval.*

Caribbean / South America				South-East Asia				Sub-Saharan Africa			
n	PY	Inc	95% CI	n	PY	Inc	95% CI	n	PY	Inc	95% CI
9	290	31.0	14.2–58.9	7	78	89.4	35.9–184.1	34	310	109.5	75.8–153.0
30	1,280	23.4	15.8–33.5	9	352	25.6	11.7–48.5	127	2,049	62.0	51.7–73.8
58	2,938	19.7	15.0–25.5	14	945	14.8	8.1–24.9	209	4,609	45.3	39.4–51.9
82	4,634	17.7	14.1–22.0	24	1,406	17.1	10.9–25.4	216	6,012	35.9	31.3–41.1
93	5,911	15.7	12.7–19.3	13	1,809	7.2	3.8–12.3	164	7,130	23.0	19.6–26.8
55	3,528	15.6	11.7–20.3	6	867	6.9	2.5–15.1	87	3,370	25.8	20.7–31.8

Appendix Table 4.5: *Absolute number of AIDS events among HIV-1-infected patients during the periods 1996-2001, 2002-2006, and 2007-2014.*

CDC event	1996-2001	2002-2006	2007-2014	Total	% total events
AIDS dementia complex / HIV encephalopathy	52	52	77	181	(3.35)
CMV disease	33	34	49	116	(2.15)
CMV retinitis	30	18	18	66	(1.22)
Candidiasis oesophageal	287	230	366	883	(16.35)
Candidiasis trachea, bronchi, lungs	8	14	11	33	(0.61)
Cervical cancer, invasive	8	4	10	22	(0.41)
Cryptococcosis extrapulmonary	26	33	34	93	(1.72)
Cryptosporidiosis, chronic intestinal (> 1 month)	23	16	12	51	(0.94)
Herpes simplex virus	37	49	69	155	(2.87)
Isosporiasis, chronic intestinal (> 1 month)	6	7	4	17	(0.31)
Kaposi's sarcoma	179	173	257	609	(11.28)
Leishmaniasis, visceral	0	2	4	6	(0.11)
Lymphoma, primary, CNS	7	3	8	18	(0.33)
MAI/M. kansasii, disseminated or extrapulmonary	33	13	32	78	(1.44)
Microsporidiosis, chronic intestinal (> 1 month)	11	1	3	15	(0.28)
Mycobacterium, other species/unidentified extrapulmonary	23	9	11	43	(0.80)
Mycobacterium, other species/unidentified pulmonary	0	2	7	9	(0.17)
Non-Hodgkin's lymphoma	71	92	134	297	(5.50)
Other CDC C-event, specify	5	4	0	9	(0.17)
Penicilliosis	0	0	2	2	(0.04)
Pneumocystis carinii pneumonia	381	297	469	1,147	(21.24)
Pneumocystis, extrapulmonary	1	1	3	5	(0.09)
Pneumonia, recurrent	58	61	100	219	(4.06)
Progressive multifocal leucoencephalopathy	22	23	49	94	(1.74)
Salmonella septicaemia, recurrent	3	0	0	3	(0.06)
Toxoplasmosis of the brain	78	105	70	253	(4.69)
Tuberculosis, extrapulmonary	92	112	89	293	(5.43)
Tuberculosis, pulmonary	136	156	121	413	(7.65)
Wasting syndrome due to HIV	53	58	121	232	(4.30)
Total	1,673	1,584	2,143	5,400	(100%)

Legend: *CDC=Centers for Disease Control and Prevention; CNS=central nervous system; CMV=cytomegalovirus; MAI=mycobacterium avium intracellulare complex.*

Appendix Table 4.6.A: Incidence of diabetes mellitus from June 2000 onwards according to gender and age.

	Men				Women			
Age	n	PY	Inc/1000PY	95% CI	n	PY	Inc/1000PY	95% CI
18-35	34	22,715	1.5	1.0-2.1	41	11,314	3.6	2.6-4.9
35-45	157	46,631	3.4	2.9-3.9	87	12,662	6.9	5.5-8.5
45-55	246	41,102	6.0	5.3-6.8	48	6,429	7.5	5.5-9.9
55-65	169	17,110	9.9	8.4-11.5	17	2,008	8.5	4.9-13.6
≥65	78	4,390	17.8	14.0-22.2	11	640	17.2	8.6-30.7
Total	684	131,948	5.2	4.8-5.6	204	33,053	6.2	5.4-7.1

Legend: PY=person years of follow up; CI=confidence interval; Inc=incidence.

Appendix Table 4.6.B: Incidence of cardiovascular disease (myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy) from June 2000 onwards according to gender and age.

	Men				Women			
Age	n	PY	Inc/1000PY	95% CI	n	PY	Inc/1000PY	95% CI
18-35	15	22,915	0.7	0.4-1.1	11	11,561	1.0	0.5-1.7
35-45	118	47,363	2.5	2.1-3.0	29	13,043	2.2	1.5-3.2
45-55	260	42,091	6.2	5.4-7.0	24	6,806	3.5	2.3-5.2
55-65	226	17,455	12.9	11.3-14.8	13	2,163	6.0	3.2-10.3
≥65	100	4,446	22.5	18.3-27.4	9	691	13.0	6.0-24.7
Total	719	134,270	5.4	5.0-5.8	86	34,264	2.5	2.0-3.1

Legend: PY=person years of follow up; CI=confidence interval; Inc=incidence.

Appendix Table 4.6.C: Incidence of chronic kidney disease (an estimated glomerular filtration rate below 60 ml/min, estimated with the Cockcroft-Gault equation, and confirmed after 3 months or more) from June 2007 onwards, according to gender and age.

	Men				Women			
Age	n	PY	Inc/1000PY	95% CI	n	PY	Inc/1000PY	95% CI
18-35	11	13,298	0.8	0.4-1.5	3	5,691	0.5	0.1-1.5
35-45	61	26,526	2.3	1.8-3.0	27	7,972	3.4	2.2-4.9
45-55	132	29,658	4.5	3.7-5.3	70	4,787	14.6	11.4-18.5
55-65	196	12,944	15.1	13.1-17.4	57	1,415	40.3	30.5-52.2
≥65	208	3,213	64.7	56.2-74.2	38	309	123.0	87.0-168.8
Total	606	85,087	7.1	6.6-7.7	195	20,174	9.7	8.4-11.1

Legend: PY=person years of follow up; CI=confidence interval; Inc=incidence.

Appendix Table 4.6.D: Incidence of non-AIDS malignancy (including Castleman's disease, but excluding precancerous stages of anal and cervical cancer, basal-cell carcinoma, and squamous-cell carcinoma of the skin) from June 2000 onwards, according to gender and age.

	Men				Women			
Age	n	PY	Inc/1000PY	95% CI	n	PY	Inc/1000PY	95% CI
18-35	35	22,847	1.5	1.1-2.1	10	11,551	0.9	0.4-1.6
35-45	163	47,258	3.4	2.9-4.0	32	13,081	2.4	1.7-3.5
45-55	270	42,377	6.4	5.6-7.2	41	6,814	6.0	4.3-8.2
55-65	220	18,231	12.1	10.5-13.8	20	2,136	9.4	5.7-14.5
≥65	108	4,743	22.8	18.7-27.5	8	723	11.1	4.8-21.8
Total	796	135,457	5.9	5.5-6.3	111	34,305	3.2	2.7-3.9

Legend: PY=person years of follow up; CI=confidence interval; Inc=incidence.

Appendix Table 4.6.E: Incidence of non-AIDS disease (first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS malignancy) from June 2000 onwards, according to gender and age.

	Men				Women			
Age	n	PY	Inc/1000PY	95% CI	n	PY	Inc/1000PY	95% CI
18-35	82	22,669	3.6	2.9-4.5	59	11,306	5.2	4.0-6.7
35-45	407	45,854	8.9	8.0-9.8	140	12,491	11.2	9.4-13.2
45-55	679	39,197	17.3	16.0-18.7	99	6,215	15.9	12.9-19.4
55-65	486	15,393	31.6	28.8-34.5	42	1,911	22.0	15.8-29.7
≥65	193	3,487	55.3	47.8-63.7	23	559	41.2	26.1-61.8
Total	1847	126,600	14.6	13.9-15.3	363	32,482	11.2	10.1-12.4

Legend: PY=person years of follow up; CI=confidence interval; Inc=incidence.

Appendix Table 4.7: Adjusted risk factors for non-AIDS morbidity.

	Non-AIDS defining disease				Cardiovascular disease			
	OR		95% CI	p-value	OR		95% CI	p-value
Female gender	0.83	0.72	0.97	0.01	0.64	0.49	0.83	0.00
Region of birth								
The Netherlands	1.00				1.00			
Other	1.09	0.97	1.22	0.15	0.81	0.66	1.00	0.05
HIV-1 transmission route				*0.006*				*0.02*
Homosexual contact	1.00				1.00			
Heterosexual contact	1.16	0.90	1.49	0.27	1.21	0.80	1.84	0.37
IDU	1.19	1.05	1.36	0.01	1.34	1.09	1.64	0.01
Age*				*<0.001*				*<0.001*
Under 35 years	0.47	0.38	0.57	0.00	0.34	0.22	0.54	0.00
35-45 years	1.00				1.00			
45-55 years	1.75	1.55	1.97	0.00	2.28	1.83	2.84	0.00
55 to 65 years	2.93	2.55	3.35	0.00	4.27	3.38	5.40	0.00
65 to 75 years	5.19	4.34	6.21	0.00	7.39	5.55	9.86	0.00
CD4 cell count**				*<0.001*				*0.009*
Less than 50 cells/mm^3	2.94	2.17	3.99	0.00	2.98	1.67	5.33	0.00
50 to 200 cells/mm^3	1.13	0.92	1.39	0.23	1.35	0.97	1.89	0.08
200 to 350 cells/mm^3	1.00				1.00			
350 to 500 cells/mm^3	0.83	0.71	0.96	0.01	1.00	0.78	1.29	0.98
500 to 750 cells/mm^3	0.78	0.67	0.90	0.00	0.86	0.67	1.11	0.25
More than 750 cells/mm^3	0.93	0.79	1.08	0.34	1.05	0.81	1.37	0.72
Per year longer with <200 CD4 cells/mm^3	1.01	0.98	1.04	0.68	0.99	0.95	1.04	0.74
Per year longer HIV RNA load>1000 copies/ml	1.00	0.98	1.02	0.93	1.00	0.97	1.04	0.78
Treatment status				*<0.001*				*0.02*
Not (yet) started on cART	1.08	0.91	1.28	0.40	1.00	0.73	1.36	0.99
Treatment-experienced at start cART	1.46	1.29	1.65	0.00	1.28	1.05	1.56	0.01
Treatment-naive at start cART	1.00				1.00			
Per year longer on cART	1.00	0.99	1.00	0.22	0.99	0.98	1.00	0.00
Per year longer on LOP/r					1.00	0.97	1.02	0.80
Per year longer on IDV					1.01	0.98	1.05	0.46
Recent use of ABC***					1.67	1.40	2.00	0.00
Per year longer on AZT								
Per year longer on d4T								

Non-AIDS malignancy				Diabetes mellitus				CKD			
OR		95% CI	p-value	OR		95% CI	p-value	OR		95% CI	p-value
1.01	0.78	1.30	0.97	0.77	0.63	0.94	0.01	2.21	1.80	2.73	0.00
1.00				1.00				1.00			
0.66	0.54	0.82	0.00	1.64	1.39	1.94	0.00	1.37	1.14	1.64	0.00
			0.38				*<0.001*				*0.002*
1.00				1.00				1.00			
0.87	0.58	1.29	0.48	1.75	1.16	2.65	0.01	2.23	1.57	3.18	0.00
0.86	0.69	1.07	0.17	1.47	1.21	1.78	0.00	1.25	1.02	1.53	0.04
			<0.001				*<0.001*				*<0.001*
0.49	0.34	0.70	0.00	0.54	0.41	0.71	0.00	0.23	0.13	0.40	0.00
1.00				1.00				1.00			
1.76	1.43	2.15	0.00	1.45	1.21	1.75	0.00	2.36	1.83	3.06	0.00
3.19	2.55	3.98	0.00	2.06	1.66	2.56	0.00	7.72	5.97	9.97	0.00
6.15	4.70	8.06	0.00	3.71	2.82	4.87	0.00	32.91	25.13	43.09	0.00
			<0.001				*<0.001*				*<0.001*
1.97	1.13	3.44	0.02	5.83	3.95	8.59	0.00	3.29	1.97	5.52	0.00
1.11	0.82	1.50	0.51	1.36	0.99	1.88	0.06	1.33	0.97	1.84	0.08
1.00				1.00				1.00			
0.75	0.60	0.93	0.01	0.80	0.62	1.01	0.07	0.94	0.74	1.20	0.64
0.63	0.50	0.79	0.00	0.88	0.70	1.10	0.27	0.82	0.65	1.04	0.10
0.70	0.55	0.90	0.00	1.00	0.78	1.28	1.00	0.80	0.62	1.04	0.09
1.03	0.99	1.07	0.16	0.98	0.93	1.02	0.35	0.98	0.94	1.02	0.32
1.01	0.98	1.04	0.50	0.99	0.96	1.02	0.43	0.98	0.95	1.01	0.16
			0.03				*0.004*				*0.29*
1.19	0.93	1.51	0.16	1.57	1.25	1.96	0.00	1.28	0.94	1.76	0.12
1.23	1.01	1.49	0.04	1.16	0.94	1.44	0.16	1.20	0.99	1.46	0.06
1.00				1.00				1.00			
1.00	0.99	1.01	0.52	0.99	0.98	1.00	0.03	1.00	0.99	1.00	0.39
				1.04	1.02	1.07	0.00				
				1.11	1.07	1.15	0.00				

	Non-AIDS defining disease				Cardiovascular disease			
	OR	95% CI		p-value	OR	95% CI		p-value
Per year longer on ddI								
Per year longer on TDF								
Body mass index*				*<0.001*				*0.20*
Less than 18 kg/m²	1.59	1.25	2.02	0.00	1.25	0.82	1.90	0.30
Between 18 and 25 kg/m²	1.00				1.00			
Between 25 and 30 kg/m²	1.11	0.99	1.24	0.07	0.87	0.73	1.04	0.14
More than 30 kg/m²	1.71	1.47	2.00	0.00	0.99	0.73	1.32	0.92
Prior cardiovascular event								
Prior diabetes								
Prior AIDS event	1.40	1.26	1.55	0.00	1.20	1.02	1.42	0.03
Hepatitis B virus positive	1.16	0.97	1.37	0.10	0.97	0.71	1.31	0.84
Hepatitis C virus positive	1.09	0.89	1.33	0.41	0.93	0.66	1.31	0.68
Hypertension	1.76	1.57	1.98	0.00	1.98	1.66	2.37	0.00
Smoking status				*<0.001*				*<0.001*
Never	1.00				1.00			
Current smoker	1.38	1.20	1.60	0.00	1.98	1.53	2.57	0.00
Past smoker	1.17	0.99	1.40	0.07	1.31	0.95	1.81	0.10
Unknown	0.99	0.85	1.15	0.90	1.00	0.74	1.36	0.99
Calendar year period				*<0.001*				*<0.001*
2000–2005	0.80	0.70	0.92	0.00	1.09	0.86	1.39	0.47
2006–2010	1.16	1.05	1.29	0.00	1.17	0.98	1.41	0.08
2011–2014	1.00				1.00			

** Time-updated.*

*** Time-updated and lagged by 3 months.*

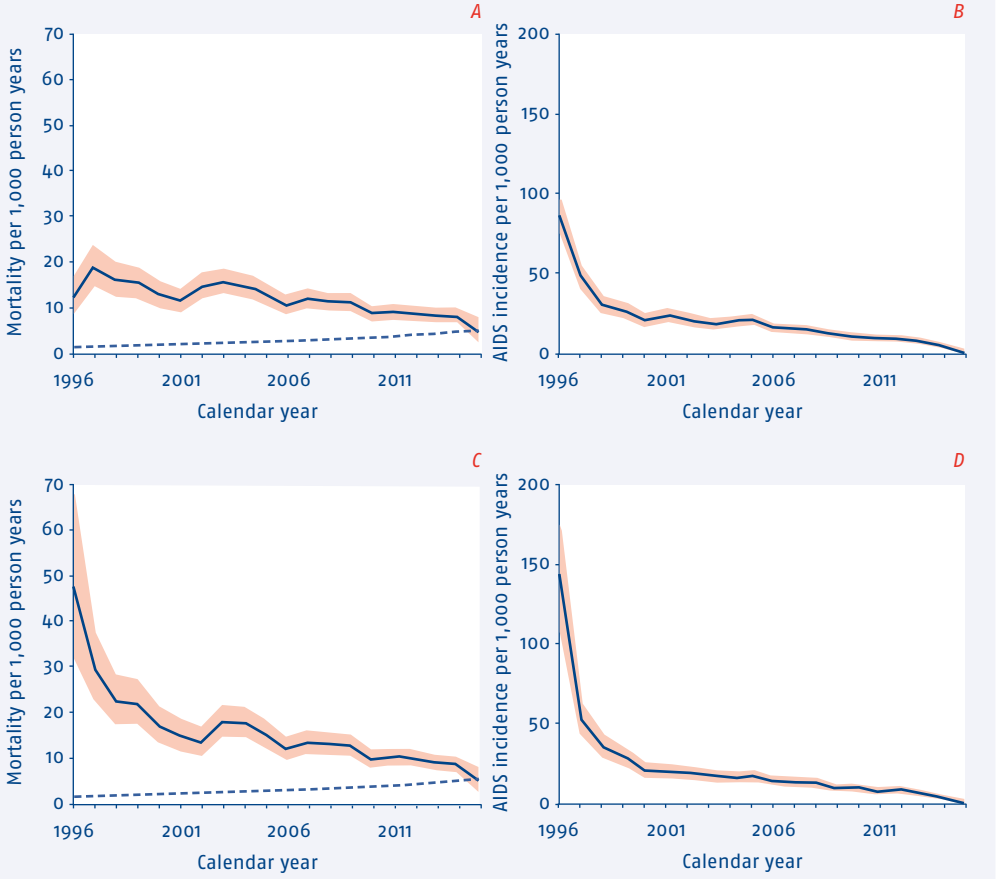
**** Current use or recently used in the past 6 months.*

P-values in italic are overall p-values.

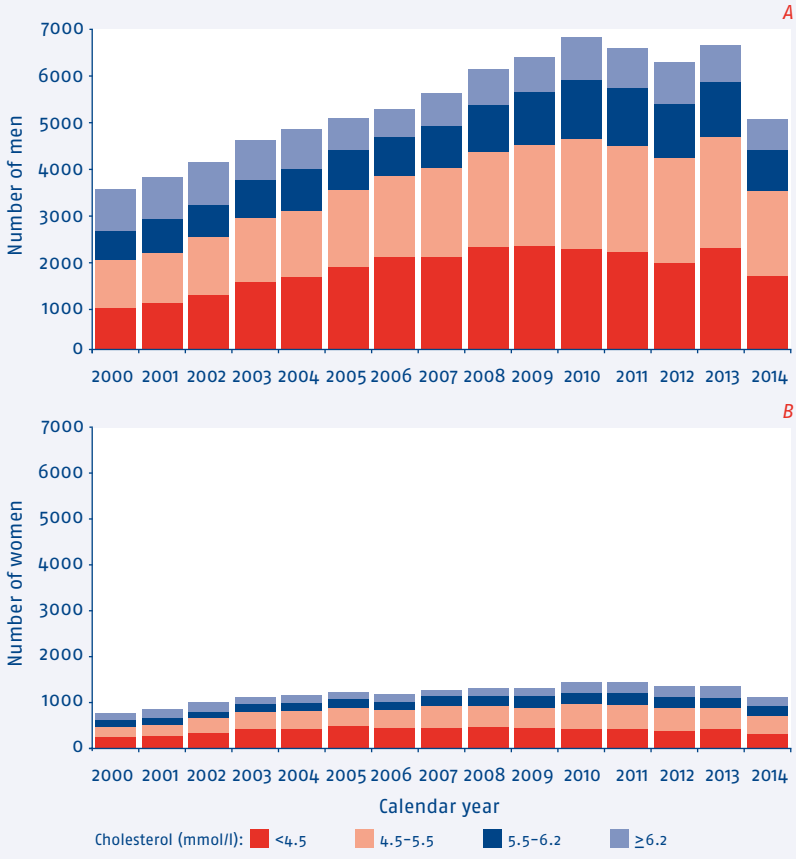
Legend: *CKD=chronic kidney disease; IDU=injecting drug use; cART=combination antiretroviral therapy; CDC=Centers for Disease Control and Prevention; LOP/r=lopinavir/ritonavir; IDV=indinavir; ABC=abacavir; AZT=zidovudine; d4T=stavudine; ddI=didanosine; BMI: <18 kg/m²=underweight; 18-25 kg/m²=normal; 25-30 kg/m²=overweight; >30 kg/m²=severely overweight.*

	Non-AIDS malignancy				Diabetes mellitus				CKD			
	OR		95% CI	p-value	OR		95% CI	p-value	OR		95% CI	p-value
					1.07	1.03	1.10	0.00				
									1.02	0.99	1.04	0.20
				<0.001				*<0.001*				*<0.001*
	1.80	1.30	2.51	0.00	1.88	1.26	2.80	0.00	4.76	3.73	6.08	0.00
	1.00				1.00				1.00			
	0.75	0.63	0.90	0.00	2.05	1.72	2.44	0.00	0.29	0.23	0.35	0.00
	0.76	0.55	1.05	0.10	4.39	3.56	5.41	0.00	0.19	0.13	0.28	0.00
									1.37	1.08	1.72	0.01
									1.85	1.49	2.27	0.00
	1.35	1.15	1.59	0.00	1.48	1.27	1.73	0.00	1.19	1.02	1.39	0.03
	1.50	1.18	1.92	0.00	1.07	0.82	1.41	0.62	1.28	0.98	2.00	0.00
	1.21	0.90	1.63	0.20	1.00	0.70	1.41	0.99	1.51	1.14	2.19	0.00
	1.37	1.13	1.65	0.00	1.96	1.65	2.32	0.00	1.85	1.57	1.76	0.12
				<0.001				*0.02*				*0.37*
	1.00				1.00				1.00			
	1.54	1.21	1.97	0.00	0.95	0.76	1.18	0.63	1.08	0.86	1.34	0.52
	1.13	0.85	1.51	0.39	1.25	0.97	1.62	0.08	1.07	0.83	1.38	0.59
	1.03	0.79	1.34	0.83	0.91	0.72	1.14	0.41	0.99	0.78	1.25	0.92
				<0.001				*0.02*				*0.37*
	0.53	0.41	0.67	0.00	1.05	0.84	1.32	0.65	.	.	.	.
	1.17	1.00	1.37	0.05	1.10	0.92	1.31	0.29	1.12	0.96	1.30	0.15
	1.00				1.00				1.00			

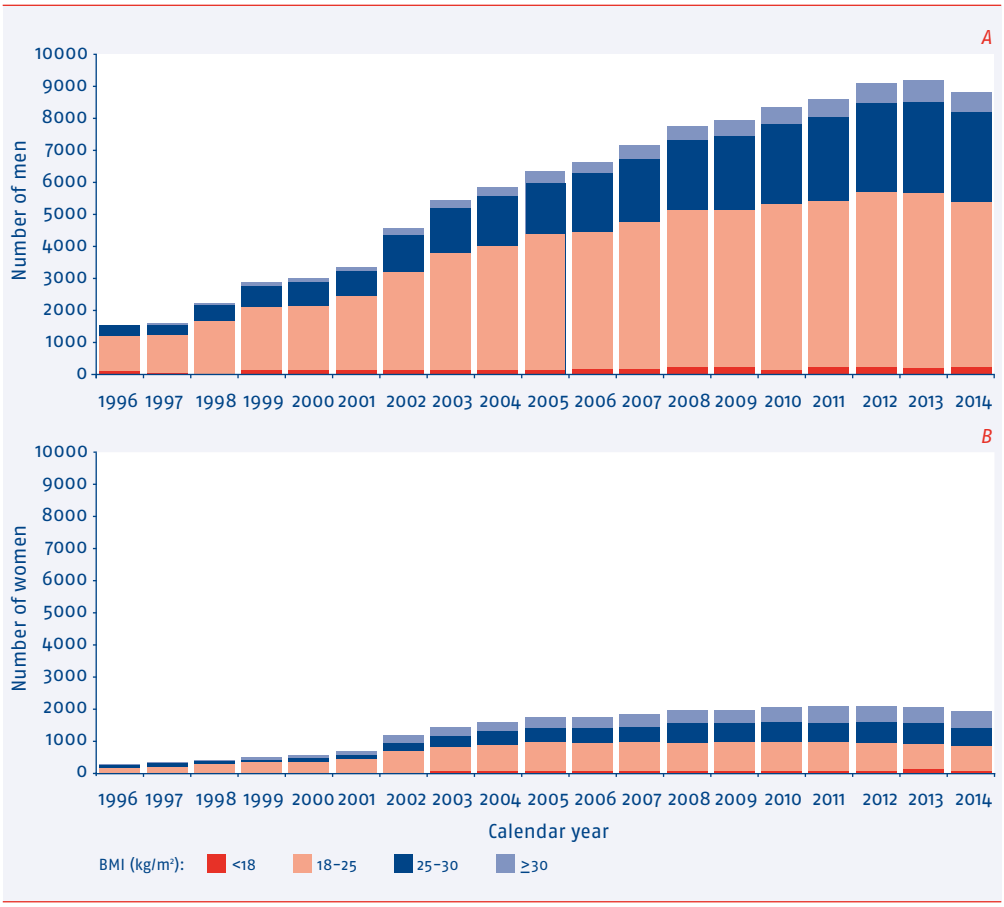
Appendix Figure 4.1: *Annual mortality (A, C) and incidence of AIDS (B, D) in 22,883 HIV-1-infected patients in the Netherlands after HIV diagnosis (A, B) and in a subpopulation of 20,703 treated patients who started combination antiretroviral therapy (cART) (C, D) from 1995 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dotted line is the mortality rate for age-matched and sex-matched individuals from the general population in the Netherlands. A: 2,320 deaths, 206,592 person years of follow up; B: 2,946 AIDS cases 6 weeks after diagnosis, 179,497 person years; C: 2,075 deaths, 162,424 person years; D: 2,063 cases 4 weeks after start of cART, 149,720 person years.*



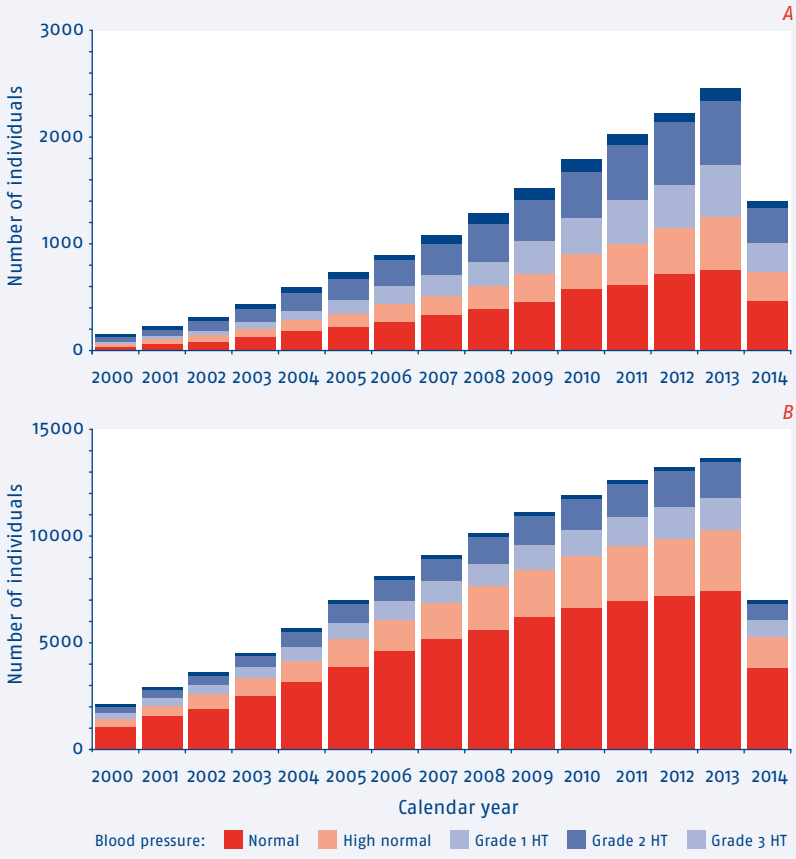
Appendix Figure 4.2: *Absolute number of men (A) and women (B) within cholesterol categories at the end of each calendar year. For each individual, the last available measurement in each year was selected.*



Appendix Figure 4.3: *Absolute number of men (A) and women (B) within body mass index (BMI) categories at the end of each calendar year. For each patient, the last available weight measurement in each year was selected.*



Appendix Figure 4.4: *Absolute number of individuals with graded blood pressure at the end of each calendar year in individuals known to be receiving antihypertensive treatment (A) and in those not recorded as being treated for hypertension (B). For each individual the last available systolic and diastolic blood pressure measurement in each year was selected. Note that the vertical axes are different in A and B. Blood pressure was graded according to the classification recommended in the guidelines for the management of arterial hypertension by the European Society of Hypertension and the European Society of Cardiology [101].*



Legend: *HT= hypertension; Normal: systolic blood pressure (SBP) <130 mmHg or diastolic blood pressure (DBP) <85 mmHg, high normal: SBP 130–139 mmHg or DBP 85–89 mmHg, grade 1 hypertension SBP 140–159 mmHg or DBP 90–99 mmHg, grade 2 hypertension SBP 160–179 mmHg or DBP 100–109 mmHg, grade 3 hypertension SBP ≥ 180 mmHg or DBP ≥ 110 mmHg.*

Appendix Table 6.1: *Characteristics of 534 HIV-1 infected children in the Netherlands on combination antiviral 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
Time between HIV-1 diagnosis and cART initiation (months) *	0.1 (0.3-2.4)	10 (4-24)	19 (2-70)	3 (1-8)
CD4 count at start of cART initiation (cells/mm^3) *	1,300 (565-2,125)	636 (425-1,044)	315 (170-440)	280 (150-400)
CD4 z-score at cART initiation*	-0.96 (-1.6 to -0.4)	-1.00 (-1.3 to -0.4)	-0.92 (-1.2 to -0.6)	-0.94 (-1.3 to -0.7)
HIV-1 RNA level at cART initiation (log cps/ml)*	5.8 (5.3-6.1)	5.1 (4.5-5.6)	4.7 (4.3-5.3)	4.9 (4.0-5.3)

**Median (IQR)*

Legend: *cART=combination antiretroviral therapy; IQR=interquartile range.*

Appendix Table 10.1: Annual number of HIV diagnoses in Curaçao stratified by sex and survival status as of May 2015.

	Alive, in clinical care		Alive, not in clinical care		Deceased		Total	
	Men	Women	Men	Women	Men	Women	Men	Women
unknown	3	2	17	7	2	7	22	16
≤1995	33	14	12	8	35	11	80	33
1996	6	10	2	2	1	1	9	13
1997	6	10	3	3	7	4	16	17
1998	8	3	11	2	8	1	27	6
1999	10	6	5	2	6	2	21	10
2000	11	8	4	6	7	4	22	18
2001	10	7	2	5	5	5	17	17
2002	14	8	8	9	6	2	28	19
2003	17	10	8	6	12	2	37	18
2004	7	10	11	4	10	2	28	16
2005	19	4	3	7	6	4	28	15
2006	17	10	8	3	3	2	28	15
2007	13	7	7	3	6	1	26	11
2008	19	12	10	6	2	1	31	19
2009	21	13	9	5	0	2	30	20
2010	16	13	5	4	2	1	23	18
2011	25	15	7	4	0	0	32	19
2012	21	19	8	5	0	0	29	24
2013	35	19	9	2	1	0	45	21
2014	23	11	–	–	0	0	23	11
2015	1	1	–	–	0	0	1	1
total	335	212	149	93	119	52	603	357

List of tables & figures

Appendix list of tables and figures

The Appendix contains tables and figures supplementary to various chapters in this report.

Acknowledgements

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Publications & presentations

The publications and presentations listed below are those available since the publication of the Monitoring Report 2014.

Publications

Evaluation of rapid progressors in HIV infection as an extreme phenotype
Olson AD, Guiguet M, Zangerle R, Gill J, Perez-Hoyos S, Lodi S, Ghosn J, Dorrucci M, Johnson A, Sannes M, Moreno S, Porter K; for CASCADE Collaboration in EuroCoord.
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Bailey H, Thorne C, Malyuta R, Townsend CL, Semenenko I, Cortina-Borja M; Ukraine European Collaborative Study Group in EuroCoord.
BMC Public Health 2014 Sep 24;14:993

Delayed HIV diagnosis and initiation of antiretroviral therapy: inequalities by educational level, COHERE inEuroCoord
Socio-economic Inequalities and HIV Writing Group for Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord.
AIDS 2014 Sep 24;28(15):2297-306

The effects of HIV-1 subtype and ethnicity on CD4 decline in antiretroviral naïve patients: a Canadian-European collaborative cohort study
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Opportunistic infections and AIDS malignancies early after initiating combination antiretroviral therapy in high-income countries
HIV-CAUSAL Collaboration.
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A clinically useful risk-score for chronic kidney disease in HIV infection
Mocroft A, Lundgren J, Ross M, Law M, Reiss P, Kirk O, Smith C, Wentworth D, Heuhaus J, Fux C, Moranne O, Morlat P, Johnson M, Ryom L; Data on Adverse Events (D:A:D) study group, the Royal Free Hospital Clinic Cohort and the INSIGHT study group.
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PLoS Med 2015 Mar 31;12(3):e1001809

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Cohen S, Ter Stege JA, Geurtsen GJ, Scherpbier HJ, Kuijpers TW, Reiss P, Schmand B, Pajkrt D.
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Podlekareva D, Grint D, Karpov I, Rakmanova A, Mansinho K, Chentsova N, Zeltina I, Losso M, Parczewski M, Lundgren JD, Mocroft A, Kirk O;EuroSIDA in EuroCoord.
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Demirkaya N, Cohen S, Wit FW, Abramoff MD, Schlingemann RO, Kuijpers TW, Reiss P, Pajkrt D, Verbraak FD.
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Vingerhoets J, Calvez V, Flandre P, Marcelin AG, Ceccherini-Silberstein F, Perno CF, Mercedes Santoro M, Bateson R, Nelson M, Cozzi-Lepri A, Grarup J,Lundgren J, Incardona F, Kaiser R, Sonnerborg A, Clotet B, Paredes R, Günthard HF, Ledergerber B, Hoogstoel A, Nijs S, Tambuyzer L, Lavreys L, Opsomer M;Etravirine Cohort Study Group.
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Liver-related death among HIV/hepatitis C virus-co-infected individuals: implications for the era of directly acting antivirals
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HIV resistance testing and detected drug resistance in Europe
Schultze A, Phillips AN, Paredes R, Battegay M, Rockstroh JK, Machala L, Tomazic J, Girard PM, Januskevica I, Gronborg-Laut K, Lundgren JD, Cozzi-Lepri A;EuroSIDA in EuroCOORD.
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Injection drug use and hepatitis C as risk factors for mortality in HIV-infected individuals: The Antiretroviral Therapy Cohort Collaboration
May MT, Justice AC, Birnie K, Ingle SM, Smit C, Smith C, Neau D, Guiguet M, Schwarze-Zander C, Moreno S, Guest JL, Monforte Ad, Tural C, Gill MJ,Bregenzer A, Kirk O, Saag M, Sterling TR, Crane HM, Sterne JA.
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Smit M, Brinkman K, Geerlings S, Smit C, Thyagarajan K, Van Sighem A, de Wolf F, Hallett TB; ATHENA observational cohort.
Lancet Infect Dis 2015 Jul;15(7):810-8

Low mother-to-child-transmission rate of hepatitis C virus in cART treated HIV-1 infected mothers
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J Clin Virol. 2015 Jul;68:11-5

Long-term changes of subcutaneous fat mass in HIV-infected children on antiretroviral therapy: A retrospective analysis of longitudinal data from two pediatric HIV cohorts
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Comparative effectiveness of strategies for antiretroviral treatment initiation in HIV-positive individuals in high-income countries: observational cohort study
Lodi S, Phillips A, Logan R, Olson A, Costagliola D, Abgrall S, van Sighem A, Reiss P, Miro JM, Ferrer E, Justice A, Gandhi N, Bucher HC, Furrer H, Moreno S, Monge S, Toulomi G, Pantazis N, Sterne J, Young JG, Meyer L, Seng R, Dabis F, Vandehende MA, Perez-Hoyos S, Jarrin I, Jose S, Sabin C, Hernan MA, on behalf of the HIV-CAUSAL Collaboration.
The Lancet HIV 2015; 2(8):e335–e343

Diminished impact of ethnicity as a risk factor for chronic kidney disease in the current HIV treatment era
Schoffelen AF, Smit C, van Lelyveld SFL, Vogt L, Bauer MP, Reiss P, Hoepelman AIM, Barth RE, on behalf of the ATHENA national observational HIV cohort.
J Infect Dis 2015 Jul 15;212(2):264-74

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Op de Coul EL, Schreuder I, Conti S, van Sighem A, Xiridou M, Van Veen MG, Heijne JC.
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Estimating HIV incidence, time to diagnosis, and the undiagnosed HIV epidemic using routine surveillance data
van Sighem A, Nakagawa F, Angelis D, Quinten C, Bezemer D, Coul EO, Egger M, Wolf F, Fraser C, Phillips A
Epidemiology 2015 Sep;26(5):653-60

Short-term weight gain after antiretroviral therapy initiation and subsequent risk of cardiovascular disease and diabetes: the D:A:D study
Achhra AC, Mocroft A, Reiss P, Sabin C, Ryom L, de Wit S, Smith CJ, d'Arminio Monforte A, Phillips A, Weber R, Lundgren J, Law MG; D:A:D Study Group.
HIV Med. 2015 Jul 28 [Epub ahead of print]

Impact of male circumcision among heterosexual HIV cases: comparisons between three low HIV prevalence countries
Chemtob D, Op de Coul E, van Sighem A, Mor Z, Cazein F, Semaille C.
Isr J Health Policy Res. 2015 Aug 4;4:36

Anal cancer in the HIV positive population: Slowly declining incidence after a decade of cART
Richel O, Van der Zee R, Smit C, De Vries H, Prins J
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Mortality declining substantially between 1996-2010 among patients starting ART
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CXCR4-tropic HIV acquired at seroconversion and rate of CD4 cell decline
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Consequences of increased testing and earlier start of therapy on the HIV epidemic among MSM in the Netherlands
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Higher prevalence of hypertension in HIV-infected individuals partially explained by increased waist-hip ratio rather than BMI, other traditional risk factors or markers of systemic inflammation
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Factors associated with presenting late or with advanced HIV disease in the Netherlands, 1996-2014
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Higher prevalence of hypertension in HIV-infected individuals partially explained by increased waist-hip ration rather than BMI, other traditional risk factors or markers of systemic inflammation
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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 characterised by failure of the immune system to protect against infections and certain cancers.

AIGHD
Amsterdam Institute for Global Health and Development.

Antibody
An immune system protein 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 therapy (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.

Baseline
An initial measurement used as the basis for future comparison. For people infected with HIV, baseline testing includes CD4 count, viral load (HIV RNA), and resistance testing. Baseline test results are used to guide HIV treatment choices and monitor effectiveness of antiretroviral therapy (ART).

cART
Combination antiretroviral treatment.

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 (> 500 per mm^3) to dangerously low levels (< 200 CD4 cells per mm^3 blood).

CDC
US Centers for Disease Control and Prevention.

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

CLB
Central Laboratory for the Blood Transfusion Service (*Centraal Laboratorium van Bloedtransfusiedienst*).

Co-infection
When a person has two or more infections at the same time. For example, a person infected with HIV may be co-infected with hepatitis C (HCV) or tuberculosis (TB) or both.

Comorbidity
When a person has two or more diseases or conditions at the same time. For example, a person with high blood pressure may also have heart disease.

Cross-resistance
After a person becomes resistant to one particular drug, they may develop resistance to similar drugs, without ever having been exposed to these drugs. This is known as cross-resistance.

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.

Epidemiology
The study of the distribution, causes, and clinical characteristics of disease or health status in a population.

Genotype
The genotype is the underlying genetic makeup of an organism.

GGD
Dutch municipal health service (www.ggd.nl).

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

Half-life
The time it takes a drug to lose half its original concentration or activity after being introduced into the body. Drug half-life is considered when determining drug dosing.

Hepatic
Pertaining to the liver.

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 Africa.

HIV Vereniging Nederland
Dutch HIV patients'association (www.hivnet.org)

HKZ
Harmonisation of Quality Assessment in Health Care (*Harmonisatie Kwaliteitsbeoordeling in de Zorgsector*).

Immune recovery
If treatment is effective and HIV is well-controlled, the immune cells regain their normal function and CD4 cell counts are close to normal. This is defined as immune recovery.

Immunologic failure
A type of HIV treatment failure. There is no consensus on the definition of immunologic failure. However, some experts define immunologic failure as the failure to achieve and maintain adequate CD4 counts despite viral suppression.

Interferon
Interferons are naturally-occurring proteins (cytokines) produced by immune cells in response to an antigen, usually a virus. Although they don't directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs the half-life of interferon. Pegylated interferon alpha is used to treat chronic hepatitis C infection.

Mono-infection
When a person has only one infection.

Mortality
Mortality rate is a measure of the frequency of occurrence of death among a defined population during a specified time period.

MSM
Men who have sex with men.

Nederlandse Federatie Universitair Medische Centra (NFU)
Netherlands Federation of University Medical Centres.

Non-AIDS events
Diseases and clinical events that are not related to AIDS (i.e., that are not listed as being associated with AIDS by the Centers for Disease Control and Prevention) and include conditions such as malignancies, end-stage renal disease, liver failure, pancreatitis, cardiovascular disease.

Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)
Antiretroviral HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleoside Reverse Transcriptase Inhibitor (NRTI)
Antiretroviral HIV drug class. Nucleoside reverse transcriptase inhibitors (NRTIs) block reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

Nucleotide
A building block of nucleic acids. DNA and RNA are nucleic acids.

Nucleotide Reverse Transcriptase Inhibitor (NtRTI)
A type of antiretroviral (ARV) HIV drug. Nucleotide reverse transcriptase inhibitors (NtRTIs) interfere with the HIV life cycle in the same way as NRTIs. Both block reverse transcription. NtRTIs are included in the NRTI drug class.

NVHB
Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*)

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

Perinatal transmission
Perinatal transmission of HIV refers to the passage of HIV from an infected mother to her child during pregnancy, labour and delivery, or breastfeeding (through breast milk).

Protease
A type of enzyme that breaks down proteins into smaller proteins or smaller protein units, such as peptides or amino acids. HIV protease cuts up large precursor proteins into smaller proteins. These smaller proteins combine with HIV's genetic material to form a new HIV virus. Protease inhibitors (PIs) prevent HIV from replicating by blocking protease.

Protease Inhibitor (PI)
Antiretroviral HIV drug class. Protease inhibitors (PIs) block protease (an HIV enzyme). This prevents new HIV from forming.

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.

Ribavirin
A type of nucleoside inhibitor prescribed for the treatment of hepatitis C in combination with an interferon. Ribavirin stops the hepatitis C virus from spreading by interfering with the synthesis of viral RNA.

RIVM
The Netherlands' 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.

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

Sustained virologic response or sustained viral suppression
The continuous, long-term suppression of a person's viral load (HIV RNA), generally to undetectable levels, as the result of treatment with antiretroviral drugs.

Tolerability
The extent to which a drug's side effects can be tolerated by the patient.

Viraemia
The presence of a virus in the blood.

Virologic failure
A type of HIV treatment failure. Virologic failure occurs when antiretroviral therapy (ART) fails to suppress and sustain a person's viral load to less than 200 copies/mL. Factors that can contribute to virologic failure include drug resistance, drug toxicity, and poor treatment adherence.

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

Viral suppression or virologic control
When antiretroviral therapy (ART) reduces a person's viral load (HIV RNA) to an undetectable level. Viral suppression does not mean a person is cured; HIV still remains in the body.

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

Some of the above definitions were taken from www.aidsinfo.hiv.gov

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