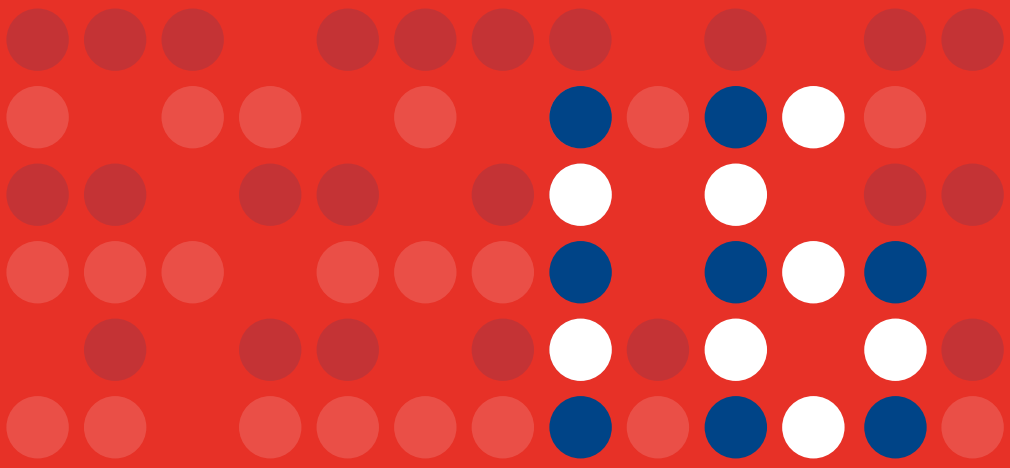
Human Immunodeficiency Virus (HIV)
Infection in the Netherlands

HIV Monitoring

HIV Monitoring Report 2016



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-positive patients in follow up in Dutch HIV treatment centres.

Stichting HIV Monitoring's mission

To further the knowledge and understanding of all relevant aspects of HIV infection, including comorbidities and co-infections (such as viral hepatitis), in HIV-positive persons in care in the Netherlands.

www.hiv-monitoring.nl

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HIV Monitoring

Monitoring Report 2016

Human Immunodeficiency Virus (HIV) Infection in the Netherlands

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Reference numbers

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Guide to buttons

Preceding chapter  Content page  Next chapter 

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The monitoring of HIV-positive adults is a collaborative effort involving Stichting HIV Monitoring (SHM) and a total of 26 health institutes that are recognised by the Dutch Minister of Health, Welfare and Sport as HIV treatment centres or subcentres. In addition, HIV-positive children and adolescents are monitored in four institutes that are recognised as paediatric HIV treatment centres.

In 2016, the following health institutes were involved as centres for adult HIV care (in alphabetical order of town):

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


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

Table of contents

Introduction

The Monitoring Report 2016 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 15th 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 pseudonymised data from HIV patients in care in the 26 officially recognised HIV treatment centres throughout the country, our work contributes significantly to the knowledge of HIV. SHM also makes centre-specific information available to each individual treatment centre 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. 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.

In this Monitoring Report, the section on the HIV Monitoring Programme 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, trends in prescription of combination antiretroviral therapy (cART), the effects of cART, the development of resistance to antiretroviral drugs, and morbidity and mortality in the HIV-infected population. In addition, this section contains information on specific patient populations, including HIV-1-infected children and pregnant women and individuals with viral hepatitis co-infections. In particular, in the latter population, this report provides updated results of treatment of HCV co-infection with the novel direct-acting antivirals (DAAs).

The Special Reports section includes a chapter on quality of care in the HIV treatment centres in the Netherlands. First introduced in last year's report, the chapter has now been expanded to present the quality of care indicators

according to centre size. Should treatment centres be interested in their centre-specific outcomes, they are invited to contact Stichting HIV Monitoring for details. As in previous years, the Special Reports section also includes a chapter on the results from the Amsterdam Cohort Studies and one on HIV in Curaçao.

This year, we once again invited a small group of HIV treating physicians and experts in public health with 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 efforts, our work would not be possible. I also extend my gratitude to the people living with HIV who generously agree to provide data to SHM. It is only through this partnership between both professionals and people living with HIV that we can further improve our insight into the many facets of HIV and HIV treatment, and thereby continue to not only improve the care for people living with HIV in the Netherlands, but also provide guidance for prevention.

Professor Peter Reiss, MD

Director, Stichting HIV Monitoring

Summary & recommendations

The HIV epidemic in the Netherlands

HIV-positive individuals registered in the Netherlands as of May 2016

As of May 2016, a total of 18,866 persons living with HIV in the Netherlands (18,657 adults, and 209 children and adolescents) were known to be in care in one of the 26 designated HIV treatment centres. Of these 18,866, 95% (17,909) had started combination antiretroviral therapy (cART), and of these 17,909, 93% (16,739) had suppressed viraemia to below 100 copies/ml at the time of their last available HIV RNA measurement. These results are impressive when compared to figures from other parts of the world.

New diagnoses in 2015

In 2015, the majority (64%) of newly diagnosed infections were in men who have sex with men (MSM), 28% were acquired through heterosexual contact and around 7% through other or unknown modes of transmission. Of note, almost one quarter of all newly-diagnosed individuals in 2015 were 50 years or older. Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to approximately 900 new diagnoses in recent years. Although this decreasing trend continued in 2015, the projected number of diagnoses for that year (865) may have been underestimated as registration of HIV diagnoses for this year has not yet been finalised. 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.

CD4 count at diagnosis and start of cART

The rates of testing for HIV appear to be increasing in certain settings. Interestingly, the proportion of individuals with a previously negative HIV test has also increased (72% of MSM, 28% of other men and 42% of women diagnosed in 2015 had a known previous negative test). Moreover, fortunately, the proportion of individuals 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 370 and 420 cells/mm^3, respectively, in 2015.

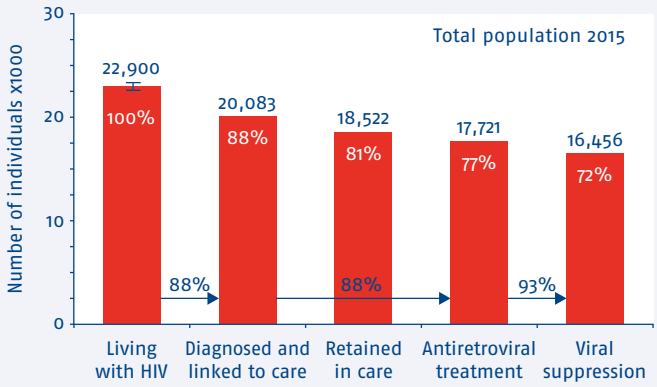
The likelihood of individuals starting cART at higher CD4 counts has also clearly increased. Whilst in 2014, 73% of individuals with a CD4 count of 500 cells/mm^3 had begun cART within 6 months of diagnosis, this proportion rose to 81% in 2015. Nonetheless, far too many individuals continue to present late for care. In 2015, 45% of newly diagnosed individuals presented late for care, i.e., with AIDS or a CD4 count less than 350 cells/mm^3, and 29% 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 other than MSM, individuals originating from South and Southeast Asia and sub-Saharan Africa, and individuals aged 45 years or older.

Continuum of HIV care in 2015

By the end of 2015, 22,900 individuals were estimated to be living with HIV in the Netherlands, of whom 2,800 were still undiagnosed. On the basis of this estimated number of 22,900 people living with HIV, a continuum of HIV care has been constructed to depict engagement in HIV care in 2015 across a few key indicators, the last one being the number of individuals with suppressed viral load (See *Figure 1*). By the end of 2015, 20,083 individuals, or 88% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM. In total, 18,522 individuals were considered to still be in care. The majority of these individuals, 17,721 in total, had started cART, and 16,456 had a most recent HIV RNA measurement below 100 copies/ml, irrespective of treatment. Overall, 72% of the total estimated population living with HIV and 82% of those diagnosed and ever linked to care had a suppressed viral load.

Figure 1: continuum of HIV care for the total estimated HIV-positive population in the Netherlands by the end of 2015.



A re-assessment of the continuum of HIV care for 2014 showed that there was a significant increase in the number of people on cART by the end of that year compared to what was reported in last year's report. Moreover, there was an even more pronounced increase in the number who achieved viral suppression. To better monitor progress towards achieving UNAIDS' 90-90-90 goals, a more timely registration of start of treatment and viral load measurements would be needed. The latter could be markedly improved by extending the automated import of laboratory measurements to all HIV treatment centres in the Netherlands.

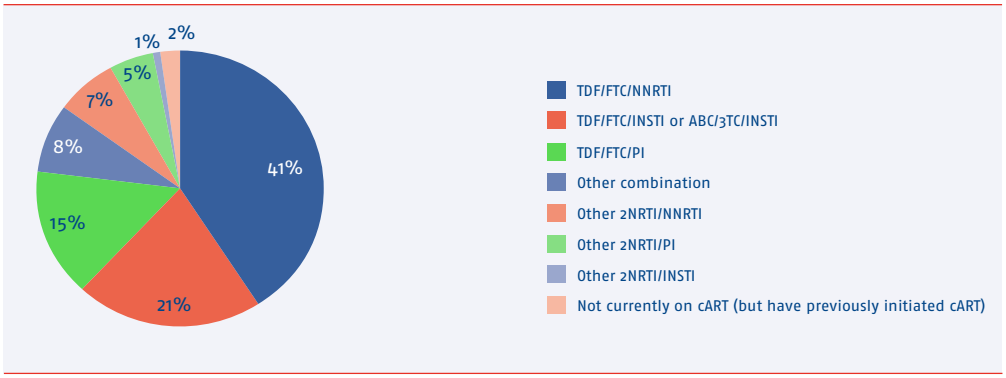
To achieve a significant decline in the rate of new infections, we continue to need improved transdisciplinary strategies for all factors sustaining the epidemic. The aim of these strategies should be to simultaneously reduce the likelihood of HIV infection in key populations at risk, identify infected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

Combination antiretroviral therapy in adults and quality of treatment and care

In care and on cART in 2015

Initiation of cART following a diagnosis of HIV infection is taking place increasingly earlier in the Netherlands. In 2015, the majority of individuals who entered care and started cART in the Netherlands did so within a month after diagnosis. Concurrently, the median CD4 count at cART initiation has increased to 420 cells/mm^3. Among all HIV-positive individuals in care in 2015 who had ever started cART, the majority received a tenofovir-emtricitabine-based cART regimen combined with either a non-nucleoside reverse transcriptase inhibitor (NNRTI; 41%), a protease inhibitor (PI; 16%), or an integrase inhibitor (15%). Overall, integrase inhibitor-based cART was used by 27% of those in care in 2015: 14% received dolutegravir, 7% cobicistat-boosted elvitegravir and 6% raltegravir. cART use in 2015 in the Netherlands among HIV-positive individuals who started treatment is presented in *Figure 2*. Of those on cART with a plasma HIV RNA measurement in 2015, 97% had a suppressed viral load.

Figure 2: cART use in 2015 in the Netherlands, among HIV-positive individuals who started treatment.



Legend: *3TC=lamivudine; ABC=abacavir; cART=combination antiretroviral therapy; FTC=emtricitabine; INSTI=integrase strand transfer inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; TDF=tenofovir disoproxil fumarate.*

Initial regimen

Three-quarters of all individuals starting cART in 2015 started integrase inhibitor-based cART: 55% received dolutegravir-based cART and 20% cobicistat-boosted elvitegravir-based cART. While the majority (61%) started tenofovir-emtricitabine-based cART, there has been a significant increase in the use of abacavir-lamivudine as the nucleoside reverse transcriptase inhibitor backbone. This trend can be explained by the introduction of the once-daily fixed dose combination of dolutegravir with abacavir-lamivudine (Triumeq®) towards the end of 2014. Of those who started cART in 2015, 40% received abacavir-lamivudine combined with dolutegravir. Although tolerability of cART has continued to improve with time and larger numbers of individuals remain on their initial cART regimen for a longer period of time, drug intolerance or toxicity is still the most common reason for a change of initial treatment.

Virological response

Both short-term and long-term virological suppression rates are high and continue to improve. Among those starting a preferred cART regimen between 2010 and 2015, 92% had a suppressed viral load (HIV RNA <100 copies/ml) after 6 months. These initial suppression rates were significantly higher among participants initiating integrase inhibitor-based cART compared to NNRTI-based or PI-based cART; this effect was strongest among individuals with a high viral load at cART initiation. Among those who initiated cART in or after 2010, 94% had a suppressed viral load after one year and 97% after four years.

Since 2000, the annual proportion of individuals with a viral load >200 copies/ml has decreased to approximately 3%. The risk of viral rebound was higher among individuals under 30 years of age, heterosexual men and women, and those who originated from South America and the Caribbean or sub-Saharan Africa. Those with higher HIV viral load at the start of cART and those starting with CD4 cell counts below 200 cells/mm^3 had an increased risk of viral rebound compared with those starting treatment at higher CD4 cell counts.

HIV drug resistance

Of the HIV-positive individuals who were in clinical care as of May 2016, resistance-associated mutations have been found in 11%, with 8% of these mutations resulting in high-level resistance to at least one antiretroviral drug. Of note, resistance test results were available for only 25% of individuals with viral failure in or after 2000 and for 17% with viral failure in or after 2010. Therefore, the true prevalence of resistance may be different.

Among 10% of individuals with resistance data available within one year of diagnosis, at least one transmitted drug resistance mutation was found; including 4% with nucleoside reverse transcriptase-associated mutations, 5% with non-nucleoside reverse transcriptase-associated mutations, and 2% with mutations in the protease gene. Between 2003 and 2015, there were no significant changes in these proportions, although there was a decreasing trend in most recent calendar years.

Immunological response

The proportion of individuals achieving immunologic recovery on cART continues to improve each year. Based on the last available CD4 and CD8 cell count measurements in 2015, 72% had a CD4 cell count of 500 cells/mm^3 or higher, and 23% had a CD4:CD8 ratio of ≥1. Nonetheless, a substantial number of individuals fail to achieve immunological recovery, which increases the risk of both traditionally HIV-associated and non-AIDS-related morbidity. This is particularly true for those who start cART at a more advanced level of immunodeficiency.

Following revised HIV treatment guidelines, prompt treatment initiation of, primarily integrase inhibitor-based, cART has been observed in the Netherlands in 2015. Currently recommended regimens are durable, effective and provide high virological suppression. Nonetheless, the long-term effects of these shifts in antiretroviral drug use should continue to be monitored.

Quality of care

Generally speaking, a number of different quality of care indicators showed limited variability across the 26 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, regardless of size. Across most of the centres an increasing proportion of individuals are starting cART sooner after entering into care, confirming that treatment centres are following new guidelines to offer cART to anyone with newly diagnosed HIV, regardless of their CD4 count. Despite the increasing number of individuals starting cART within 6 months after entering care, some centres could further improve this number among those individuals who enter care with CD4 cell counts above 350 cells/mm^3.

Variation in HCV screening

More substantial variation was observed in repeat HCV screening in MSM. However, this may, to some extent, be explained by centres applying a policy of targeted screening guided by the presence of incident transaminase elevations and/or by differences in the MSM population with respect to known risk-taking behaviour for HCV acquisition. Regular screening for HCV among HCV/HIV co-infected individuals who have been successfully treated for HCV is recommended for early detection of HCV re-infections. Therefore, continued monitoring of repeat HCV screening rates and other reported trends seems warranted.

Morbidity and mortality

Mortality rates remain low in HIV-positive individuals 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 comorbidities, including non-AIDS-defining malignancies (NADM), cardiovascular disease (CVD) and chronic liver disease, comprise a sizable fraction of those other causes. Of note, however, the proportion of individuals dying of AIDS (26% of the total number of deaths) remained substantial between 2007 and 2015. This was largely driven by late presentation and late entry into care, and once again stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

Older age and comorbidities

Not surprisingly, older age was an important risk factor for comorbidities 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 2015, 23% were 50 years or older. At the same time, the overall patient population with HIV in care in the Netherlands continues to age, with 45%

currently older than 50 years (42% in 2014, 39% in 2013). Of particular concern is the increasing proportion of individuals with multiple comorbidities, the risk of which appears to be increased in those with HIV, as demonstrated, for example, 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.

Cardiovascular risk

Despite the increasing age of the HIV-positive population, the proportion at high or very high cardiovascular risk only increased slightly over the period 2000-2015. 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 anti-platelet therapy as secondary prevention following a myocardial infarction or ischaemic stroke, and the low uptake of these medications in the prevention of primary cardiovascular disease.

Non-AIDS malignancies

The crude incidence of non-AIDS malignancies in the Netherlands has remained stable over time, but 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, screening and treatment for early (pre-malignant) stages of anal cancer, 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 individuals diagnosed with other non-AIDS malignancies increased with increasing age.

Awareness of the role of modifiable, often lifestyle-related risk factors, such as smoking, and their management by both physicians and people living with HIV offer important hope of ensuring a lower comorbidity burden and resilient ageing. This is particularly relevant for older individuals or those with another strong comorbidity risk factor, and 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 clearly room for improvement in the use of known effective biomedical interventions for primary and secondary cardiovascular disease prevention according to general guidelines.

Hepatitis B and C co-infections

Screening for hepatitis B (HBV) and C (HCV) co-infection has 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-positive individuals in care in the Netherlands. Approximately 12% of individuals had evidence of ever having been exposed to HCV, 6% were documented as having chronic infection and 2% had acute infection. Seven percent of individuals were shown to have chronic HBV infection.

Overall, individuals with HCV or HBV co-infection remain at increased risk of liver-related morbidity and mortality. For individuals 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.

An estimated 28% of HIV-positive individuals overall and 20% of MSM either had not been exposed to HBV or had not been successfully vaccinated and may remain at risk of acquiring HBV. These findings illustrate the importance of continuing our efforts to increase successful HBV vaccination rates in this subgroup, particularly in those who are not receiving a tenofovir-containing antiretroviral regimen.

HCV genotype 1 infection was the most common genotype in individuals with either chronic or acute HCV infection, and most individuals with HCV infection were male and from the Netherlands or other European countries. Importantly, the incidence of acute HCV infection observed in 2015 amongst MSM remains high at a rate of 5.9 diagnoses per 1,000 person years (3.7 per 1,000 person years in 2014). This clearly indicates the need for continued preventive efforts in these men, including the use of the novel highly effective short-course well-tolerated interferon-free combination therapies for HCV, which, by virtue of their high effectiveness, may not only benefit the individual patient, but also importantly reduce the risk of onward transmission.

HCV & direct-acting antiviral agents

Our data clearly show that, with the advent of novel direct-acting antiviral agents (DAAs) in 2014 and 2015, pegylated interferon (PEG-IFN)-containing regimens have largely been replaced in clinical practice by a variety of novel DAAs and more HIV-positive individuals with HCV-co-infection are being treated for HCV infection. More than 500 individuals have received, or are currently receiving, treatment

with novel DAAs including one or more of the currently available novel DAAs sofosbuvir, simeprevir, daclatasvir, ledipasvir, ombitasvir, paritaprevir or dasabuvir. Of note, 98% of all individuals with sufficient follow-up data to calculate a sustained virological response were found to have been cured.

Very importantly, these developments have already resulted in a lower total number of HCV-co-infected individuals who remain in need of effective treatment compared to last year's report (499 in 2016, 876 individuals in 2015 vs. 907 in 2014), in spite of an increase in the total number of individuals with HCV co-infection currently retained in care (1,420 in 2016, 1,260 in 2015, and 1,187 in 2014). However, an alarmingly high rate of detectable HCV RNA test results after successful treatment was observed, which strongly suggests HCV re-infection and ongoing transmission of HCV.

The rapidly expanding availability of novel interferon-free regimens for HCV, together with optimised screening for HCV co-infection with time will hopefully limit the impact of HCV co-infection on long-term liver-related morbidity and mortality. To reduce the rate of incident HCV infection among the key affected population of MSM, regular screening for HCV among successfully-treated individuals is recommended for early detection of HCV re-infections, in combination with preventive behavioural interventions aimed at MSM.

HIV in pregnant women and in children

Pregnant women

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. Moreover, approximately 7% of HIV-positive pregnant women do not have fully suppressed viraemia around the time of delivery.

To ensure zero vertical transmissions of HIV, there is a need for continued vigilance for new HIV infections and successful viral suppression at delivery.

Children

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 have started treatment below two years of age.

An increasing number of children living with HIV in the Netherlands are transitioning into adult care. However, almost 35% of the children who transitioned into adult care did not have fully suppressed viraemia at time of transition.

The large number of children who have inadequately-suppressed viraemia at the time of transition to adult care 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 (ACS) on HIV infection and AIDS started shortly after the first cases of AIDS were diagnosed in the Netherlands, enrolling men who have sex with men (MSM) in a prospective cohort study from October 1984 onwards. A second cohort involving people who use drugs (PWUD) was initiated in 1985. The ACS aims 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. More recently, ACS research has broadened to include the epidemiology of other blood-borne and sexually transmitted infections (STI) and their interaction with HIV.

Together with the AMC Department of Infectious Diseases, Department of Global Health, the Amsterdam Institute of Global Health and Development, and SHM, the Public Health Service 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 comorbidities, 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.

Within the ACS, different institutes collaborate to bring together the data and biological sample collections and to conduct research. Research highlights in 2015 within the ACS research programme include ongoing work into high-risk human papillomavirus (hrHPV) infections in MSM. Using the cohort from a previous study, H2M (HIV and HPV in MSM), that compared the prevalence, incidence, and clearance of hrHPV between HIV-negative and HIV-positive MSM, the H2M2 study was initiated in 2015 to identify potential predictors for high-grade anal intra-epithelial neoplasia in the HIV-infected MSM population. In addition, a second new study (the H2M3 study) aims to study long-term incidence and clearance of anal and penile hrHPV infections. Other research within the ACS research programme included work on the envelope glycoprotein (Env) trimer, whereby the conformation of soluble Env trimers was stabilised in closed, ground states. These closed trimers may be useful components of vaccines aimed at inducing broadly neutralizing antibodies. Finally, ACS research identified an important cellular component involved in HIV replication, namely the GTPase-activating protein-(SH3 domain)-binding protein 1 (G3BP1) that restricts HIV-1 replication.

HIV in Curaçao

SHM continues to provide assistance to Stichting Rode Kruis Bloedbank with data collection and monitoring of individuals with HIV in care at the St Elisabeth Hospital in Willemstad in Curaçao. In recent years, HIV-positive individuals 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, combination antiretroviral therapy is being started at increasingly higher CD4 cell counts. Although early start of treatment appears to be possible, long-term continuous follow up should be guaranteed to optimise the effect of treatment.

Monitoring programme report

1. The HIV epidemic in the Netherlands

Ard van Sighem and Eline op de Coul

Introduction

As of May 2016, 25,326 HIV-positive patients had ever been registered by Stichting HIV Monitoring (SHM). Of those, 24,313 were followed in one of the HIV treatment centres in the Netherlands (*Figure 1.1*), and together had a total follow-up time since diagnosis of 240,822 person years. The remaining 1,013 were registered via the St. Elisabeth Hospital in Willemstad, Curaçao (see Chapter 9). Of the 24,313 patients, the majority were infected with HIV-1 (24,026; 99%). A small group of patients, 97 in total, were infected with HIV-2, while 57 patients had antibodies against both HIV-1 and HIV-2. Serological results were not yet available in the SHM database for 133 recently-registered patients.

This chapter will first focus on characteristics of HIV-1-positive patients at the time of diagnosis or at the time of entering HIV care, followed by a brief overview of the small group of patients who are HIV-2-positive. The second part will discuss the HIV-positive patients who were still in care as of May 2016.

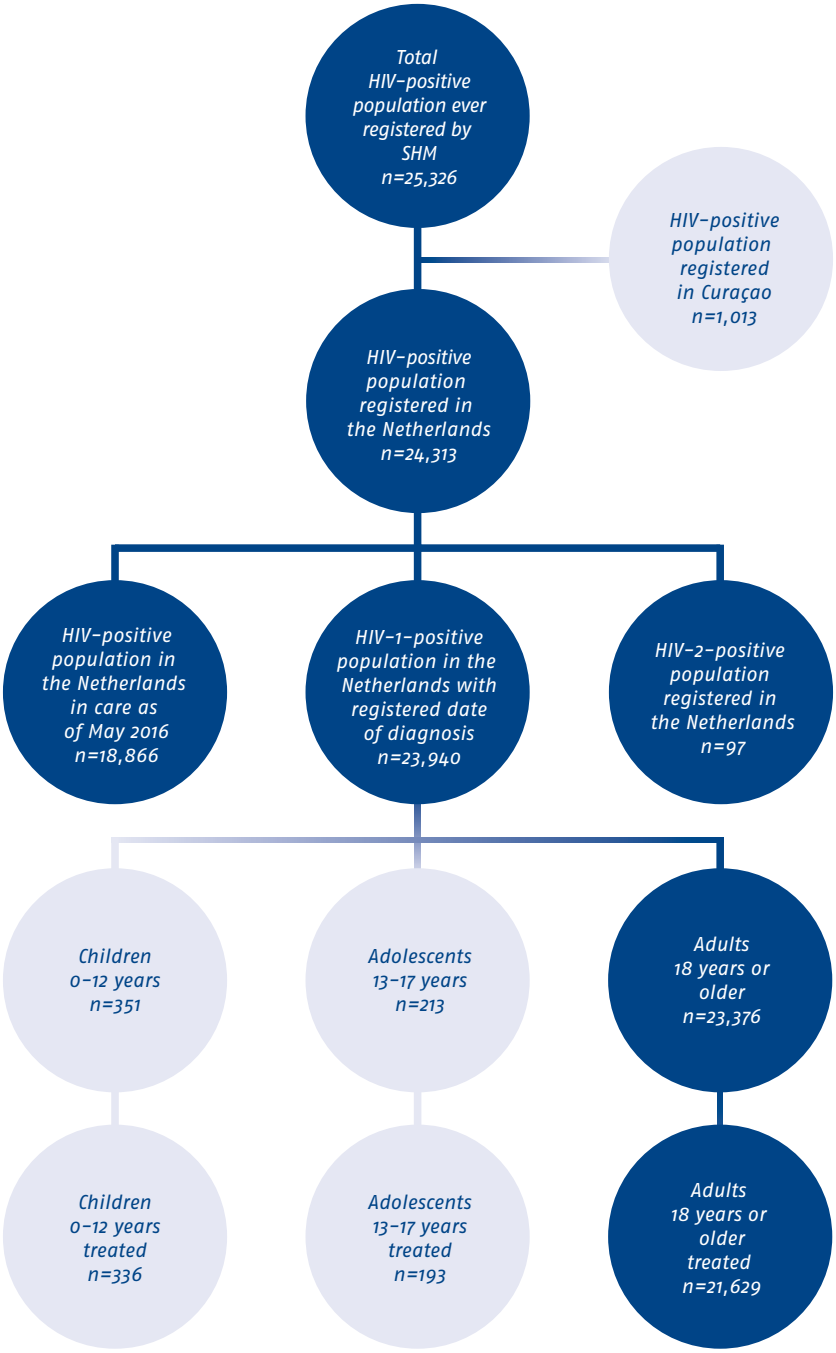
Population – HIV-1

HIV-1-positive individuals

Altogether, 23,376 patients were ever diagnosed with HIV-1 as adults and had a recorded date of diagnosis (*Figure 1.1*). The majority of these patients were men who have sex with men (MSM; 13,955 [60%]), while 3,224 men (14%) and 3,893 (17%) women reportedly acquired their HIV infection via heterosexual contact (*Appendix Table 1.1*). For 749 (3%) of the patients, the reported mode of transmission was injecting drug use, while 280 patients (1%) were infected by exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 5% (1,275) of infections.

< Back to page 56

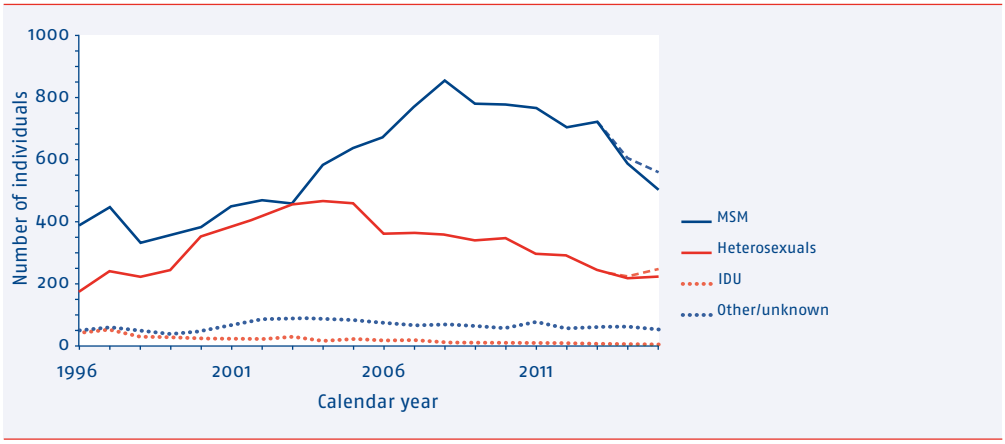
Figure 1.1: Overview of the HIV-positive population registered by Stichting HIV Monitoring (SHM) as of May 2016.



Decreasing number of diagnoses

Since the 1990s, the annual number of new diagnoses among MSM increased from approximately 400 to well above 800 in 2008 (*Figure 1.2*). From 2009 onwards, the registered number of new diagnoses steadily declined. In 2015, the decreasing trend has continued and the projected number of new HIV diagnoses in MSM, taking into account a backlog [a] in registration of HIV cases, was approximately 550. A similar decrease in HIV diagnoses was observed in STI clinics, which reported 6% fewer diagnoses in MSM than in 2014 [1].

Figure 1.2: *Annual number of new HIV-1 diagnoses among adults, according to most likely mode of transmission. In 2015, men who have sex with men (MSM) accounted for 65% of new diagnoses, infections via heterosexual contact for 28%, infections via injecting drug use (IDU) for 0%, and infections via other or unknown modes of transmission for 7% of the annual number of diagnoses. The dashed lines indicate the projected number of diagnoses when the backlog in registration of HIV cases (3% in 2014, 11% in 2015) is taken into account.*



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

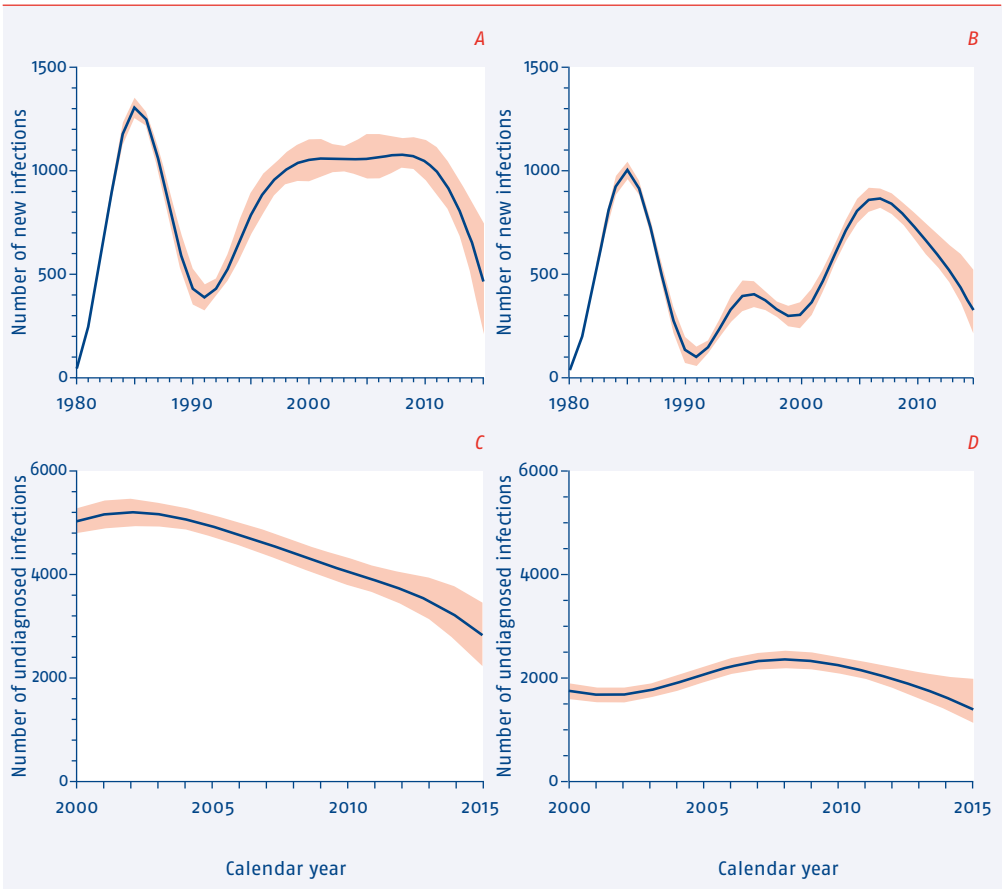
In the heterosexual population, the number of new diagnoses has declined to between 200 and 300 cases per year in the last few years. This decline, as shown later in this chapter, is largely the result of a reduced number of diagnoses in migrant populations. Finally, injecting drug use is rarely reported any longer as the most probable mode of transmission, which reflects the decreasing popularity of injecting drugs.

(a) As it may take some time before people living with HIV are registered in the SHM database by their treating physician, there is a certain backlog for the most recent calendar years. Based on past trends, this backlog is estimated to be 3% in 2014 and 11% in 2015.

Decreasing number of infections

The observed changes over time in the number of HIV diagnoses are, in part, a consequence of changes in the annual number of newly acquired HIV infections. According to a tool recently made available by the European Centre for Disease Prevention and Control (ECDC), there were approximately 1,000 new HIV infections each year between 2000 and 2010[2]. Thereafter, the number of new infections decreased to 450 (95% confidence interval [CI] 200-750) in 2015 (*Figure 1.3A*). In MSM, the number of new HIV infections reached a peak of 850 (95% CI 800-900) around 2007 and then decreased to approximately 350 (95% CI 200-550) in 2015 (*Figure 1.3B*). From 2000 onwards, the number of people living with undiagnosed HIV decreased, although this decrease was less pronounced among MSM (*Figure 1.3C* and *1.3D*).

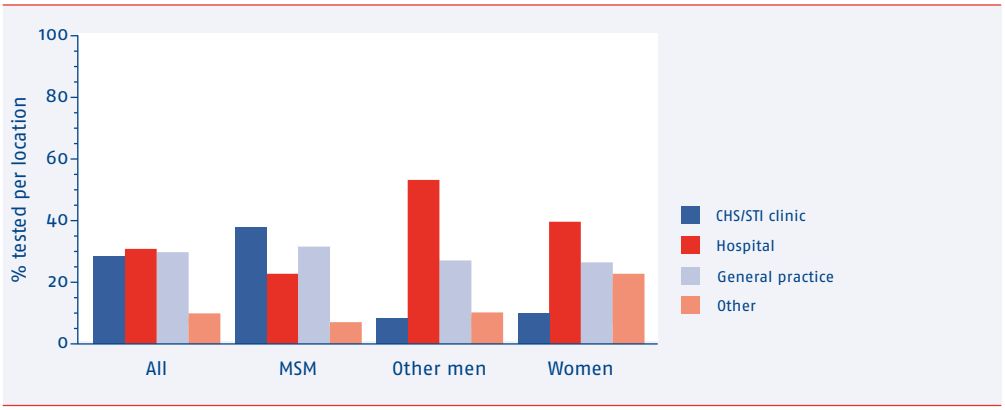
Figure 1.3: *Estimated annual number of newly-acquired HIV infections and number of people living with undiagnosed HIV (A, C) in the entire HIV-positive population in the Netherlands and (B, D) in men who have sex with men.*



Testing location

Information on the location of testing was available for 96% of patients diagnosed in 2008 or later. Overall, 29% of these patients received their first HIV-positive test result at a community health service (CHS) or STI clinic, 31% at a hospital, and 30% at a general practice (*Figure 1.4*). Among those tested at community health services or STI clinics, 89% were MSM, 6% were other men, and 5% were women. These numbers are comparable to those directly reported by STI clinics in 2015: 90% MSM, 4% heterosexual men, and 6% women[1].

Figure 1.4: Proportion of patients diagnosed from 2008 onwards, stratified by location of testing and transmission risk group.



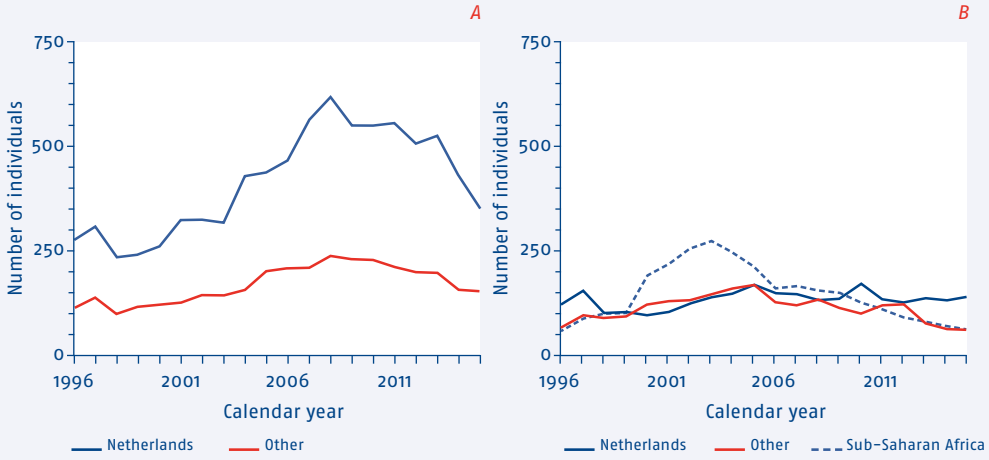
Legend: MSM=men who have sex with men; CHS=community health service; STI=sexually transmitted infection.

Geographical region of origin

In total, 71% of patients who acquired HIV via homosexual contact originated from the Netherlands, 11% from other European countries, 7% from South America, and 4% from the Caribbean (*Figure 1.5A*). In recent years, the proportion of MSM of Dutch origin was also 71% (*Appendix Table 1.2*), while minor changes were observed in the proportion of patients from western and central Europe.

Among women and other men, only 37% originated from the Netherlands, while 34% originated from sub-Saharan Africa, 9% from South America, 5% from the Caribbean, and 4% from South and Southeast Asia (*Figure 1.5B*). 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. From 2013 onwards, 49% of the diagnosed patients were of Dutch origin, and 26% originated from sub-Saharan Africa.

Figure 1.5: Annual number of diagnoses by region of origin among (A) men who have sex with men (MSM) and (B) other patients aged 18 years or older at the time of diagnosis. Of the 13,955 MSM, 9,874 (71%) originated from the Netherlands, 1,468 (11%) from other European countries, 926 (7%) from South America, and 497 (4%) from the Caribbean. Among the other 9,421 patients, 3,184 (34%) originated from sub-Saharan Africa, 3,476 (37%) from the Netherlands, 803 (9%) from South America, 433 (5%) from the Caribbean, and 382 (4%) from South and Southeast Asia. Note: data collection for 2014 and 2015 has not yet been finalised.

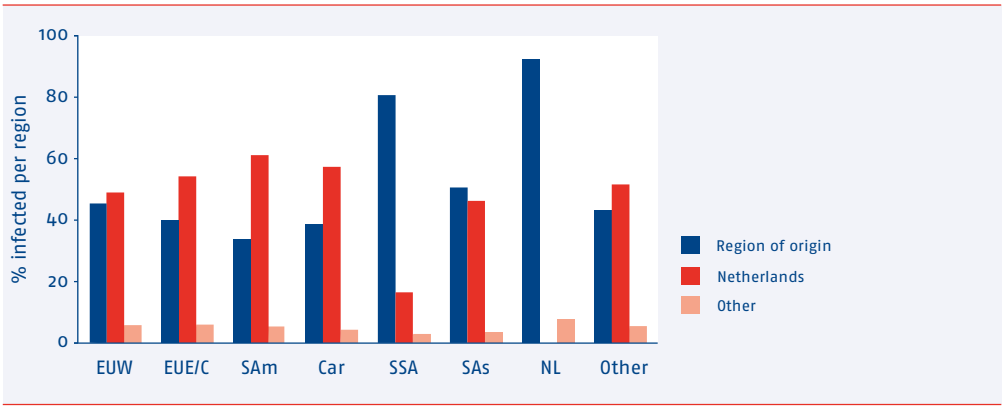


Overall, 22% of the patients newly diagnosed since 2013 were living in the Amsterdam CHS region and 13% in the Rotterdam CHS region. These proportions were 17% and 12%, respectively, for patients of Dutch origin and 30% and 15%, respectively, for patients originating from other countries. Among MSM, 24% were living in Amsterdam and 16% in Rotterdam, while in other groups these proportions were 16% and 12%. Other CHS regions with at least 4% of new diagnoses were Den Haag (5%), Hart voor Brabant (5%, including Den Bosch and Tilburg), and Gelderland-Midden (4%, including Arnhem).

Geographical region of infection

The most likely country where infection was presumably acquired was reported for 17,078 (73%) of the diagnosed adult population. The majority of the patients born in the Netherlands (92%) reported having been infected in the Netherlands (*Figure 1.6*). Most of the patients born in sub-Saharan Africa 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 Southeast Asia, were reported to have been infected in the Netherlands.

Figure 1.6: 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 Southeast 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. This proportion was compatible with the HIV-1 subtype of the HIV-positive patients. Overall, 93% of MSM 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 other 6,513 patients with a reported region of infection, 52% were infected in the Netherlands, while 29% reported having been infected in sub-Saharan Africa. Of the 1,678 Dutch men who reported a country of infection and were not infected via homosexual contact, 81% were infected in the Netherlands, 8% in South and Southeast Asia, and 7% in sub-Saharan Africa. Of the 1,044 Dutch women, 89% reported having been infected in the Netherlands and 6% in sub-Saharan Africa, whereas less than 1% were infected in South and Southeast Asia. Overall, 48% of the non-MSM 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 97%.

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 median age at the time of diagnosis was 35 (interquartile range [IQR] 30-44) years; in 2015, it was 39 (IQR 30-49) years. Over the entire period from

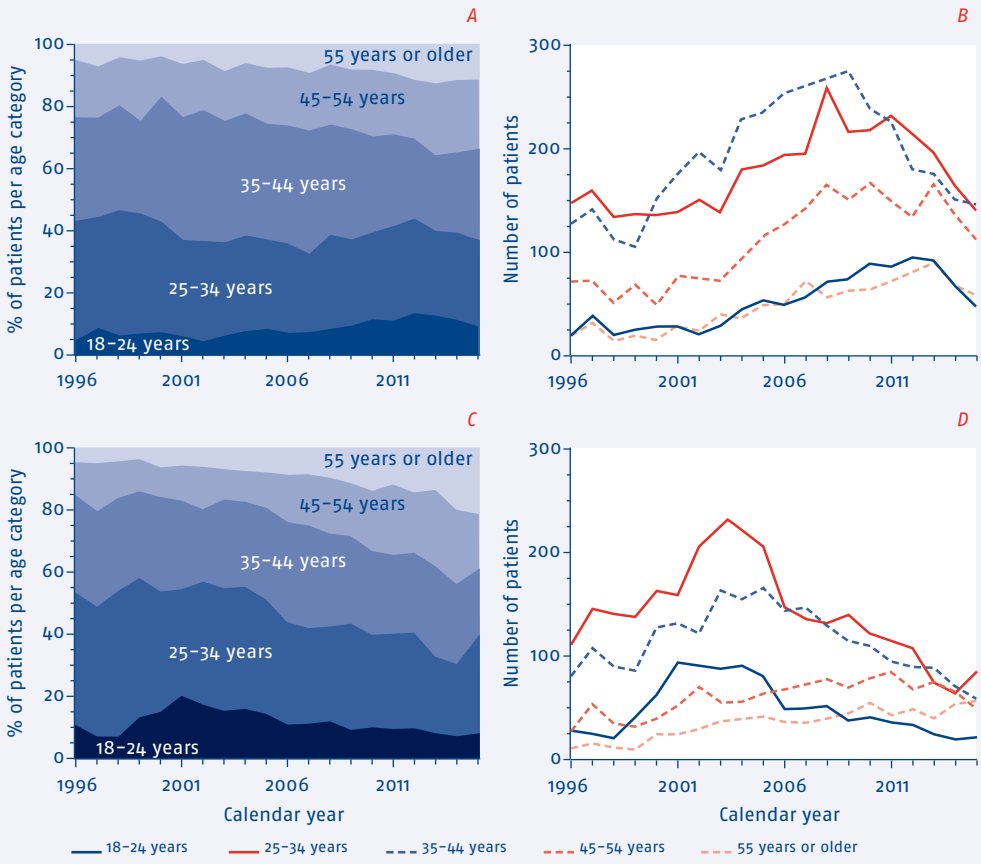
1996 through 2015, 15% of adults who received a diagnosis of HIV were 50 years or older; in 2015, 23% were 50 years or older. There were considerable age differences between MSM, other men and women diagnosed in 2013 or later. MSM born in the Netherlands were diagnosed at a median age of 42 (32-51) years, while those of foreign origin were diagnosed at 33 (27-42) years. Among other patients of Dutch origin, the median age at the time of diagnosis was 44 (29-55) years for women and 46 (37-56) years for men. Patients born in sub-Saharan Africa (women: 35 years; men: 39 years) or elsewhere (women: 37 years; men: 41 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 other patients there were no notable changes up to 2003 (*Figure 1.7*). Thereafter, the age of other patients at diagnosis started to increase concomitantly with the decreasing number of diagnoses among patients from sub-Saharan Africa, who were generally younger than individuals of Dutch or other origin.

Young adults

The number of diagnoses among young adults less than 25 years of age and not infected via homosexual contact was approximately 90 in the early 2000s and decreased to approximately 20 in 2015, or to 8% of the annual number of diagnoses (*Figure 1.7*). Among MSM, both the number and proportion of diagnoses among young adults increased over time and, in 2013, young adults accounted for 13% (92) of the diagnoses. Thereafter, the number of diagnoses in young adults decreased to approximately 60 in 2015, which is 11% of all MSM diagnosed in that year.

Figure 1.7: Age distribution at the time of diagnosis among HIV-1-positive (A, B) men who have sex with men (MSM) and (C, D) other men and women. Between 1996 and 2015, the proportion of MSM aged 45 years or older at the time of diagnosis increased from 24% to 34%, while these proportions were 15% and 39% for other patients. During the same period, the proportion of patients between 25 and 34 years of age decreased from 38% to 28% for MSM and from 43% to 31% for other patients.



Entry into care

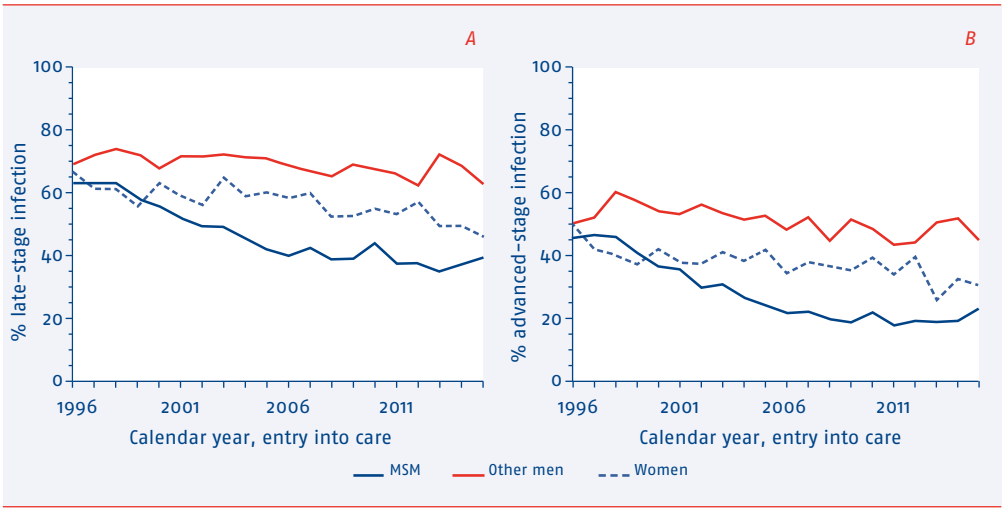
Of all patients diagnosed with HIV in 2008 or later for whom the location of testing was known, excluding those diagnosed abroad, 87% had entered into care within 4 weeks, and 93% within 6 weeks of receiving their diagnosis. Overall, 92% of patients who received their first HIV-positive test at a CHS or STI clinic were in care within 6 weeks, as were 94% of those who tested HIV-positive in a hospital, 92% of

those diagnosed at a general practice, and 88% of those diagnosed at other locations. Overall, the proportion in care within 6 weeks was similar for MSM (92%), other men (93%), and women (92%). For women and other men, the proportion in care within 6 weeks did not differ by age at the time of diagnosis. On the other hand, 93% of MSM diagnosed at 35 years of age or older were in care within 6 weeks, compared with only 87% 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[3]. Although the proportion of late presenters has decreased over time, in 2015, 45% of patients entered clinical care late in their infection (*Figure 1.8*; *Appendix Figure 1.1*). 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 29% in 2015.

Figure 1.8: *Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection at the time of entry into care. From 1996 (2013) onwards, 52% (44%) presented with late HIV disease: men who have sex with men (MSM) 44% (37%), other men 69% (67%), and women 57% (48%). Overall, 34% (27%) were advanced presenters: MSM 26% (20%), other men 51% (49%), and women 38% (30%). Late stage infection: CD4 counts below 350 cells/mm^3 or having AIDS, regardless of CD4 count. Advanced stage infection: CD4 counts below 200 cells/mm^3 or having AIDS.*



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

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 30% had CD4 counts below 200 cells/mm^3, while 16% had already been diagnosed with AIDS. For patients entering clinical care in recent years (2013 or later), these proportions were 35%, 21%, 19%, and 25%, respectively; 13% had already been diagnosed with AIDS.

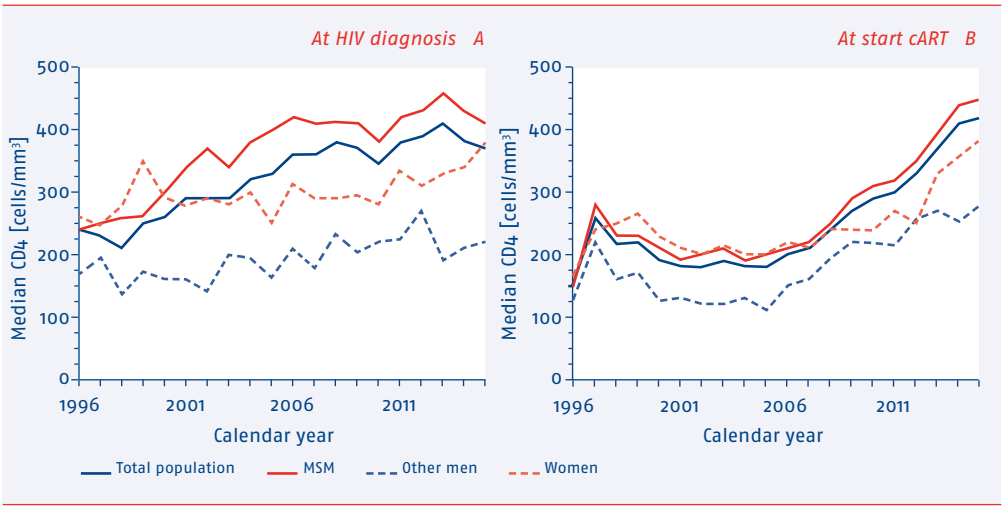
Among patients entering clinical care in 2013 or later, 37% of MSM, 67% of other men, and 48% of women presented with late-stage HIV infection. Patients of sub-Saharan African origin and not infected via homosexual contact were more likely to present with a late-stage infection (65%) compared with their peers of Dutch origin (55%). Late-stage infection at the time of entry into care was also often found in non-MSM patients originating from South America (63%) or from South and Southeast Asia (66%). In this latter group, 61% presented for care with advanced HIV infection, compared to 42% of South Americans, 39% of sub-Saharan Africans, and 40% of Dutch patients.

Late presentation was also more common in patients entering care at older ages. Late presentation was seen in 48% of MSM, 75% of other men, and 52% of women entering care in 2013 or later at 45 years of age or older, compared with 17% of MSM, 54% of other men, and 29% of women 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 (70%) compared with those who were tested at a general practice (42%), a CHS or STI clinic (25%), or another testing location (35%).

Increasing CD4 cell counts

Between 1996 and 2015, median CD4 counts in the total adult population at the time of diagnosis increased from 239 to 370 cells/mm^3 (*Figure 1.9A*). This overall increase was mainly the result of a rise in CD4 counts in MSM, whereas CD4 counts in women and in other men showed more modest increases.

Figure 1.9: *Changes over calendar time in median CD4 counts (A) at HIV diagnosis and (B) at the start of combination antiretroviral therapy (cART). Between 1996 and 2015, CD4 counts at the time of diagnosis increased from 239 (interquartile range [IQR], 80–419) to 370 (IQR 150–560) cells/mm³ in the total adult population. The increase was most apparent for men who have sex with men (MSM): 240 (IQR 80–420) cells/mm³ in 1996 and 410 (IQR 200–585) cells/mm³ in 2015. During the same period, CD4 counts in other men increased from 168 (IQR 40–400) to 220 (IQR 70–430) cells/mm³, whereas CD4 counts in women increased from 260 (IQR 94–450) to 380 (IQR 159–630) cells/mm³. (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 2015, CD4 counts were 420 (IQR 240–610) cells/mm³ in the total population, 450 (IQR 290–640) cells/mm³ in MSM, 280 (IQR 110–460) cells/mm³ in other men, and 385 (IQR 200–615) cells/mm³ in women.*



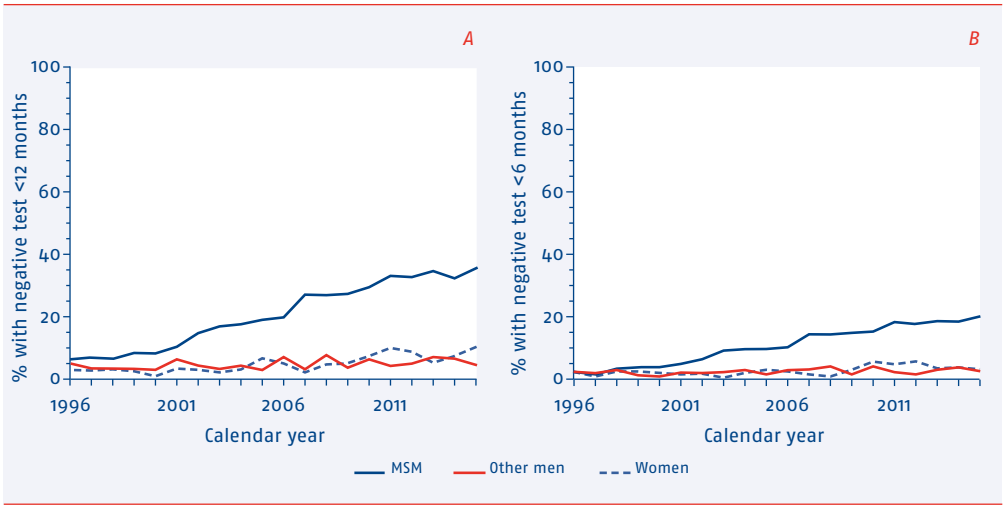
Legend: *MSM=men who have sex with men; cART=combination antiretroviral therapy.*

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/mm³ within only 1 year after seroconversion[4].

Another indication of earlier diagnosis is the increase in the proportion of patients who were diagnosed with strong evidence of a recent infection, because they had a known negative HIV test 6 or 12 months, at most, before their first positive test (*Figure 1.10*). Among MSM diagnosed in 2013 or later, 35% had a negative test in the 12 months before diagnosis, while 19% had a negative test in the 6 months before diagnosis. For other patients, these proportions were considerably lower: only 7% had a negative test in the 12 months before diagnosis, while 4% had a negative test in the 6 months before diagnosis; there has been no apparent improvement in these figures in the most recent calendar years.

Figure 1.10: *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. Altogether, 36% of men who have sex with men (MSM), 5% of other men, and 10% of women diagnosed in 2015 had a last negative test at most 12 months before diagnosis, whereas 20% of MSM, 3% of other men, and 3% of women had a last negative test at most 6 months before diagnosis.*



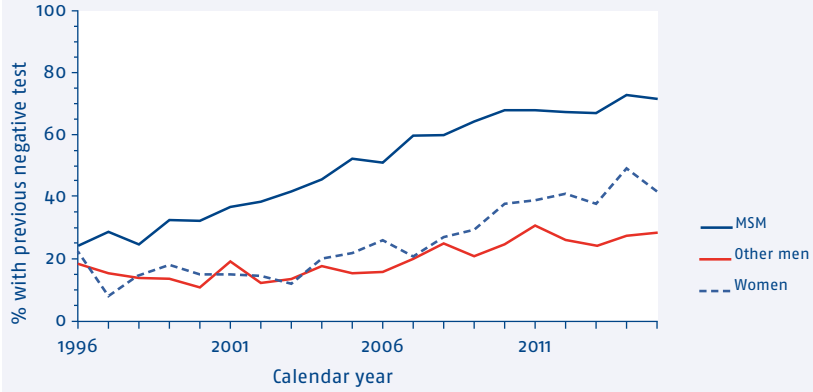
Legend: *MSM=men who have sex with men.*

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 (*Figure 1.11*). In 2015, 72% of MSM, 28% of other men, and 42% of women newly diagnosed with HIV had a known previous test with a negative result. The proportion with a previously known negative test

was highest among those diagnosed at a CHS or STI clinic (83%), compared with 34% of those diagnosed in a hospital, 63% of those tested at a general practice, and 54% of those diagnosed elsewhere.

Figure 1.11: *Proportion of patients diagnosed after a previously negative HIV test. Altogether, 72% of men who have sex with men (MSM), 28% of other men, and 42% of women diagnosed in 2015 had a previously negative HIV test.*



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

Treated population

Of the 23,376 adult patients ever registered with an HIV-1 infection, 21,629 (93%) patients had started cART by May 2016. The majority of these patients (88%) started cART while being antiretroviral therapy-naive. For the entire group of adults, the total follow-up time since start of cART was 182,500 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 1.9B*). In 2015, median CD4 counts at the start of treatment had increased to 420 cells/mm^3. Of those starting cART in 2015, 22% of patients started treatment at CD4 counts already below 200 cells/mm^3, 16% started at CD4 counts between 200 and 349 cells/mm^3, 25% started at CD4 counts between 350 and 499 cells/mm^3, and 37% 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 1.2*). The proportion of patients who started treatment within 6 months was smaller for those with higher CD4 counts, but has rapidly increased in recent years, reflecting changes in treatment guidelines towards starting treatment at higher CD4 counts. In 2015, for all CD4 strata, 80% or more of patients who were diagnosed with HIV or who entered care in that year had started treatment within 6 months. The tendency to start treatment earlier after diagnosis is reflected in converging CD4 counts at the time of diagnosis and at start of cART (*Figure 1.13*).

Figure 1.12: *(A) Proportion of patients who started combination antiretroviral treatment (cART) within 6 months after HIV diagnosis by CD4 count at the time of diagnosis. (B) Proportion of patients who started cART within 6 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 6 months of follow up after diagnosis or entry into care. Of all patients diagnosed in 2015, 100% of those with CD4 counts below 200 cells/mm^3, 97% of those with CD4 counts between 200 and 349 cells/mm^3, 83% of those with CD4 counts between 350 and 499 cells/mm^3, and 81% of those with CD4 counts of 500 cells/mm^3 or above had started cART within 6 months of diagnosis. In patients who entered HIV care in 2015, 100% of those with CD4 counts below 200 cells/mm^3, 94% of those with CD4 counts between 200 and 349 cells/mm^3, 85% of those with CD4 counts between 350 and 499 cells/mm^3, and 85% of those with CD4 counts of 500 cells/mm^3 or above had started cART within 6 months of entry.*

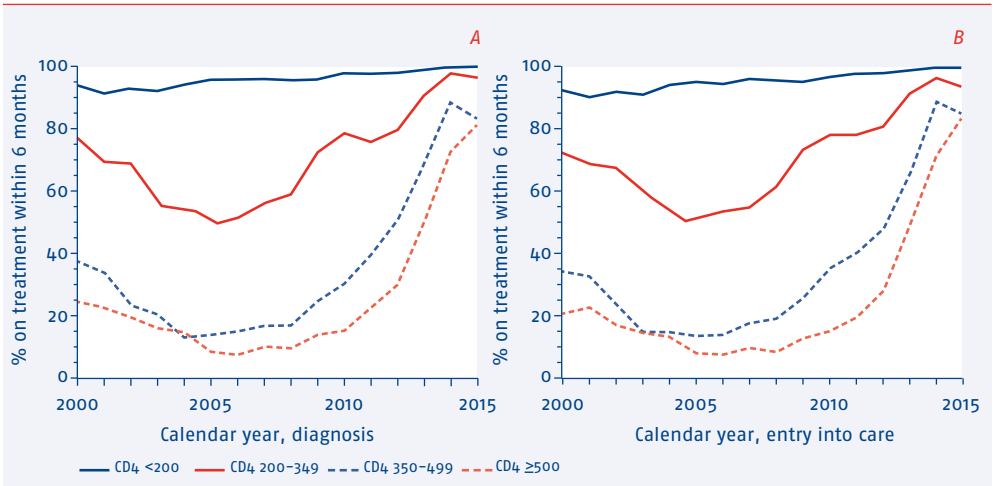
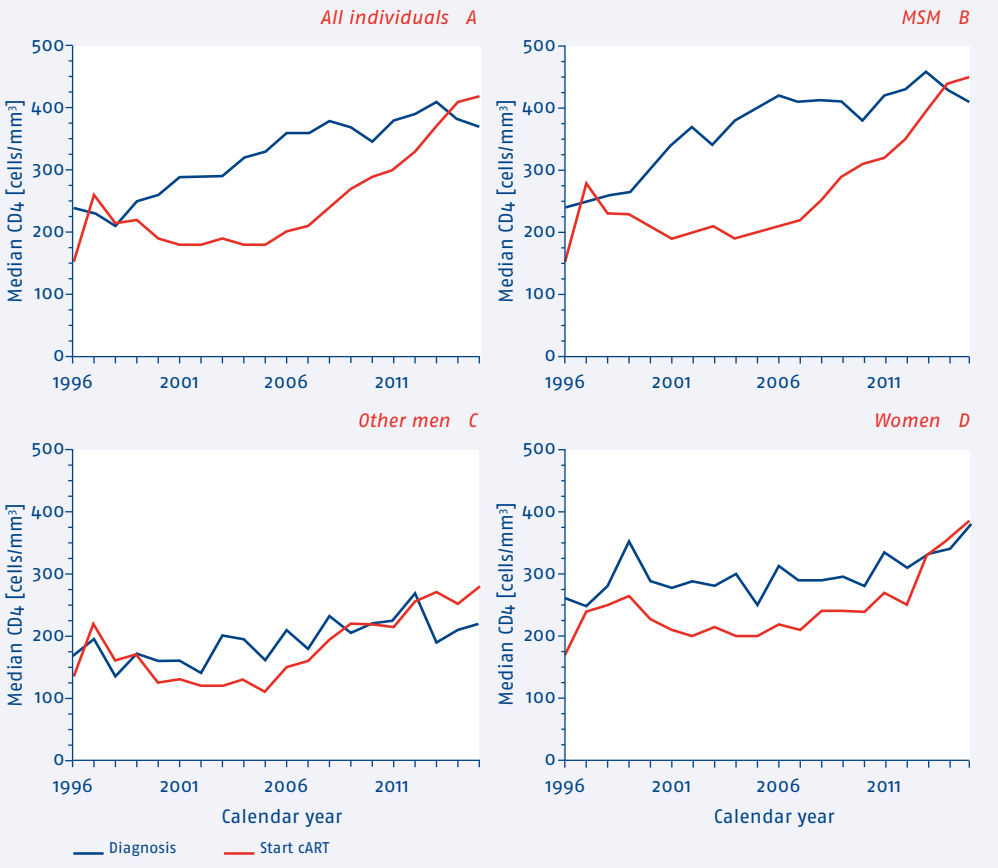


Figure 1.13: Changes over calendar time in median CD4 counts at HIV diagnosis and at the start of combination antiretroviral therapy (cART) for (A) all patients with an HIV-1 diagnosis, and for (B) men who have sex with men, (C) other men, and (D) women. The lines in each panel are a combination of Figures 1.9A and 1.9B.



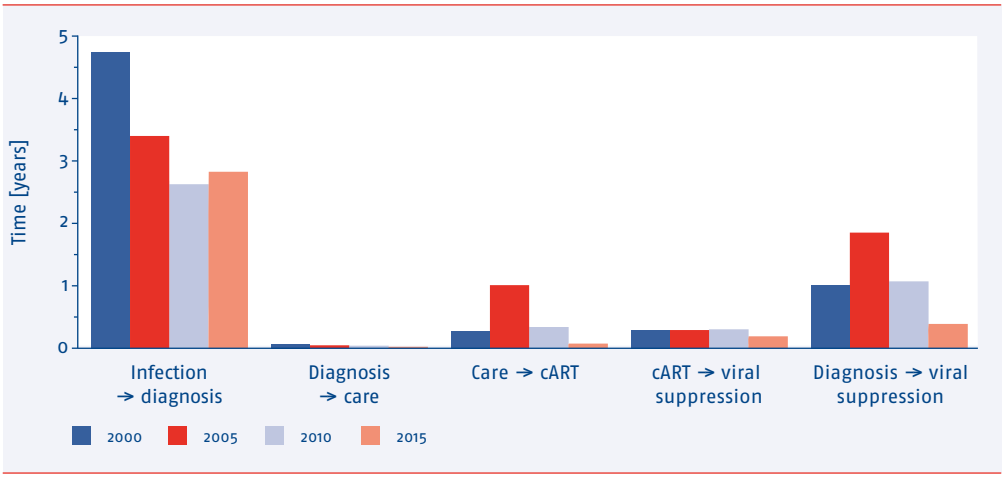
Legend: MSM=men who have sex with men; cART=combination antiretroviral therapy.

Time between HIV infection and viral suppression

Not only for people living with HIV, but also from a public health perspective, it is of paramount importance that the time between the moment a person is infected with HIV and the moment viral suppression is reached is minimised[5]. After all, people with a suppressed viral load have a near-zero probability of being able to transmit their virus to uninfected partners[6, 7]. To reach viral suppression, people with HIV must first be diagnosed, then linked to care, and subsequently start

treatment. Over time, significant improvements have been realised in most of these different steps in the HIV care continuum (*Figure 1.14*). Between 2000 and 2015, the median time from infection to diagnosis in the entire HIV-1-positive population was estimated to decrease from 4.7 (IQR 2.3-8.4) to 2.8 (1.3-5.1) years. During this same period, the median time from diagnosis to viral suppression decreased from 1.02 (IQR 0.44-4.27) years to 0.31 (0.17-0.50) years, mainly as a result of starting treatment earlier after entry into care.

Figure 1.14: *Estimated time to reach key stages in the HIV care continuum for HIV-1-positive patients, including time from infection to diagnosis, from diagnosis to entry into care, from entry into care to starting combination antiretroviral treatment (cART), from starting cART to reaching viral suppression (defined as an RNA measurement below 100 copies/ml), and from diagnosis to viral suppression.*



Legend: *cART=combination antiretroviral therapy.*

Population – HIV-2

HIV-2-positive individuals

In total, 97 of the 24,313 registered patients, including 45 men and 52 women, were infected with HIV-2. The majority (78, or 80%) of these patients were infected via heterosexual contact. HIV-2 is endemic in western Africa, and 63 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 reported to have acquired their HIV infection in the Netherlands. A total of 64 patients were still in clinical care, 15 patients had died, and 6 had moved abroad. The mean age of the patients still in care was 56 years, and 78% were 50 years or older.

The mean age at the time of diagnosis was 43 years, which was considerably higher than for HIV-1-positive patients. For the 81 patients who were diagnosed in 1996 or later, the median CD4 count at the time of diagnosis was 310 (90-681) cells/mm^3. From 1996 onwards, 47% of the patients were late presenters, and 38% presented for care with advanced HIV disease[3]. 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, 41% had CD4 counts of 500 cells/mm^3 or higher, while relatively few patients (22%) had CD4 counts between 200 and 499 cells/mm^3.

Treatment

By May 2016, 56 HIV-2-positive patients had ever started cART. Of the 37 of these patients who were still in care, 19 used a backbone of abacavir/lamivudine, 11 tenofovir/emtricitabine, and 2 zidovudine/lamivudine. Additional drugs in the regimen included ritonavir-boosted darunavir in 17 patients, ritonavir-boosted lopinavir in 8 patients, atazanavir in 4 patients (all ritonavir-boosted, except one), and dolutegravir in 4 patients.

At start of cART, 23 patients had HIV-2 RNA levels above 500 copies/ml, while 14 had levels below this threshold. Of the 64 patients who were still in care, 48 had a most recent viral load measurement below 500 copies/ml, 2 had a viral load above 500 copies/ml, and for 14 patients no HIV-2 RNA result was available. In total, 25 patients had not, or not yet, started treatment. These patients still had high CD4 counts (median 770 (550-950) cells/mm^3), and only one had an HIV-2 viral load above 500 copies/ml (9 not determined).

Table 1.1: Characteristics of the 18,866 HIV-positive patients in clinical care as of May 2016. An extended version of this table is available in appendix to this report (Appendix Table 1.3).

	Men (n=15,275, 81%)		Women (n=3,591, 19%)		Total (n=18,866)	
	n	%	n	%	n	%
Transmission						
MSM	11,616	76	-	-	11,616	62
Heterosexual	2,392	16	3,117	87	5,509	29
IDU	231	2	92	3	323	2
Blood or blood products	144	1	95	3	239	1
Other/unknown	892	6	287	8	1,179	6
Current age (years)						
0-12	56	0	77	2	133	1
13-17	47	0	29	1	76	0
18-24	261	2	85	2	346	2
25-34	1,706	11	583	16	2,289	12
35-44	3,317	22	1,113	31	4,430	23
45-54	5,364	35	1,035	29	6,399	34
55-64	3,161	21	476	13	3,637	19
65-74	1,179	8	155	4	1,334	7
≥75	184	1	38	1	222	1
Region of origin						
The Netherlands	10,271	67	1,084	30	11,355	60
Sub-Saharan Africa	1,088	7	1,479	41	2,567	14
Western Europe	868	6	132	4	1,000	5
South America	981	6	321	9	1,302	7
Caribbean	601	4	171	5	772	4
Other	1,408	9	394	11	1,802	10
Unknown	58	0	10	0	68	0
Years aware of HIV infection						
<1	531	3	104	3	635	3
1-2	1,514	10	230	6	1,744	9
3-4	1,716	11	291	8	2,007	11
5-9	4,303	28	867	24	5,170	27
10-19	5,200	34	1,649	46	6,849	36
≥20	1,893	12	420	12	2,313	12
Unknown	118	1	30	1	148	1

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

Population in care

Patients in clinical care

In total, 18,866 (78%) of the 24,313 registered patients, comprising 18,657 adults and 209 minors less than 18 years of age, were still under clinical observation (*Figure 1.1*; *Table 1.1*; *Appendix Table 1.3*) as of May 2016. Of the 5,447 patients who were no longer in clinical care, 2,589 (48%) were known to have died, and 1,392 (26%) to have moved abroad. Patients were considered to be in clinical care if data were available in 2015 or 2016 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.

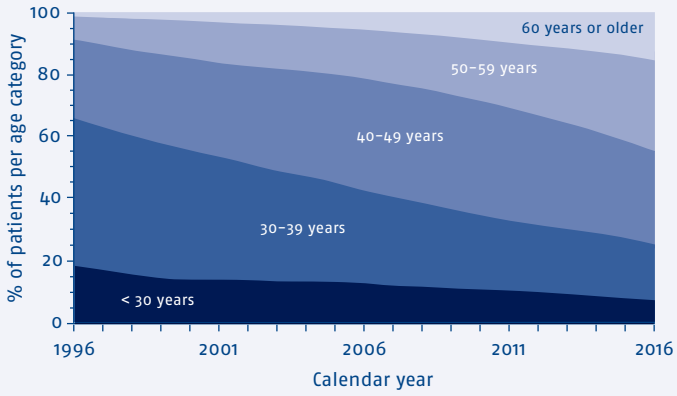
Retention in care

Of the 12,119 patients who enrolled in HIV care between 2005 and 2014, 613, or 5%, were lost to care before 2015 and were not reported as having died or moved abroad. Retention in care was highest for patients of Dutch origin: 96% were estimated to be still in care after 10 years. Of the patients of sub-Saharan African origin, 74% of men and 83% of women were still in care after 10 years, as were 86% of men and 86% of women originating from other regions. Retention in care improved with increasing age at the time of entry into care: for every additional 5 years of age at the time of entry, patients were 9% less likely to be lost to care.

Ageing population

The median age of the population in clinical care currently stands at 48 (IQR 40-56) and has been increasing since 1996 (*Figure 1.15*). This increase in age is mainly a result of the improved life expectancy of HIV-positive patients after the introduction of cART. In addition, patients are being diagnosed at increasingly older ages, as has been discussed earlier in this chapter. As a result, more than two out of five patients currently in care (45%) are 50 years or older, including 48% of men and 31% of women; 15% of the patients are 60 years or older (*Appendix Table 1.3*). As the HIV-positive population continues to age, it is to be expected that the number of patients with age-related comorbidities will increase in the coming years, thereby complicating the management of their HIV infection (see Chapter 3).

Figure 1.15: 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 2016, these proportions were 7% and 45%, respectively, while 15% 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 2016 were diagnosed with HIV 11.2 years ago. Thus, a large group (49%) of those in care have 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 10.7 years for men who have sex with men (MSM), 11.3 years for other men, and 11.8 years for women. The majority of injecting drug users (89%) 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, 95% of the patients in care were being treated with cART, compared with 93% in last year's report[8]. The most frequently-prescribed currently-used regimens, which accounted for 69% of all treatment combinations, were a combination of tenofovir/emtricitabine and either efavirenz (18%), nevirapine (12%), rilpivirine (10%), ritonavir-boosted darunavir (8%), cobicistat-boosted elvitegravir (7%), or ritonavir-boosted atazanavir (5%), and a combination of abacavir, lamivudine, and dolutegravir (9%). A backbone of tenofovir/emtricitabine was used by 69% of the patients, while abacavir/lamivudine was used by 20% and zidovudine/lamivudine by 3%. Additional drugs in the regimen included

efavirenz, used by 20% of the patients, nevirapine (19%), darunavir (16%), dolutegravir (15%), rilpivirine (10%), atazanavir (8%), and elvitegravir (7%). The majority of patients, 87%, used a once-daily regimen. Antiretroviral treatment is discussed in more detail in Chapter 2.

Clinical condition

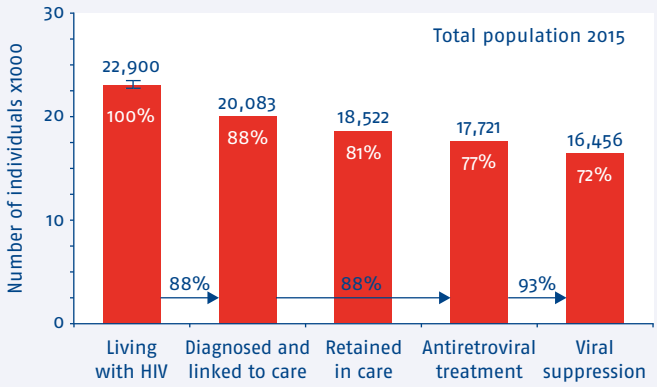
The median current CD4 count of the patients in care was relatively high at 640 (IQR 470-830) cells/mm^3, partly as a result of treatment and partly as a result of earlier diagnosis, as reported earlier in this chapter. CD4 counts were similar between MSM and women, but men who acquired their infection via other modes of transmission had lower CD4 counts (*Appendix Table 1.3*). For all patients in care, the most recent viral load measurement was below 500 copies/ml for 91% and below 100 copies/ml for 89%. About one-fifth (21%) 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

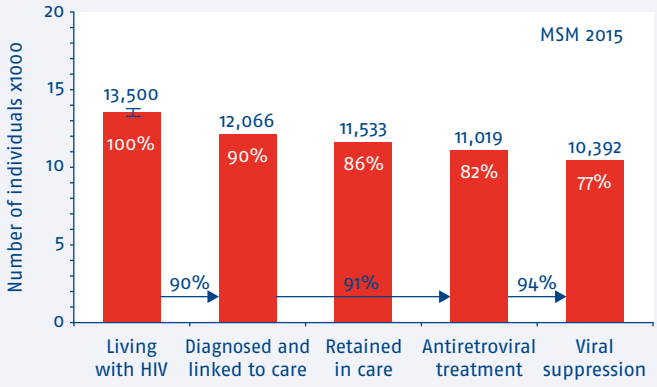
The total number of people living with HIV by the end of 2015, including those not yet diagnosed, was estimated at 22,900 (95% CI 22,300-23,500), of whom 2,800 (2,200-3,400) were still undiagnosed[(2)]. In total, 20,083 patients, or 88% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM, while 18,522 patients were considered to be retained in care (i.e., they had had at least one HIV RNA or CD4 count measurement or a clinic visit in 2015) (*Figure 1.16A*). The majority of these patients (17,721 in total) had started cART, and 16,456 had a most recent HIV RNA measurement below 100 copies/ml, irrespective of treatment. Overall, 72% of the total estimated population living with HIV and 82% of those diagnosed and ever linked to care had a suppressed viral load.

The number of MSM living with HIV was estimated to be 13,500 (13,200-14,100), of whom 1,400 (1,100-2,000) were still undiagnosed. Of these MSM, 12,066 (90%) had been diagnosed and linked to care, 11,533 (86%) were still in care, 11,019 (82%) had started cART, and 10,392 (77%) had a most recent HIV RNA below 100 copies/ml (*Figure 1.16B*).

Figure 1.16: Continuum of HIV care for (A, C) the total estimated HIV-positive population and for (B, D) men who have sex with men estimated to be living with HIV in the Netherlands by the end of 2015 and by the end of 2014. Percentages at the top of the bars are calculated relative to the number living with HIV, while percentages at the bottom correspond to UNAIDS' 90-90-90 targets. Numbers were adjusted for a backlog in registration of HIV cases (3% in 2014, 11% in 2015).



A



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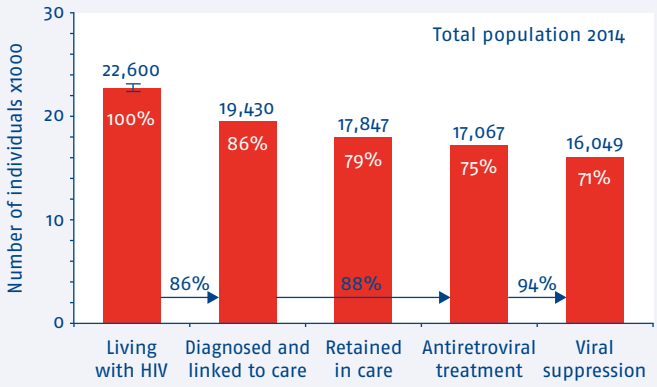

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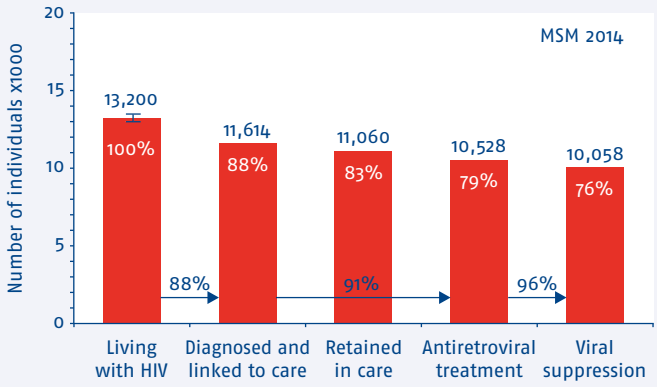

D

We also re-estimated the continuum of HIV care for 2014 and found that, by the end of that year, 22,600 (22,200-23,200) people were living with HIV in the Netherlands compared to the estimated 22,100 (21,700-22,800) reported in last year's Monitoring Report[8]. The estimate for 2014 is higher in this year's report due to small changes in the number of HIV infections (*Figure 1.3A*). While the number diagnosed and the number retained in care were very similar to last year's report, the number of those who started cART (17,067 compared to 16,821 last year) and the number with viral suppression (16,049 compared to 15,463) were considerably higher in this year's report. Apparently, there was some degree of backlog in collecting information on start of treatment and on viral load measurements in last year's report, which may also be present in the reported continuum of HIV care for 2015.

Conclusion

Since 2008 there has been a decrease in the annual number of new HIV diagnoses to approximately 900 new diagnoses in most recent years. This decreasing trend continued in 2015, although there is some uncertainty concerning the number of diagnoses in this year because data collection for 2015 has not yet been completed. The decrease in HIV diagnoses is mainly a consequence of a decrease in the estimated annual number of newly acquired HIV infections.

In addition, there were significant decreases in the time from infection to diagnosis and in the time to reaching other stages in the HIV care continuum. As a result, HIV-positive people are being diagnosed increasingly earlier in the course of their infection. Furthermore, a gradually decreasing proportion of patients are diagnosed with CD4 counts below 350 cells/mm^3. Conversely, the proportion diagnosed with evidence of a recent infection is increasing, although this is more evident among MSM than among other men and among women. In most recent calendar years, however, the downward trend in the proportion of MSM diagnosed with a late-stage or advanced-stage HIV infection appears to have halted.

In recent years, testing for HIV appears to have 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 a CHS or an STI clinic 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 presenters. These observations illustrate that patients tested at a CHS or STI clinic 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 HIV.

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 2015, more than 80% of patients diagnosed with CD4 cells above 500 cells/mm^3 were on cART within 6 months after entering HIV care. As a result, at least 89% of patients in care and 72% of the total estimated population of persons living with HIV in the Netherlands, including those not yet diagnosed, have a suppressed viral load.

Approximately 600 (5%) patients who enrolled in HIV care between 2005 and 2014 were lost to care before 2015. Retention in care is high for patients of Dutch origin, but appears worryingly low for foreign-born patients. Some of the patients who are lost to care may in fact have moved abroad and may now be in care elsewhere.

However, this cannot be confirmed as their medical data do not appear to have been transferred to a new hospital.

Recommendations

A re-assessment of the continuum of HIV care for 2014 showed that there was a significant increase in the number of people on cART by the end of that year compared to what was reported in last year's report. Moreover, there was an even more pronounced increase in the number who achieved viral suppression. To better monitor progress towards achieving UNAIDS' 90-90-90 goals, a more timely registration of start of treatment and viral load measurements would be needed. The latter could be markedly improved by extending the automated import of laboratory measurements to all HIV treatment centres in the Netherlands.

The decrease 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, treatment, and especially testing, need to be scaled up even further. A major step towards achieving this goal would be to reconsider the current restrictions on community-based and home-based HIV testing, as well as increasing awareness of sexual risk behaviour and extending the existing armoury of prevention measures with pre-exposure prophylaxis.

2. Response to combination antiretroviral therapy (cART)

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Introduction

Since the introduction of combination antiretroviral therapy (cART) in 1996, there have been substantial advances in the use of antiretroviral drugs for the treatment and prevention of HIV infection. The primary goal of cART is to prevent progression of HIV disease, improve clinical outcomes and limit transmission[9, 10]. The randomized clinical trials HPTN 052, Temprano ANRS 12136 and START showed that the best time to start cART is when CD4 cell counts are still above 500 CD4 cells/mm^3, reducing HIV-related and non-HIV related morbidity and mortality by as much as 44-57%[11, 12, 13]. These findings have resulted in global treatment guidelines recommending that all HIV-infected individuals who are willing and ready to start treatment should be given the option of starting cART immediately after diagnosis.

An additional benefit of treatment with cART is the prevention of onward HIV transmission. In studies in HIV-serodiscordant couples, both in heterosexual couples and in men who have sex with men (MSM), transmission has been shown to be more likely with higher HIV RNA levels[7, 14, 15, 16]. Moreover, a randomised controlled trial in HIV-serodiscordant couples in which the HIV-positive partner had a CD4 cell count between 350 and 500 cells/mm^3 confirmed that, besides preventing primary clinical events, AIDS and tuberculosis[13], the immediate start of cART is also more effective at preventing transmission of HIV than the deferment of treatment until the CD4 count has dropped to ≤250 cells/mm^3[6]. Thus, in addition to preventing disease progression in HIV-positive individuals, cART also benefits public health by preventing onward HIV transmission[7].

The guidelines by the U.S. Department of Health and Human Services (DHHS), European AIDS Clinical Society, International AIDS Society-USA and World Health Organization currently all recommend starting cART in all HIV-positive individuals, irrespective of CD4 cell count[17, 18, 19, 20]. The DHHS guidelines[19] are generally followed by the Dutch Association of HIV Treating Physicians (Nederlandse Vereniging van HIV Behandelaren, NVHB). Furthermore, cART regimens including an integrase strand transfer inhibitor (hereafter referred to as an integrase inhibitor, INSTI) as the third agent are preferred, along with the options of

< Back to page 42

ritonavir-boosted darunavir as a protease inhibitor (PI) and rilpivirine as a non-nucleoside reverse transcriptase inhibitor (NNRTI) option (the latter if viral load is <100,000 copies/ml and CD4 count >200 cells/mm^3), all in combination with a double nucleoside backbone (either tenofovir-emtricitabine or abacavir-lamivudine)[17]. Efavirenz is no longer recommended as preferred first-line cART[17, 19]. This chapter reports the impact of these guidelines on the prescription of antiretroviral drugs and their outcomes in the Netherlands.

Treatment with cART generally results in sustained suppression of HIV viral load to levels below the threshold of quantification and, as such, viral replication is suppressed in the overall majority of treated individuals. However, some studies of treatment intensification suggest that active replication persists in some infected individuals[21]. Furthermore, individuals may have difficulty maintaining optimal adherence to the treatment regimen, for example, because of drug-related toxicities, which can result in drug concentrations that may be too low to completely halt the replication of HIV and may therefore increase the risk of the selection of drug-resistant viral variants. Consequently, monitoring of longer-term virological response is important, particularly as viraemia has been associated with an impaired clinical outcome and smaller increases in CD4 cell count[22, 23, 24, 25, 26]. In addition, frequent or persistent periods of viraemia have been reported to be associated with the emergence of drug resistance and treatment failure[27, 28].

In this chapter we describe trends over time in the use of cART and in the virological and immunological responses to cART. New antiretroviral drugs, now widely available in the Netherlands, are assessed as well. We also look at the presence of HIV drug resistance in the total treated HIV-positive population followed by Stichting HIV Monitoring (SHM) and the extent to which resistant virus strains are transmitted to uninfected individuals. *Box 2.1* gives an overview of the number of individuals included in the various analyses described in this chapter.

Box 2.1: Outline of the ATHENA cohort in the Netherlands described in Chapter 2.

23,376 HIV-1 positive adults (aged ≥18 years at the time of diagnosis) are registered in the ATHENA cohort

Starting combination antiretroviral therapy (cART)
Of 21,377 individuals known to have initiated cART between January 1995 and December 2015*:
- 17,064 individuals were in care and had a clinical visit in 2015.

Changes in cART use 2010–2015
Of the 21,377 individuals known to have initiated cART between January 1995 and December 2015*:
- 7,503 initiated cART between January 2010 and December 2015.

Viral response
Of the 21,377 individuals known to have initiated cART between January 1995 and December 2015*:
- 17,174 individuals were ART-naive and had a sensitive viral load test result after ≥3 months of cART initiation,
  ➔ of those, 4,078 had initiated a cART regimen** since 2010.
- 13,621 individuals initiated cART between January 2010 and December 2015, were ART-naive and had a sensitive viral load test result after ≥3 months of cART initiation.

HIV drug resistance
Of the 24,313 HIV-1 and HIV-2 positive individuals from the ATHENA cohort:
- 18,866 individuals were in care by May 2016.

Immunological response
Of the 21,377 individuals known to have initiated cART between January 1995 and December 2015*;
- 20,342 had immunology data available after initiating cART.
- 17,747 were ART-naive at cART initiation and had immunology data available at, and after, initiating cART.
- 4,506 and 3,601 individuals were ART-naive, had CD4 count <350 cells/mm^3 at cART initiation, and had CD4 cell count data available after two and three years, respectively, of suppressive cART.

**Please note that while cART was formally introduced in the Netherlands mid-1996, some individuals were already using a combination of three antiretroviral drugs from two different antiretroviral drugs classes before that time. Therefore, a small number had already started cART in 1995.*

*** Most commonly used cART regimens at time of initiation included: tenofovir-emtricitabine combined with efavirenz, rilpivirine, ritonavir-boosted darunavir, ritonavir-boosted atazanavir, cobicistat-boosted elvitegravir, or dolutegravir; or abacavir-lamivudine combined with dolutegravir.*

***Legend:** ART=combination antiretroviral therapy; cART=combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drugs classes).*

Starting cART

Of the 23,376 HIV-1 positive individuals registered by SHM who were aged 18 years or older at the time of diagnosis, 21,377 were known to have initiated cART between January 1995 and December 2015 (*Box 2.1*). Of these, 2,600 (12.2%) had prior exposure to mono- or dual-antiretroviral therapy (ART) at the start of cART, and 18,777 (87.8%) were ART-naive. The number of pre-treated individuals initiating cART has decreased over time to approximately 1% in 2014-2015. We grouped individuals according to calendar year of starting cART (*Table 2.1*): 4,473 started between 1995 and the end of 1999, 4,035 started between 2000 and the end of 2004, 5,356 started between 2005 and the end of 2009, 6,713 started between 2010 and the end of 2014, and 800 started in 2015. Individuals starting cART in 2016 were not included in the current analysis because their follow up is currently too short to allow meaningful reporting of their virological and immunological response to cART.

Table 2.1: Characteristics of HIV-positive individuals starting combination antiretroviral therapy in 1995-2015.

Year of starting cART	1995-1999		2000-2004	
Total (n, %)	4,473	100.0	4,035	100.0
DEMOGRAPHIC CHARACTERISTICS				
Age at start of cART (median, IQR)	37	[33-45]	37	[31-44]
Male gender (n, %)	3,748	83.8	2,901	71.9
Transmission risk group (n, %)				
Men who have sex with men			1,822	45.2
Heterosexual contact	1,042	23.3	1,738	43.1
Injecting drug user	326	7.3	169	4.2
Blood or blood products	83	1.9	62	1.5
Other/unknown	221	4.9	244	6.1
Region of origin (n, %)				
The Netherlands	2,887	64.5	1,905	47.2
Western Europe/North America/Australia	543	12.1	312	7.7
Eastern/central Europe	54	1.2	81	2.0
South America and the Caribbean	397	8.9	495	12.3
Sub-Saharan Africa	399	8.9	1,010	25.0
Other*	193	4.3	232	5.8
Socio-economic status**				
1 Very wealthy	223	5.0	182	4.5
2 Wealthy	950	21.2	789	19.6
3 Average	1,033	23.1	1,119	27.7
4 Less-favoured	1,068	23.9	994	24.6
5 Deprived	667	14.9	809	20.1
Missing	532	11.9	142	3.5

	2005–2009		2010–2014		2015			All
	5,356	100.0	6,713	100.0	800	100.0	**21,377**	**100.0**
	40	[33–47]	40	[40–32]	39.18	[30–49]	**39**	**[32–47]**
	4,264	79.6	5,800	86.4	689	86.1	**17,402**	**81.4**
	3,102	57.9	4,627	68.9	542	67.8	**12,894**	**60.3**
	1,790	33.4	1,692	25.2	209	26.1	**6,471**	**30.3**
	111	2.1	49	0.7	4	0.5	**659**	**3.1**
	51	1.0	58	0.9	3	0.4	**257**	**1.2**
	302	5.6	283	4.2	42	5.3	**1,092**	**5.1**
	2,958	55.2	4,231	63.0	488	61.0	**12,469**	**58.3**
	409	7.6	396	5.9	45	5.6	**1,705**	**8.0**
	154	2.9	297	4.4	45	5.6	**631**	**3.0**
	646	12.1	736	11.0	92	11.5	**2,366**	**11.1**
	877	16.4	664	9.9	69	8.6	**3,019**	**14.1**
	312	5.8	389	5.8	61	7.6	**1,187**	**5.6**
	251	4.7	346	5.2	32	4.0	**1,034**	**4.8**
	1,171	21.9	1,432	21.3	167	20.9	**4,509**	**21.1**
	1,529	28.6	1,976	29.4	230	28.8	**5,887**	**27.5**
	1,324	24.7	1,578	23.5	201	25.1	**5,165**	**24.2**
	956	17.9	1,229	18.3	159	19.9	**3,820**	**17.9**
	125	2.3	152	2.3	11	1.4	**962**	**4.5**

Table 2.1: Continued.

Year of starting cART	1995–1999		2000–2004	
CLINICAL CHARACTERISTICS				
CD4 cell count at start of cART (median cells/mm^3, IQR)	200	[80–340]	180	[73–300]
HIV RNA at start cART (median $\log_{10}$, IQR)	4.8	[4.0–5.3]	5.0	[4.5–5.4]
AIDS diagnosis at start of cART (n, %)	1,043	23.3	991	24.6
Hepatitis B status at start of cART (n, %)				
Hepatitis B –	3,955	88.4	3,635	90.1
Hepatitis B+	293	6.6	238	5.9
Unknown	225	5.0	162	4.0
Hepatitis C status at start of cART (n, %)				
Hepatitis C –	3,917	87.6	3,607	89.4
Hepatitis RNA+	50	1.1	94	2.3
Hepatitis C antibody +	108	2.4	79	2.0
Unknown	398	8.9	255	6.3
ART-naive at start cART	2,425	54.2	3,696	91.6
cART started during pregnancy	37	0.8	276	6.8
cART started during recent infection	170	6.0	191	6.7

**The 61 individuals from other regions of origin who started in 2015 were from Southeast Asia (n=25), North Africa and the Middle East (n=22), and Oceania and the Pacific (n=8), while the region of origin was unknown for 6 individuals.*

***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. Source: Sociaal Cultureel Planbureau [29].*

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

2005-2009		2010-2014		2015		All	
230	[120-302]	330	[210-452]	420	[240-610]	**250**	**[120-380]**
5.0	[4.5-5.4]	4.9	[4.3-5.4]	4.7	[4.2-5.4]	**4.9**	**[4.3-5.3]**
1,048	19.6	882	13.1	92	11.5	**4,056**	**19.0**
4,894	91.4	6,199	92.3	725	90.6	**19,408**	**90.8**
315	5.9	249	3.7	23	2.9	**1,118**	**5.2**
147	2.7	265	4.0	52	6.5	**851**	**4.0**
4,989	93.2	6,299	93.8	741	92.6	**19,553**	**91.5**
125	2.3	120	1.8	11	1.4	**400**	**1.9**
40	0.8	38	0.6	4	0.5	**269**	**1.3**
202	3.8	256	3.8	44	5.5	**1,155**	**5.4**
5,228	97.6	6,635	98.8	793	99.1	**18,777**	**87.8**
259	4.8	93	1.4	6	0.8	**671**	**3.1**
638	14.4	1,446	23.5	211	27.0	**2,656**	**15.6**

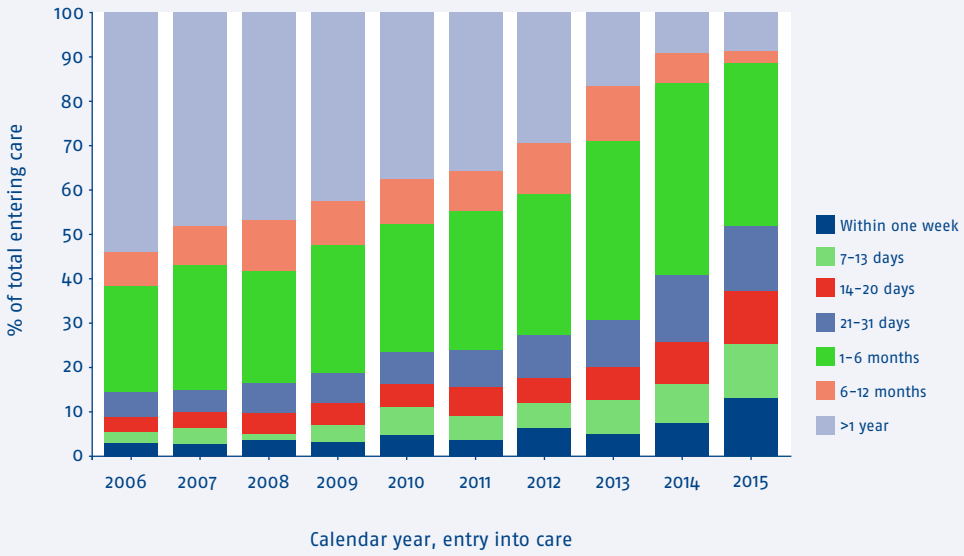
Of the 21,377 individuals who initiated cART since January 1995, 17,402 were men (81.4%), of whom 12,894 (74.1%) were MSM. Overall, 12,469 (58.3%) originated from the Netherlands. Although the proportion of individuals from the Netherlands was stable over time, the distribution with respect to region of origin for non-Dutch individuals changed over time. During the past 20 years, there was a slight increase in individuals from eastern and central Europe. In the period 1995-1999, 1.2% originated from eastern and central Europe compared to 5.6% in 2015. Simultaneously, the number of individuals from western Europe/North America/ Australia decreased from 12.1% in 1995-1999 to 5.6% in 2015.

As described in Chapter 1, prompt initiation of cART following an HIV-positive diagnosis has increased over time, reflecting implementation of HIV treatment guidelines (*Figure 2.1*). Among individuals with a known date of HIV diagnosis who started cART in the Netherlands, the median time between an HIV-positive diagnosis and cART initiation dropped from 154 days (interquartile range [IQR] 34-725) for those who entered care in 2010 to 123 days (IQR 34-630) in 2011; the

median time then dropped to 91 days (IQR 29-445) in 2012, 60 days (IQR 26-228) in 2013 and 39 days (IQR 21-85) in 2014. In 2015, most individuals entering care and initiating cART did so within a month after diagnosis (median 30 days, IQR 14-59). Likewise, the time between entering care and starting cART decreased over time. Of all participants initiating cART in 2015, less than 1% spent more than 6 months in care before starting cART (*Appendix Figure 2.1*). Moreover, the percentage of individuals with an AIDS diagnosis at the start of cART has also declined over time. Increasing numbers of individuals starting cART did so within 12 months of the last negative HIV test. This trend was accompanied by an increase in the median CD4 cell count at the start of cART, rising from 230 cells/mm^3 (IQR 120-302) in 2005-2009 to 330 cells/mm^3 (IQR 210-452) in 2010-2014 to 420 cells/mm^3 (IQR 240-610) in 2015 (p for trend <.0001). Finally, the prevalence of positive serology for hepatitis B virus (HBV) at the time of cART initiation has declined over time to 3% in 2015.

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.

Figure 2.1: *Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) from 2006-2015*.*



**The time between entry into HIV care and initiation of cART therapy can be found in Appendix Figure 2.1.*
Legend: *cART=combination antiretroviral therapy.*

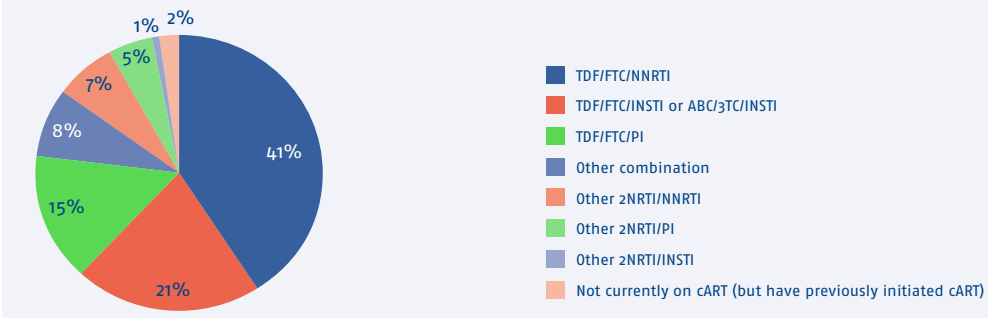
In care in 2015

Of the 21,377 HIV-positive individuals who were known to have initiated cART between January 1995 and December 2015, 17,064 were alive, in care and had a clinical visit in the Netherlands in 2015. *Table 2.2* shows their treatment and clinical characteristics in 2015. Overall, 81.9% were men, and 63.6% were MSM. The median age on 31 December 2015 was 49 (IQR 41-56) years. The majority (61.4%) originated from the Netherlands, followed by sub-Saharan Africa (12.5%) and South America and the Caribbean (11.0%).

Among those 17,064 individuals, the majority received a tenofovir-emtricitabine-based regimen (61.6%) combined with an NNRTI (40.7%), a PI (15.5%) or an INSTI (14.6%). The distribution of cART use is presented in *Figure 2.2*. Overall, and irrespective of the other regimen components, INSTI-based cART was used by 27.2% of those in care in 2015; 14.2% received dolutegravir, 6.9% cobicistat-boosted elvitegravir and 6.1% raltegravir. Of those who started cART in 2015, 75.0% was prescribed an INSTI-based regimen: 54.9% was prescribed dolutegravir and 20.1% cobicistat-boosted elvitegravir. Most individuals who initiated cART in 2015 were prescribed abacavir-lamivudine combined with dolutegravir (39.6%). Additionally, 237 (1.6%) individuals who had previously initiated cART were no longer using any ART in 2015.

On the basis of the last available CD4 and CD8 cell count measurements in 2015, 71.6% had a CD4 cell count of 500 cells/mm^3 or higher, and 22.6% had a CD4:CD8 ratio of 1 or higher. Of all individuals in care with a plasma HIV RNA measurement in 2015, 83.6% had a viral load <50 copies/ml, and 96.0% had a viral load <200 copies/ml. Of those receiving cART with a plasma HIV RNA measurement in 2015, 84.3% had a viral load <50 copies/ml and 96.7% had a viral load <200 copies/ml.

Figure 2.2: *Combination antiretroviral therapy (cART) use in HIV-positive individuals on cART in the Netherlands in 2015.*



Legend: *3TC=lamivudine; ABC=abacavir; cART=combination antiretroviral therapy; FTC=emtricitabine; INSTI=integrase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; TDF=tenofovir disoproxil fumarate.*

Table 2.2: Characteristics of HIV-positive individuals in care in 2015.

Calendar year of cART initiation	1995-1999		2000-2004	
Total (n, %)	2,853	16.7	2,856	16.7
Men (n, %)	2,361	82.8	2,073	72.6
Age on 31 December 2015 (median years, IQR)	55	[50-61]	51	[45-57]
Transmission risk group (n, %)				
Men who have sex with men	1,856	65.1	1,447	50.7
Heterosexual contact	714	25.0	1,170	41.0
Injecting drug use	122	4.3	66	2.3
Blood or blood products	57	2.0	43	1.5
Other/unknown	104	3.7	130	4.6
Region of origin (n, %)				
The Netherlands	1,885	66.1	1,503	52.6
Western Europe/North America/Australia	289	10.1	168	5.9
Eastern/central Europe	35	1.2	56	2.0
South America and the Caribbean	265	9.3	348	12.2
Sub-Saharan Africa	247	8.7	610	21.4
Other	132	4.6	171	6.0
ART regimen				
Not on cART	22	0.8	54	1.9
TDF/FTC/EFV	256	9.0	471	16.5
TDF/FTC/NVP	522	18.3	458	16.0
TDF/FTC/RPV	109	3.8	184	6.4
TDF/FTC/DRV/r	182	6.4	191	6.7
TDF/FTC/ATV/r	120	4.2	136	4.8
TDF/FTC/LPV/r	23	0.8	35	1.2
TDF/FTV/EVG/c	50	1.8	95	3.3
TDF/FTC/DTG	65	2.3	70	2.5
TDF/FTC/RAL	57	2.0	48	1.7
ABC/3TC/DTG	113	4.0	208	7.3
Other:2NRTI+NNRTI	398	14.0	366	12.8
Other:2NRTI+PI	195	6.8	190	6.7
Other:2NRTI+INSTI	42	1.47	30	1.05
Other:NNRTI+INSTI	4	0.1	2	0.1
Other:PI+INSTI	44	1.5	40	1.4
Other:NRTI+PI+INSTI*	68	2.4	30	1.1
Other:NNRTI+PI+INSTI*	68	2.4	26	0.9
Other	515	18.1	222	7.8

2005–2009		2010–2014		2015		All (1995–2015)	
4,422	25.9	6,150	36.0	783	4.6	**17,064**	**100.0**
3,539	80.0	5,327	86.6	674	86.1	**13,974**	**81.9**
48	[42–55]	44	[36–52]	40	[31–50]	**49**	**[41–56]**
2,688	60.8	4,326	70.3	530	67.7	**10,847**	**63.6**
1,415	32.0	1,515	24.6	205	26.2	**5,019**	**29.4**
77	1.7	36	0.6	4	0.5	**305**	**1.8**
38	0.9	52	0.9	3	0.4	**193**	**1.1**
204	4.6	218	3.5	41	5.2	**697**	**4.1**
2,613	59.1	4,002	65.1	481	61.4	**10,484**	**61.4**
272	6.2	329	5.4	43	5.5	**1,101**	**6.5**
120	2.7	252	4.1	44	5.6	**507**	**3.0**
515	0.0	652	10.6	88	11.2	**1,868**	**11.0**
642	14.5	560	9.1	66	8.4	**2,125**	**12.5**
260	0.0	355	5.8	61	7.8	**979**	**5.7**
74	1.7	110	1.8	13	1.7	**273**	**1.6**
1,185	26.8	1,143	18.6	35	4.5	**3,090**	**18.1**
631	14.3	564	9.2	4	0.5	**2,179**	**12.8**
368	8.3	981	16.0	41	5.2	**1,683**	**9.9**
337	7.6	798	13.0	54	6.9	**1,562**	**9.2**
327	7.4	345	5.6	17	2.2	**945**	**5.5**
56	1.3	15	0.2	5	0.6	**134**	**0.8**
151	3.4	711	11.6	155	19.8	**1,162**	**6.8**
105	2.4	210	3.4	99	12.6	**549**	**3.2**
99	2.2	166	2.7	4	0.5	**374**	**2.2**
341	7.7	587	9.5	310	39.6	**1,559**	**9.1**
278	6.3	148	2.4	8	1.0	**1,198**	**7.0**
224	5.1	165	2.7	8	1.0	**782**	**4.6**
40	0.9	38	0.62	1	0.13	**151**	**0.9**
2.0	0.1	.	.	.	.	**8**	**0.1**
30.0	0.7	25	0.4	4	0.5	**143**	**0.8**
17.0	0.4	15	0.2	.	.	**130**	**0.8**
35.0	0.8	27	0.4	19	2.4	**175**	**1.0**
122.0	2.8	102	1.7	6	0.8	**967**	**5.7**

Table 2.2: Continued.

Calendar year of cART initiation	1995–1999		2000–2004	
Last CD4 count in 2015 (cells/mm^3)				
<50	3	0.1	8	0.4
50–199	50	2.2	43	1.9
200–349	183	8.0	178	7.7
350–499	357	15.7	400	17.3
500–749	808	35.5	842	36.5
≥750	878	38.5	839	36.3
Last CD4:CD8 ratio in 2015 (n, %)				
<0.50	477	24.1	398	20.1
≥0.50, <1.00	999	50.5	1,068	54.0
≥1.00	503	25.4	513	25.9
Last plasma HIV RNA in 2015 (n, %)				
Viral load <50 copies/ml	2,258	86.1	2,270	84.4
Viral load <200 ccopies/ml	2,573	98.1	2,602	96.7

**≥1 drug per class*

Legend: *3TC=lamivudine; cART= combination antiretroviral therapy; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; IQR=interquartile range; LPV=lopinavir; TDF=tenofovir; PI=protease inhibitor; RAL=raltegravir; RPV=rilpivirine; /r=ritonavir-boosted; NRTI=non-nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; INSTI=integrase inhibitor.*

	2005–2009		2010–2014		2015		All (1995–2015)	
	8	0.2	6	0.1	22	2.9	**47**	**0.3**
	66	1.8	128	2.5	75	9.9	**362**	**2.6**
	74	7.6	438	8.4	104	13.7	**1,177**	**8.3**
	660	18.3	894	17.2	127	16.8	**2,438**	**17.2**
	1,401	38.9	2,008	38.6	34	30.9	**5,293**	**37.4**
	1,197	33.2	1,723	33.2	196	25.9	**4,833**	**34.2**
	606	19.4	1,055	23.7	324	4.947.0	**2,860**	**23.5**
	1,784	57.2	2,462	55.4	258	39.4	**6,571**	**54.0**
	730	23.4	927	20.9	73	11.2	**2,746**	**22.6**
	3,549	85.0	4,942	84.7	427	56.5	**13,446**	**83.6**
	4,055	97.1	5,676	97.3	524	69.3	**15,430**	**96.0**

Changes in use of initial antiretroviral therapy 2010–2015

Data from recent clinical trials of new antiretroviral drugs, such as dolutegravir and cobicistat-boosted elvitegravir, have shown good outcomes in terms of viral suppression, convenience, tolerability and toxicity. Over the past years, these new antiretroviral drugs have been approved on the basis of proven clinical benefits over existing drugs for initial treatment regimens (*Box 2.2*). In this section, we evaluate the implementation following approval of these new drugs in the Netherlands.

***Box 2.2:** Approval dates in the Netherlands of new antiretroviral drugs.*

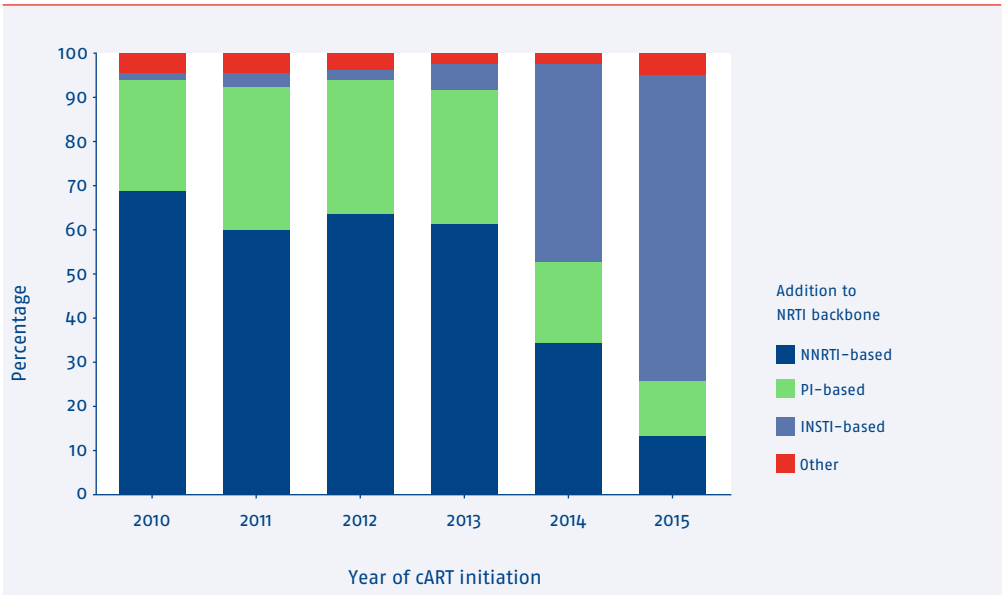
Medicine	Authorisation date
RPV and TDF/FTC/RPV (Eviplera®)	November 28, 2011
TDF/FTC/EVG/c (Stribild®)	May 24, 2013
DTG (Tivicay®)	January 16, 2014
ABC/3TC/DTG (Triumeq®)	September 1, 2014
TAF/FTC/EVG/c (Genvoya®)	November 19, 2015

***Legend:** 3TC=lamivudine; ABC=abacavir; DTG=dolutegravir; EVG/c=cobicistat-boosted elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine. Source: Medicines Evaluation Board [30].*

Initial regimen

Out of 21,377 HIV-positive individuals who were known to have initiated cART between January 1995 and December 2015, 7,503 (35.1%) initiated cART between January 2010 and December 2015. *Figure 2.3* shows the trends over time by drug class in third-drug additions to the nucleoside reverse transcriptase inhibitor (NRTI) backbone used as part of the initial cART regimen in these individuals. The use of INSTI with the NRTI backbone as initial therapy rose from 1.5% in 2010 to 5.9% in 2013, to 45.1% in 2014 and to 69.3% in 2015. The third-drug additions to the NRTI backbone as part of the initial cART regimen are specified by drug in *Figure 2.4A*. After its introduction in 2014, dolutegravir was prescribed as part of the initial regimen in 6.5% in 2014 and 48.9% in 2015. Cobicistat-boosted elvitegravir was introduced in the Netherlands at the end of 2013 and was used in 2.6%, 35.4% and 19.6% of the initial regimens in 2013, 2014 and 2015, respectively. With the introduction of cobicistat-boosted elvitegravir and dolutegravir, the use of NNRTIs in the initial regimen decreased from ≥60% in 2010-13 to 34.3% in 2014 and 13.5% in 2015. The use of PIs in the initial regimen decreased from 25-32% in 2010-13 to 18.2% in 2014 and 12.3% in 2015. Up to 5% received more than one addition to the NRTI backbone.

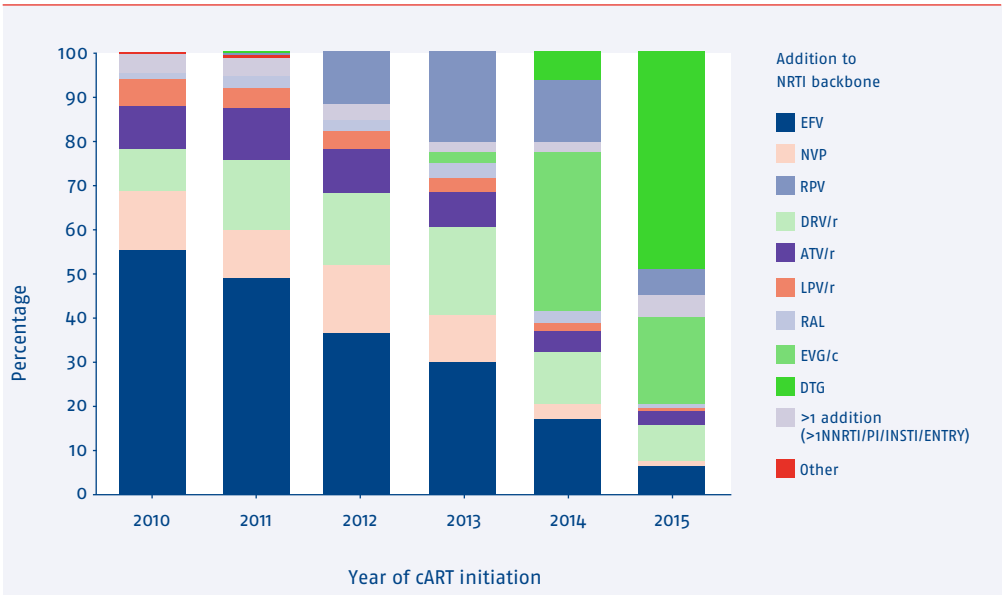
Figure 2.3: Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen.



Legend: cART=combination antiretroviral therapy; INSTI=integrase inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.

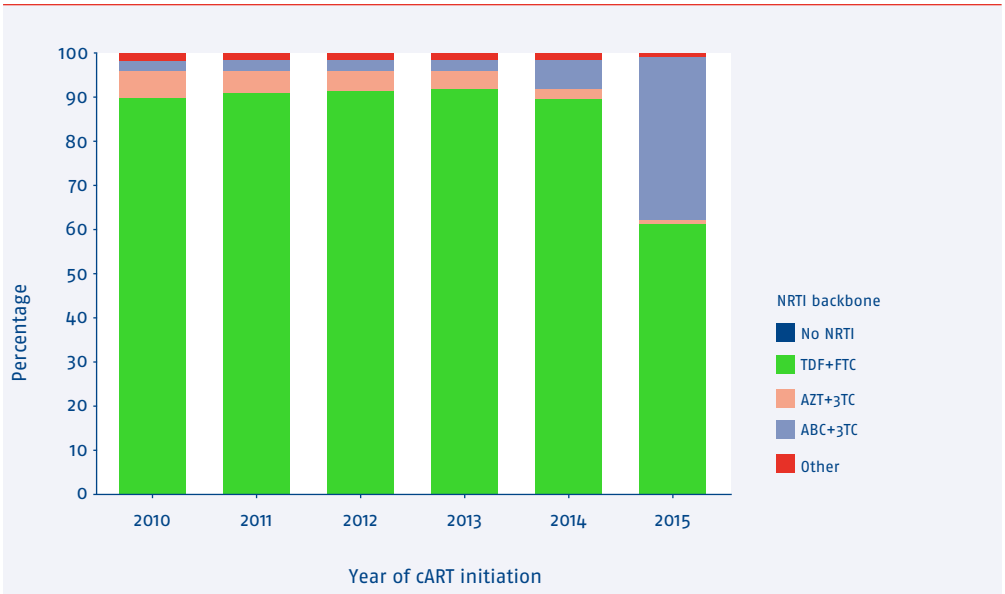
Figure 2.4B provides an overview of the initial components of the NRTI backbone used between 2010 and 2015. In 2015, the combination of tenofovir and emtricitabine was used in 61.3% (490 out of 800) initial cART regimens. The use of abacavir in combination with lamivudine, which was introduced as a once-daily fixed-dose combination with dolutegravir (Triumeq®) by the end of 2014, increased from 2-3% of all initial regimens in 2010-2013 to 9.7% in 2014 and 37% in 2015. The combination of zidovudine and lamivudine decreased over time from 6.4% in 2010, to 4.1% in 2013 and to 0.9% in 2015.

Figure 2.4A: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen



Legend: *cART=combination antiretroviral therapy; 3TC=lamivudine; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG/c=cobicistat-boosted elvitegravir; ENTRY=entry inhibitor; INSTI=integrase inhibitor; LPV=lopinavir; NRTI=nucleoside reverse transcriptase inhibitor; NVP=nevirapine; NNRTI=non-NRTI; PI=protease inhibitor; RAL=raltegravir; /r=ritonavir-boosted.*

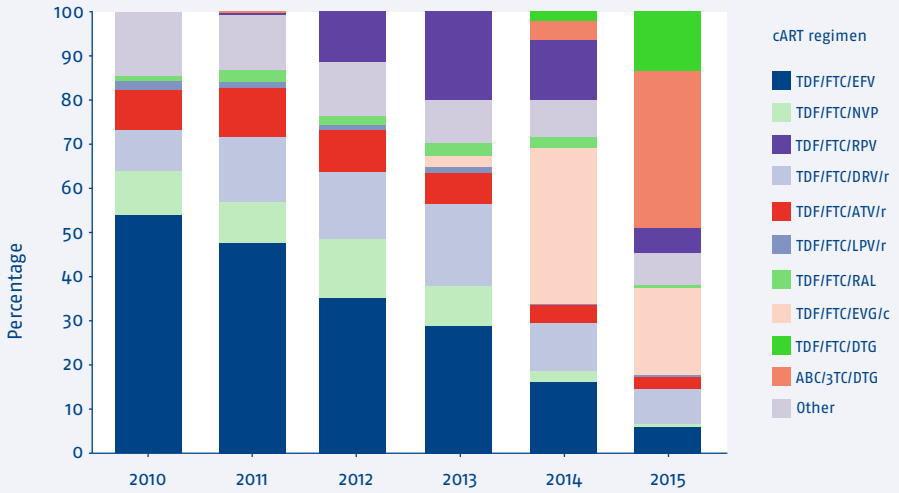
Figure 2.4B: Nucleoside reverse transcriptase backbone used as part of the initial regimen



Legend: cART=combination antiretroviral therapy; 3TC=lamivudine; ABC=abacavir; AZT=zidovudine; FTC=emtricitabine; NRTI=nucleoside reverse transcriptase inhibitor; TDF=tenofovir disoproxil fumarate.

The specific complete cART regimens initiated between 2010 and 2015 are shown in *Figure 2.5*. In 2015, most individuals (n=423; 52.9%) started a dolutegravir-based regimen. Dolutegravir was combined with abacavir and lamivudine as part of the once-daily fixed-dose combination (Triumeq®) for 288 individuals (36.0% of total/68.1% of dolutegravir users), and it was provided separately with tenofovir and emtricitabine (Truvada®) for 135 individuals (16.9% of total/31.9% of dolutegravir users). Next, the single-tablet regimen of tenofovir combined with emtricitabine and cobicistat-boosted elvitegravir (Stribild®) was prescribed for 160 (20.0%) of all individuals initiating cART in 2015, which was a reduction compared to 35.4% in 2014. This reduction is likely due to the introduction of the once-daily fixed-dose combination with dolutegravir (Triumeq®). Finally, the use of the integrase inhibitor raltegravir, not recommended in starting regimens because it needs to be taken twice daily, has decreased from <4% in 2011-2014 to <1% in 2015.

Figure 2.5: Initial combination antiretroviral therapy (cART) regimen.



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

Discontinuation of the initial regimen

Among the 21,377 individuals who ever started cART, we assessed the time spent on the initial cART regimen. Discontinuation of the initial cART regimen was defined as a change in, or stop of, ≥1 of the drugs of the regimen. Simplification to a fixed-drug combination pill with the same drugs was not considered discontinuation. For example, a switch from efavirenz with tenofovir-emtricitabine (Truvada®) to the fixed drug combination efavirenz-tenofovir-emtricitabine (Atripla®) was not considered discontinuation of the initial regimen, but a change from efavirenz-tenofovir-emtricitabine to cobicistat-boosted elvitegravir-tenofovir-emtricitabine was. One exception, however, was made for changes from dolutegravir combined with tenofovir-emtricitabine (Truvada®) to the fixed drug combination of dolutegravir-abacavir-lamivudine (Triumeq®) in cases where simplification was the only recorded reason for regimen change; for the purpose of our analysis, this was not considered to represent discontinuation of the initial regimen.

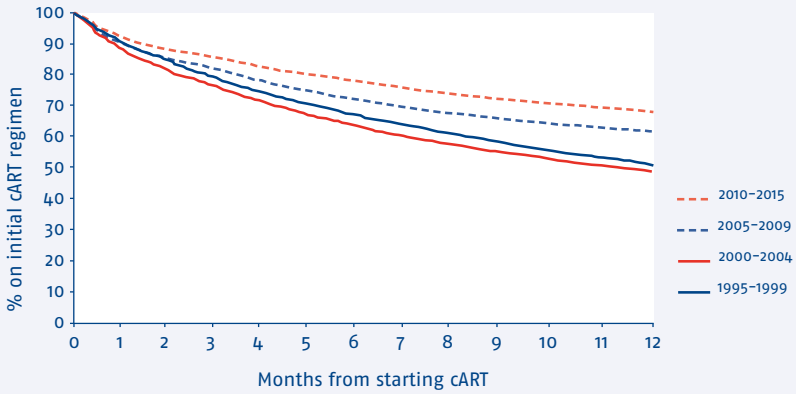
Overall, 16,021 out of 21,377 individuals had discontinued their initial regimen and 5,217 were still on their initial regimen; 139 had discontinued their initial regimen but without a recorded stop date. If the initial regimen was continued, time was censored at the date of last recorded contact with care. In total, 16,021 (75.4%) out of 21,238 individuals discontinued their initial regimen after a median of 10 (IQR 3-30) months. The time to discontinuation of the initial regimen during the first year of cART, stratified by cART era, is shown in *Figure 2.6*. Individuals who initiated cART in 2010-2015 were significantly less likely to discontinue their initial regimen than those who initiated cART in earlier years (log-rank test p<0.001).

We further assessed the discontinuation rates of the initial regimen during the first year of treatment among individuals who started one of preferred initial regimens in 2010 and beyond. Preferred regimens considered were tenofovir-emtricitabine combined with either efavirenz, rilpivirine, ritonavir-boosted darunavir, ritonavir-boosted atazanavir, cobicistat-boosted elvitegravir, or dolutegravir; or abacavir-lamivudine combined with dolutegravir. We included only individuals who were ART-naive, had been in follow up for at least 6 months after initiating cART and were not participating in the primo-SHM study. In total, 5,259 individuals fulfilled these criteria.

One year after cART initiation, 1,285 (24.4%) out of 5,259 individuals had discontinued their initial regimen (*Figure 2.7*). The main reason for regimen discontinuation was toxicity (n=758; 59.0%). Differences in treatment modification were found when comparing the third-drug component. The discontinuation rate due to toxicity was significantly higher for those initiating efavirenz-based cART compared with those initiating any of the other regimens (21 [95%CI 19.2-22.9] per 1,000 person years; p<0.001). In general, discontinuation due to toxicity was lowest in individuals on the cobicistat-boosted elvitegravir-based cART (incidence rate 5.6 [95%CI 4.0-7.8] per 1,000 person years) and rilpivirine-based cART (incidence rate 5.9 [95%CI 4.4-8.1] per 1,000 person years). While the discontinuation rate of dolutegravir-based cART was slightly higher (8.8 [95%CI 5.5-14.0] per 1,000 person years), there was no significant difference compared to cobicistat-boosted elvitegravir-based cART discontinuation; however, follow up time for these newer drugs currently remains relatively short.

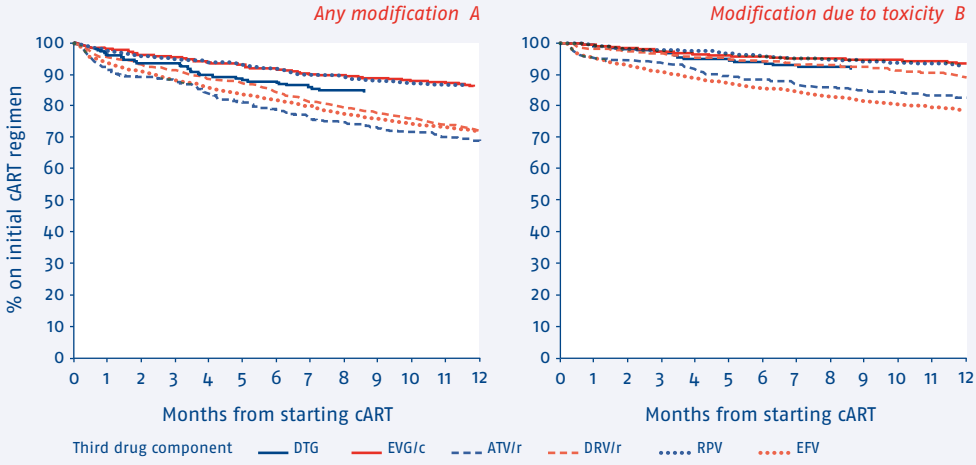
Among the 758 individuals who modified their initial cART regimen due to toxicity within a year, 1,065 adverse effects were recorded. The predominant effects recorded were: central nervous system effects (47.9%; mainly mood changes, insomnia, depression and dizziness), gastrointestinal effects (11.2%; mainly nausea and diarrhoea), rash (9.3%; due to medication) and hepatic effects (8.4%). These effects are stratified by cART regimen in *Figure 2.8*.

Figure 2.6: Kaplan-Meier estimate of time on initial combination antiretroviral therapy (cART) regimen, during the first year of treatment, by calendar year period of initiation (log-rank test p<0.001).



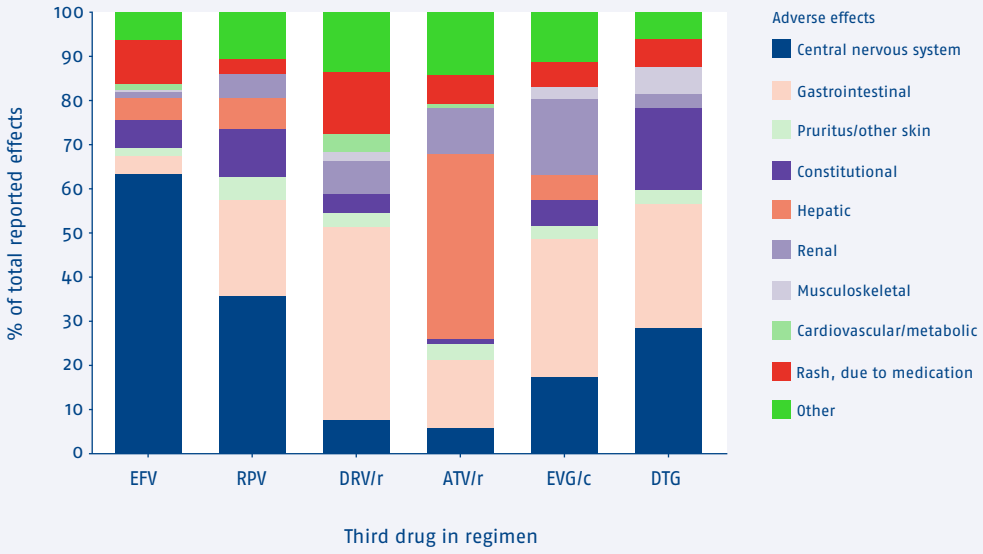
Legend: cART=combination antiretroviral therapy.

Figure 2.7: Kaplan-Meier estimate of time on initial regimen during the first year of treatment, by third-drug component, illustrating A) Any modification of the initial regimen, and B) Modification of the initial regimen due to toxicity.



Legend: cART=combination antiretroviral therapy; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG/c=cobicistat-boosted elvitegravir; RPV=rilpivirine; /r=ritonavir-boosted.

Figure 2.8: Adverse effects in 758 individuals discontinuing their initial regimen due to toxicity during the first year of cART, by third drug component.



Virological response

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 most assays have a lower detection limit of 20-50 HIV RNA copies/ml. The main definitions for HIV RNA outcomes used in this chapter are listed in *Box 2.3*.

In the Netherlands, a total of 21,377 individuals have started cART since January 1995. For the current analysis on virological outcomes, we will focus on the 18,777 (87.8%) ART-naive individuals starting cART. We also excluded 646 women who were pregnant at the time of cART initiation, because cART may have been interrupted at the end of the pregnancy. We used only viral load measures with a lower detection limit of ≤100 copies/ml, which have been gradually introduced into routine clinical practice since 1999. Subsequently, we excluded 462 individuals without any test result of viral load after at least 3 months of cART initiation. Results in the following section on viral response to cART are therefore restricted to the remaining 17,174 individuals.

Box 2.3: Definitions of HIV RNA outcomes.

Initial virological success
Viral load <100 copies/ml within 6 months (±3 months) after starting cART.

Viral suppression
Any viral load measurements <100 copies/ml, at least 3 months after cART initiation.

Viral rebound
First of two consecutive viral load measurements ≥200 copies/ml after 6 months (>180 days) of cART.

Sustained viral suppression
Initial virological success combined without any viral load >500 copies/ml thereafter.

Legend: cART=combination antiretroviral therapy.

Initial virological success

Out of 17,174 included individuals with a recorded sensitive viral load test result after at least 3 months of cART initiation, 14,727 (85.8%) had a viral load measurement 6 months after cART initiation. Of these 14,727 individuals, 12,529 (85.1%) achieved initial virological success, i.e., a plasma viral load <100 HIV RNA copies/ml (*Box 2.3*). The percentage of individuals with initial virological success has improved over time from 44.3% (95% confidence interval [CI] 41.3-47.3) in those starting cART between 1995 and 1999 to 83.2% (95% CI 81.8-84.6) in those starting between 2000 and 2004, 88.0% (95% CI 87.1-89.0) in those starting between 2005 and 2009, 90.6% (95% CI 89.9-91.4) in those starting between 2010 and 2014 and to 93.5% (95% CI 90.9-96.0) in those starting in 2015.

Initial virological success of initial regimen

We analysed the short-term virological efficacy of initial cART regimens in individuals who started cART in or after 2010. To compare the initial virological response between the starting regimens, we selected 5,094 (67.8%) of the 7,503 individuals described under 'Changes in use of initial antiretroviral therapy 2010-15' who were not participants in the primo-SHM study and had an HIV RNA test result available both at the start of cART and 6 months (±3 months) after the start of cART in 2010-2015. We further selected 4,078 participants who initiated cART based on tenofovir-emtricitabine combined with efavirenz (44%), rilpivirine (12%), ritonavir-boosted darunavir (19%), ritonavir-boosted atazanavir (9%), cobicistat-boosted elvitegravir (11%), or dolutegravir (1.5%), or abacavir-lamivudine combined with dolutegravir (4%).

We evaluated initial virological success rates by drug and drug class through logistic regression analysis (*Table 2.3*). Initial virological success was defined as an HIV RNA measurement <100 copies/ml within 6 (±3) months of cART (*Box 2.3*). The HIV RNA measurement closest to 6 months (±3) after cART initiation was included in the analysis, irrespective of the viral load of that measurement. In total, 91.9% (95% CI 91.1-92.8) showed initial virological suppression after a mean of 178 days (standard deviation [SD] 37) on cART. Overall, individuals on an INSTI-based regimen showed significantly higher rates of initial virological success; 96.0% (95% CI 94.5-97.5) of individuals on an INSTI-based regimen had initial virological success, compared to 88.3% (95% CI 86.4-90.2) on a PI-based regimen and 92.6% (95% CI 91.5-93.7) on an NNRTI-based regimen. The effect of cART regimen on the initial virological suppression rate was strongest in individuals with an HIV RNA load ≥100,000 copies/ml at cART initiation.

Table 2.3: Initial viral success rates (see definition in Box 2.3), by initial regimen. Patient characteristics, which can be associated with the initial prescribed regimen, were not taken into account in this analysis.

	Total n=4,078 (100%)	Viral load <100,000 at start n=2,374 (58.2%)			Viral load ≥100,000 at start n=1,704 (41.8%)		
	n (%)	Initial viral success %	95% CI	p-value	Initial viral success %	95% CI	p-value
Regimen							
TDF/FTC/EFV	1,795 (43.9)	95.9	94.7-97.2	reference	87.1	84.8-89.4	reference
TDF/FTC/RPV	472 (11.6)	95.5	93.6-97.4	0.52	not recommended		-
TDF/FTC/DRV/r	769 (18.9)	94.9	92.5-97.3	0.30	83.5	80.1-86.9	0.01*
TDF/FTC/ATV/r	376 (9.2)	93.0	89.3-96.7	0.04*	84.2	79.0-89.4	0.05*
TDF/FTC/EVG/c	448 (11.0)	96.7	94.8-98.7	0.62	93.6	89.6-97.7	0.11
TDF/FTC/DTG	763 (1.5)	97.2	91.9-100	0.71	88.9	77.0-100	0.90
ABC/3TC/DTG	159 (3.9)	98.1	95.4-100	0.27	96.4	91.4-100	0.07
Third drug in regimen							
EFV	1,795 (43.9)	95.9	94.7-97.2	reference	87.1	84.8-89.4	reference
RPV	472 (11.6)	95.5	93.6-97.4	0.66	not recommended		-
DRV/r	769 (18.9)	94.9	92.5-97.3	0.35	83.5	80.1-86.9	0.01*
ATV/r	376 (9.2)	93.0	92.5-97.3	0.04*	84.2	79.0-89.4	0.06
EVG/c	448 (11.0)	96.7	94.8-98.7	0.43	93.6	89.6-97.7	0.05
DTG	222 (5.4)	97.9	95.5-100	0.18	93.9	88.7-99.1	0.10
Regimen class							
NNRTI-based	2,263 (55.5)	95.8	94.8-96.8	reference	87.1	84.8-89.4	reference
PI-based	1,145 (28.1)	94.2	92.1-96.3	0.07	83.7	80.9-86.6	<0.01*
INSTI-based	670 (16.4)	97.1	95.5-98.7	0.03*	93.7	90.5-96.9	<0.01*
All regimens		**95.7**	**94.9-96.5**		**86.7**	**85.1-88.3**	

**p<0.05.*

Legend: *CI=confidence interval; ABC=abacavir; 3TC=lamivudine; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG/c=cobicistat-boosted elvitegravir; FTC=emtricitabine; INSTI=integrase strand transfer inhibitor; NNRTI=non-nucleoside reverse transcriptase inhibitor; TDF=tenofovir disoproxil fumarate; PI=protease inhibitor; RPV=rilpivirine; /r=ritonavir-boosted.*

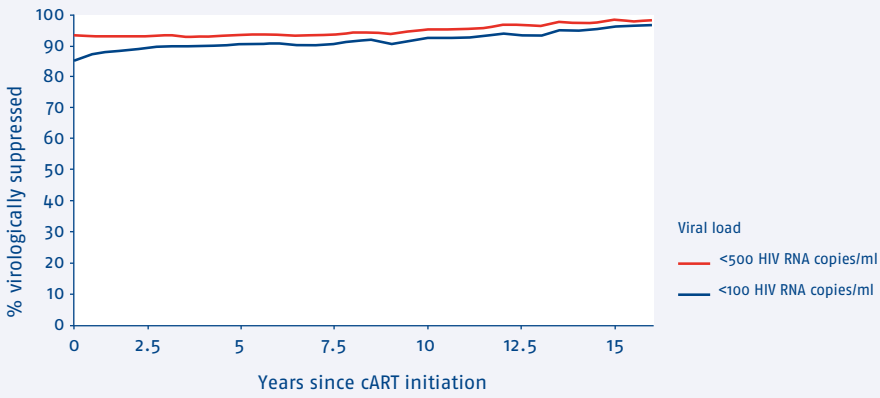
Viral suppression

Figure 2.9 shows the viral suppression rates over time on cART among 17,174 previously therapy-naive individuals in six-month intervals. The HIV RNA measurement closest to each six-month time point (±3 months) after cART initiation was included in the analysis, irrespective of the viral load of that measurement. Overall, the suppression rates increased over time on cART from 87.4% (95% CI 86.9-88.0) at one year after start of cART to >90% after four years

of use. In line with differences for the initial virological success rates, the long-term viral suppression rates vary when stratified by period of cART initiation.

Viral suppression rates have improved over time. In individuals initiating cART in or after 2010, suppression rates ranged from 94.2% (95% CI 93.6-94.8) after one year of cART to 96.6% (95% CI 95.7-97.4) after four years of use. It should be noted that, 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. Viral suppression over time in all cART eras is plotted in *Appendix Figures 2.2A-D*.

Figure 2.9: *Viral suppression after start of combination antiretroviral therapy (cART) in previously treatment-naive individuals*. In total, 17,174 previously therapy-naive individuals were included in this analysis; this number decreased over time due to differences in follow-up time.*



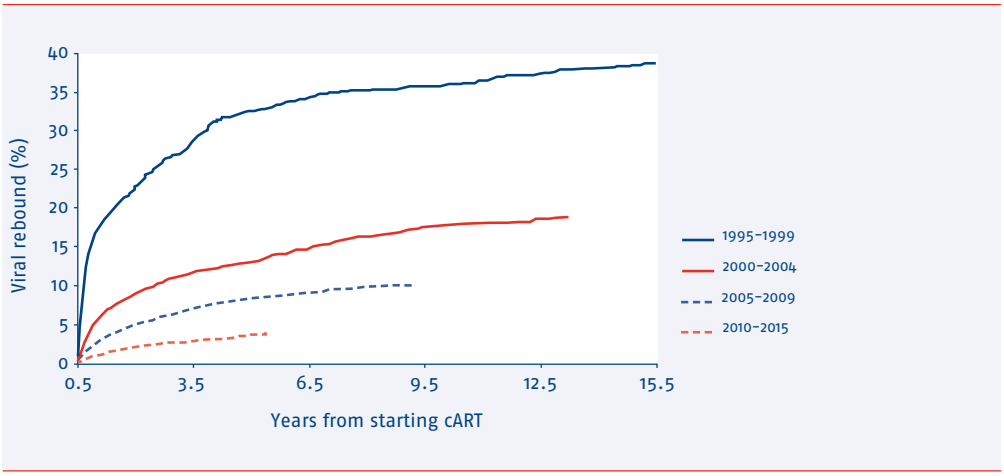
**For stratification by calendar period of therapy initiation, see Appendix Figures 2.2A-D.*
Legend: *cART=combination antiretroviral therapy.*

Viral rebound

Since 2000, the annual proportion of individuals with a viral load above 200 copies/ml has decreased to approximately 3%. In the same time period, the difference between individuals pre-treated with monotherapy or dual therapy and those starting cART while ART-naive has disappeared. We therefore limited our further analysis to individuals who were ART-naive when they started cART. We assessed the incidence and risk of viral rebound, i.e., the first of two consecutive viral load measurements ≥200 copies/ml after six months of cART (*Box 2.3*). Time was censored when individuals interrupted cART for longer than two weeks.

In total, 15,680 individuals were ART-naive and had a sensitive viral load test result after six months of continuous cART. In total, 1,728 (11.0%) individuals experienced a viral rebound after a median of 1.4 (IQR 0.7-3.4) years on cART. The Kaplan-Meier curve in *Figure 2.10* shows the incidence of viral rebound by cART era.

Figure 2.10: *Kaplan–Meier estimates of viral rebound* according to calendar period of starting combination antiretroviral therapy (cART) in previously treatment–naive individuals.*

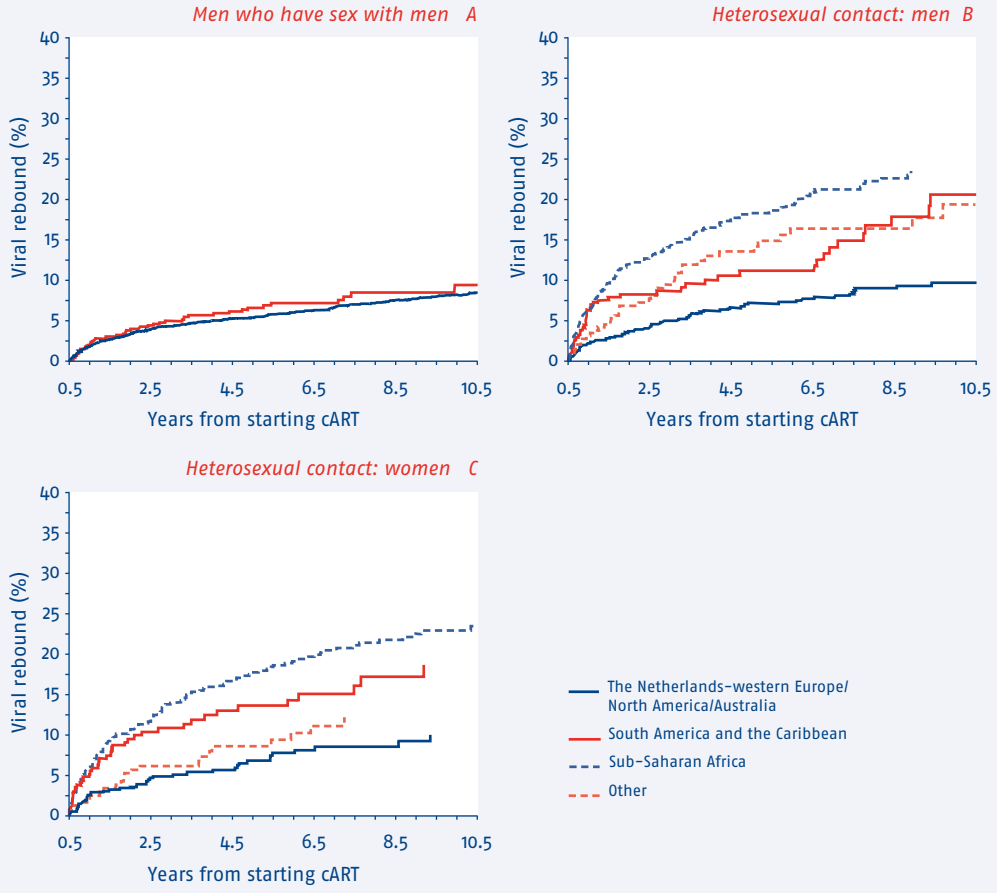


**Viral rebound is defined as the first of two consecutive viral load measurements ≥200 copies/ml after 6 months (>180 days) of cART (Box 2.3).*

Legend: *cART=combination antiretroviral therapy.*

We subsequently limited this analysis to the 13,621 individuals who initiated cART in 2000 or thereafter. In total, 1,016 (7.5%) of these individuals experienced a viral rebound after a median of 1.6 (IQR 0.8-3.5) years on cART. The Kaplan-Meier curves in *Figure 2.11* show their incidence of viral rebound by region of origin and risk group. MSM were found to have an overall lower risk of viral rebound compared with men and women infected through heterosexual contact. Among heterosexuals, the risk of viral rebound was lowest in those originating from western Europe/North America/Australia. *Appendix Figures 2.3* and *2.4* show the separate curves by region of origin and risk group.

Figure 2.11: *Kaplan–Meier estimates of viral rebound according to transmission risk group and region of origin*: (A) Men who have sex with men; (B) Heterosexual contact: men; (C) Heterosexual contact: women.*



**Appendix Figures 2.3 and 2.4 show the curves plotted separately by region of origin and risk group.*
Legend: *cART=combination antiretroviral therapy.*

Additionally, we assessed the risk factors for viral rebound in a multivariable Cox model (*Table 2.4*). The risk of viral rebound was higher among individuals less than 30 years of age, men and women infected through heterosexual contact, and those who originated from South America and the Caribbean or sub-Saharan Africa. Those with a higher HIV viral load at the start and those starting at CD4 cell counts <200 cells/mm^3 had an increased risk of viral rebound compared with those

starting at higher CD4 cell counts. We did not find a significant difference in risk between starting at 350-500 CD4 cells/mm^3 and starting at 500 CD4 cells/mm^3 or more (p=0.937). The risk of viral rebound decreased with later calendar year of cART initiation. This probably reflects changes in HIV care and cART regimens over time.

Table 2.4: *Factors independently associated with viral rebound after combination antiretroviral therapy (cART) initiation since 2000. Multivariable Cox regression analysis determines the time-to-viral rebound (see definition in Box 2.3). Hazard ratios were adjusted for all variables listed in the table. Included individuals initiated cART from 2000 onwards. Time was censored when individuals interrupted therapy for longer than two weeks.*

	Adjusted hazard ratio	95%CI lower	95%CI higher	p-value
Age at cART initiation (in years)				
<30	1.51	1.24	1.84	<.0001
30-40	1 (reference)			
40-50	0.96	0.80	1.15	0.652
>50	1.09	0.88	1.36	0.420
Risk group				
Men who have sex with men	1 (reference)			
Heterosexual women	1.38	1.12	1.72	0.003
Heterosexual men	1.31	1.08	1.59	0.006
Region of origin				
The Netherlands/Western Europe/North America/Australia	1 (reference)			
South America and the Caribbean	1.41	1.12	1.77	0.004
Sub-Saharan Africa	1.83	1.48	2.27	<.0001
Other	1.01	0.77	1.33	0.949
Year of cART initiation				
2000-2004	2.82	2.26	3.54	<.0001
2005-2009	1.84	1.47	2.31	<.0001
2010-2015	1 (reference)			
CD4 cell count at cART initiation (cells/mm^3)				
<50	1.88	1.35	2.62	0.000
50-199	1.62	1.19	2.22	0.003
200-349	1.16	0.84	1.59	0.364
350-499	1 (reference)			
≥500	0.98	0.60	1.61	0.937

Table 2.4: Continued.

	Adjusted hazard ratio	95%CI lower	95%CI higher	p-value
HIV RNA load at baseline (log_{10})				
<4	1 (reference)			
4-5	2.28	1.54	3.38	<.0001
≥5	3.30	2.24	4.86	<.0001
Recent infection				
No	1 (reference)			
Yes	0.82	0.61	1.10	0.186
Hepatitis C virus status at cART initiation				
HCV negative	1 (reference)			
HCV RNA positive	1.12	0.68	1.84	0.667
HCV Ab positive	1.69	0.90	3.16	0.102
Unknown	1.05	0.73	1.52	0.783
Hepatitis B virus status at cART initiation				
HBV negative	1 (reference)			
HBV positive	1.56	1.21	2.01	0.001
Unknown	1.03	0.64	1.65	0.903

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

HIV drug resistance

In individuals on cART experiencing virological failure, antiretroviral drug resistance was determined. At the time of failure, genotypic sequences of the reverse transcriptase and protease genes available to SHM were scanned for specific mutations known to be associated with resistance to the three originally most commonly used classes of drugs, including lamivudine-emtricitabine, other NRTIs, NNRTIs, and PIs. In recent years, new drug classes have also been introduced, including INSTI and entry inhibitors, and genotypic sequences of the relevant genes are collected increasingly frequently during routine clinical care. However, at the time of analysis only a limited number of sequences of the integrase gene were available in the SHM database, which restricts interpretation.

Drug resistance mutations were assessed with the 2015 IAS-USA HIV drug resistance mutation list[31]. 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[32].

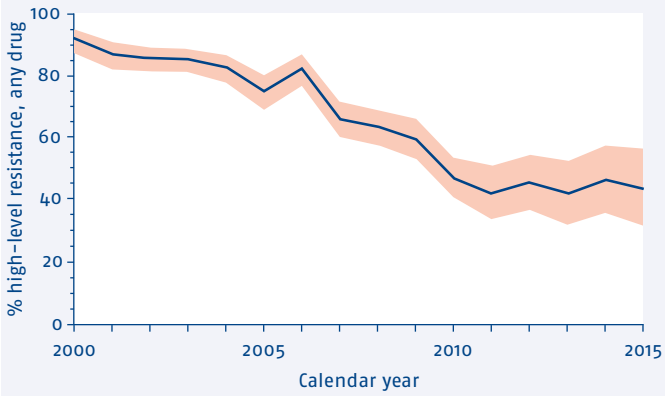
Acquired drug resistance

In total, 4,780 sequences were obtained from 2,927 individuals after the start of cART in 1996 or later. Overall, individuals pre-treated with mono- or dual-NRTI therapy were disproportionally represented with 1,775 sequences (37%), even though pre-treated individuals represented only 11% of all treated individuals in clinical care. However, from 2008 onwards, this discrepancy became less marked, with only 17% of the sequences being from pre-treated individuals. Overall, 3,723 sequences (78%) were obtained while individuals were receiving treatment, whereas the other (22%) sequences were from individuals who had a treatment interruption. High-level resistance to at least one antiretroviral drug was found in 73% of these 3,723 sequences, including in 88% of the sequences obtained from pre-treated individuals and in 62% of those from individuals who had started cART while being ART-naive. It is interesting that 8% of the sequences from pre-treated individuals and 24% of those from previously ART-naive individuals were susceptible to all antiretroviral drugs, probably indicating that the individuals were not taking their prescribed medication at the time the blood sample was obtained.

Overall, the proportion of sequences with high-level resistance at the time of viral failure decreased from 92% in 2000 to 43% in 2015 (*Figure 2.12*). Generally, HIV-positive individuals who were pre-treated with monotherapy or dual therapy had

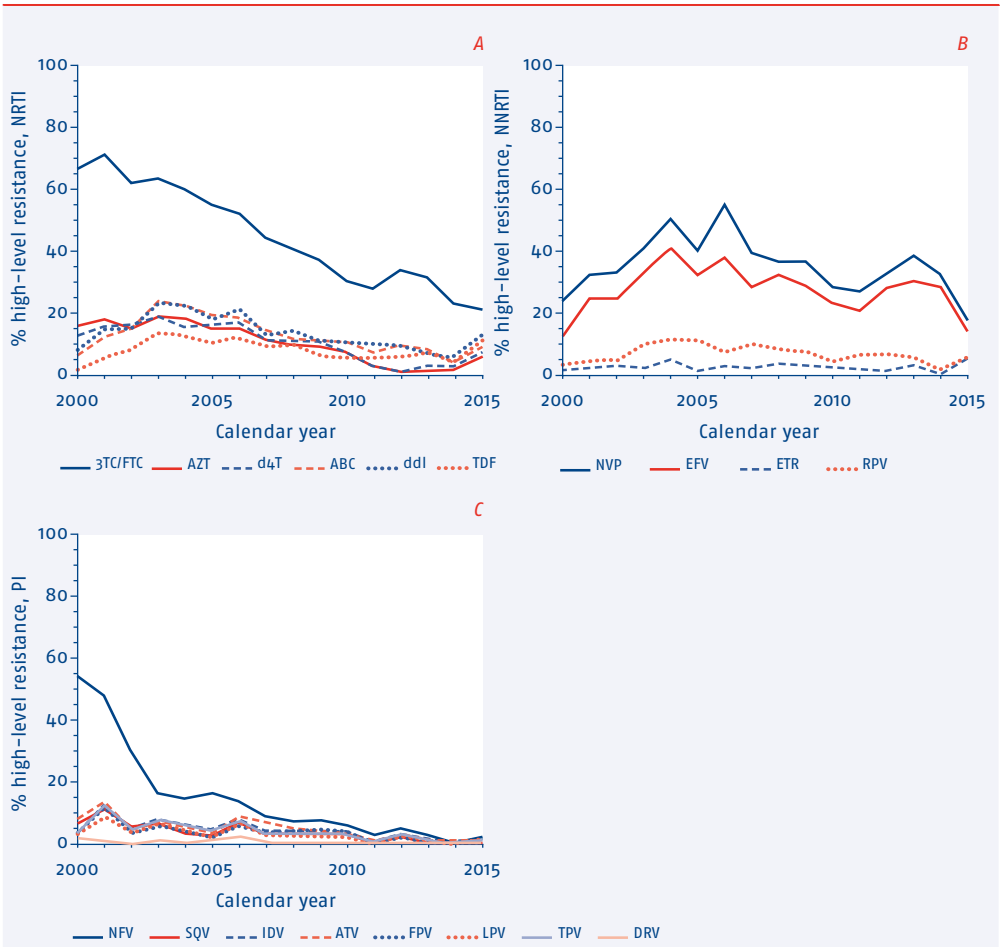
higher levels of resistance at the time of failure compared to those who were ART-naive (*Appendix Figure 2.5*). Both the number of pre-treated individuals and the number of sequences from pre-treated individuals were low in recent years and were often too low to be meaningful. The annual proportion of available sequences with high-level drug resistance by pre-treatment status is provided in *Appendix Figure 2.6*.

Figure 2.12: *Annual proportion of sequences obtained at the time of virological failure with evidence of high-level resistance to any antiretroviral drug. The shaded area represents the 95% confidence interval.*



In the remainder of our analyses, we focused on ART-naive individuals only. *Figure 2.13* shows the proportion of sequences with high-level resistance after viral failure over time, by drug class. Overall, the annual proportion of individuals with acquired drug resistance is low and has decreased sharply over the past calendar years.

Figure 2.13: Annual proportion of available sequences with evidence of high-level resistance after viral failure from individuals who received combination antiretroviral therapy and who had previously been treatment-naive. Resistance was assessed using the Stanford algorithm[32]. 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.



Legend: NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; 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 disoproxil fumarate; EFV=efavirenz; NVP=nevirapine; ETR=etravirine; RPV=rilpivirine.

Prevalence of acquired drug resistance

In total, as of May 2016, resistance-associated mutations had been found in 2,137 (11.3%) of the 18,866 HIV-positive individuals who were still in clinical care. Of note, a resistance test result was available for only 7,815 (41%) of the individuals in care. For 1,591 (8.4%) of the individuals in care, these mutations resulted in high-level resistance to at least one antiretroviral drug. Since genotypic resistance test results were available for only 25% of individuals with viral failure in or after 2000 and for 17% with viral failure in or after 2010, the true prevalence of resistance may be different.

Of the 1,591 individuals with evidence of high-level resistance, 71% had resistance to lamivudine-emtricitabine, while 50% had resistance to at least one other NRTI. Resistance to at least one PI was found in 30% of cases and to at least one NNRTI in 62% of cases. High-level resistance to drugs from one drug class was observed in 39% of individuals, resistance to two classes in 46% and resistance to all three original drug classes in 15% (i.e., NNRTIs, NRTIs and PIs). Predicted levels of resistance for each antiretroviral drug are shown in *Appendix Tables 2.1* and *2.2*.

Transmitted drug resistance

Screening for transmitted resistance

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[33, 34, 35].

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 5,478 individuals screened for transmitted drug resistance, which comprises 37% of all individuals diagnosed with HIV during that period, but only 23% of individuals diagnosed in 2012 or later. To reduce a possible effect of back mutation on observed levels of resistance, only individuals 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, individuals were divided into two complementary groups: one including individuals with a recent infection (n=1,192; 22%) and the other including those with a non-recent infection (n=4,286;

78%). An infection was considered recent when the time between the last negative HIV test, if available, and the first positive test was no longer than 12 months. Individuals without a previously negative test or with a negative test more than 12 months before the first positive test were considered to have non-recent infections. The characteristics of these two groups differed markedly. Dutch MSM represented 67% of the recently infected group, but only 44% of the group of more long-standing infections. In contrast, individuals of sub-Saharan African origin accounted for only 3% of those with recent infections and 15% of those with long-standing infections.

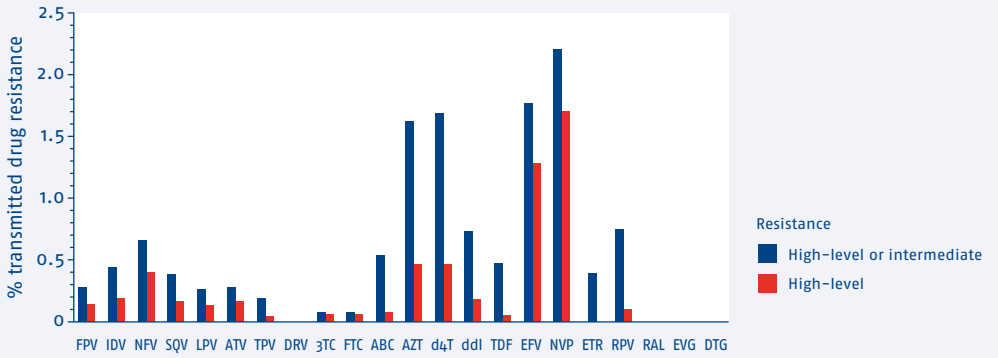
Transmitted drug resistance

Overall, at least one resistance-associated mutation was found in 10% of the 5,478 individuals with a genotypic sequence within one year of diagnosis, including 4% with mutations associated with NRTI resistance, 5% with mutations associated with NNRTI resistance, and 2% with mutations in the protease gene. Between 2003 and 2015, there were no significant changes in these proportions, although there was a decreasing trend in most recent calendar years.

In total, 108 individuals had high-level resistance to drugs from one class, 13 individuals had high-level resistance to drugs from two classes, and four individuals had high-level resistance to drugs from three classes. It should be emphasised that this does not mean that entire drug classes were 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 individuals with resistance to all three classes, fully efficacious cART combinations can often still be constructed.

High-level resistance to at least one antiretroviral drug was found in 2.3% of the individuals, whereas intermediate levels of resistance were found in 2.1% of this group. The proportion of individuals 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 2.14*). In addition, 1.3% of the individuals had high-level resistance to efavirenz, while 1.7% were resistant to nevirapine. In recent years, no changes were observed in the proportion of individuals with predicted high-level resistance. No transmitted INSTI resistance was detected; however, the number of integrase sequences was small.

Figure 2.14: The proportion of individuals predicted to have high or intermediate levels of transmitted drug resistance, since 2003. Resistance was assessed using the Stanford algorithm[32].



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 disoproxil fumarate; EFV=efavirenz; NVP=nevirapine; ETR=etravirine; RPV=rilpivirine; RAL=raltegravir; EVG=elvitegravir; DTG=dolutegravir.

Immunological response

After initiation of cART, most HIV-positive 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 they vary according to factors such as age, ethnicity, sex, and smoking behaviour. Failure to suppress viraemia is associated with poorer recovery of CD4 cell count[22, 36]. 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 independently predict time to death and non-AIDS-defining endpoints[37, 38, 39, 40]. In the general population, a low CD4:CD8 ratio has been found to be associated with immunosenescence and increased all-cause mortality[41, 42, 43]. The clinical benefit of cART is strongly related to the level of recovery of the immune status (also see Chapter 3)[44, 45, 46, 47, 48]. In this section, we describe long-term

CD4 cell count and CD4:CD8 ratio responses after the start of cART among individuals who started cART from 1995 onwards. Additionally, we assess the factors associated with incomplete immunological recovery (CD4 count <350 cells/mm^3) 3 years after sustained viral suppression on cART.

Immunological response – by calendar year

Of 21,377 individuals who initiated cART between 1995-2015, 20,342 (95.2%) had immunology data available after initiating cART. *Figure 2.15* and *2.16* show the last known immune status of these individuals in care each calendar year after the start of cART, the CD4 cell count and CD4:CD8 ratio. After starting cART, the percentage of individuals with counts <350 cells/mm^3 dropped from 82.5% in 1996 to 34.4% in 2000 and 10.9% in 2015 (*Figure 2.15*). Likewise, the absolute number of individuals with CD4 cell counts <350 cells/mm^3 at the end of each calendar year decreased from 2,203 in 2008 to 1,819 in 2012 and 1,499 in 2015 (*Appendix Figure 2.7*). 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 and longer cART use, which has been observed since 2007. Finally, *Figure 2.16* shows that among individuals who ever started cART, the percentage of those with a CD4:CD8 ratio of 1 or above increased from 10.1% in 2000 to 21.6% in 2010 and 30.5% in 2015. The absolute number of individuals in these CD4:CD8 categories is plotted in *Appendix Figure 2.8*.

Figure 2.15: Last available CD4 cell count (cells/mm³) in each calendar year after the start of combination antiretroviral therapy (cART).

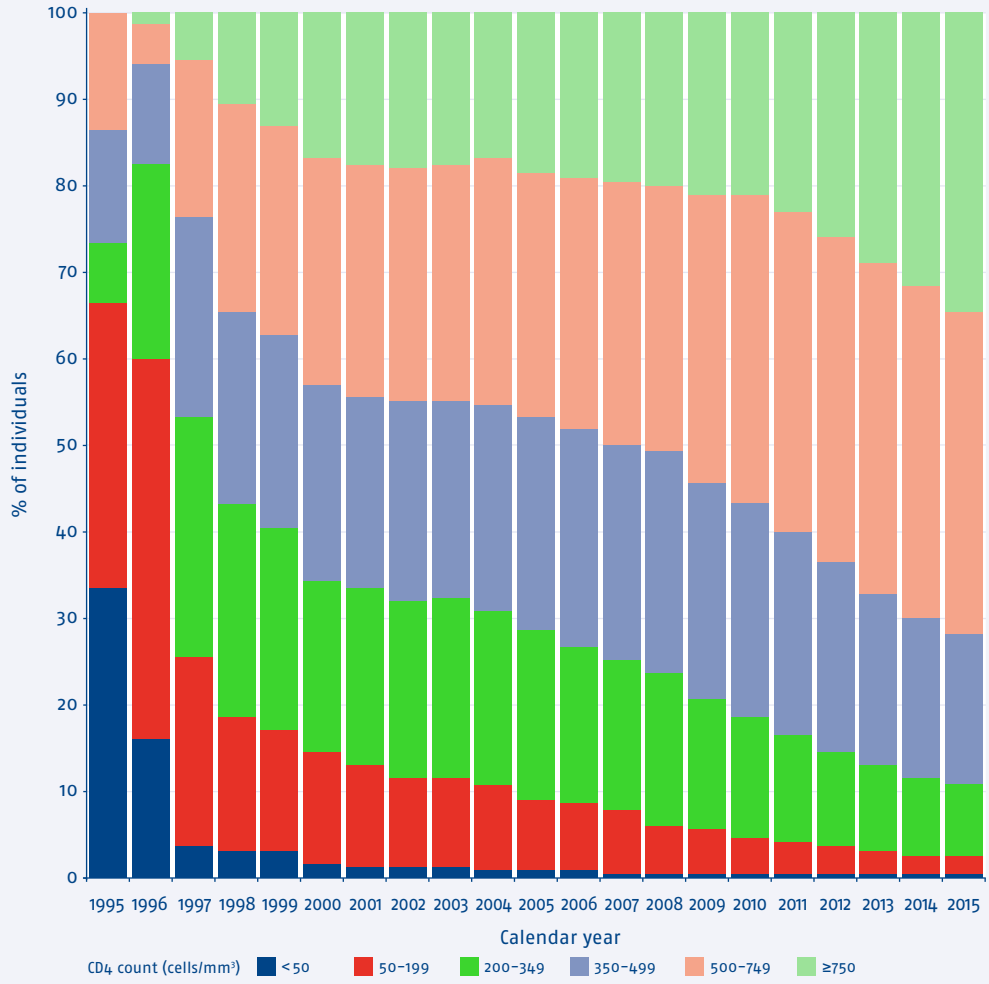
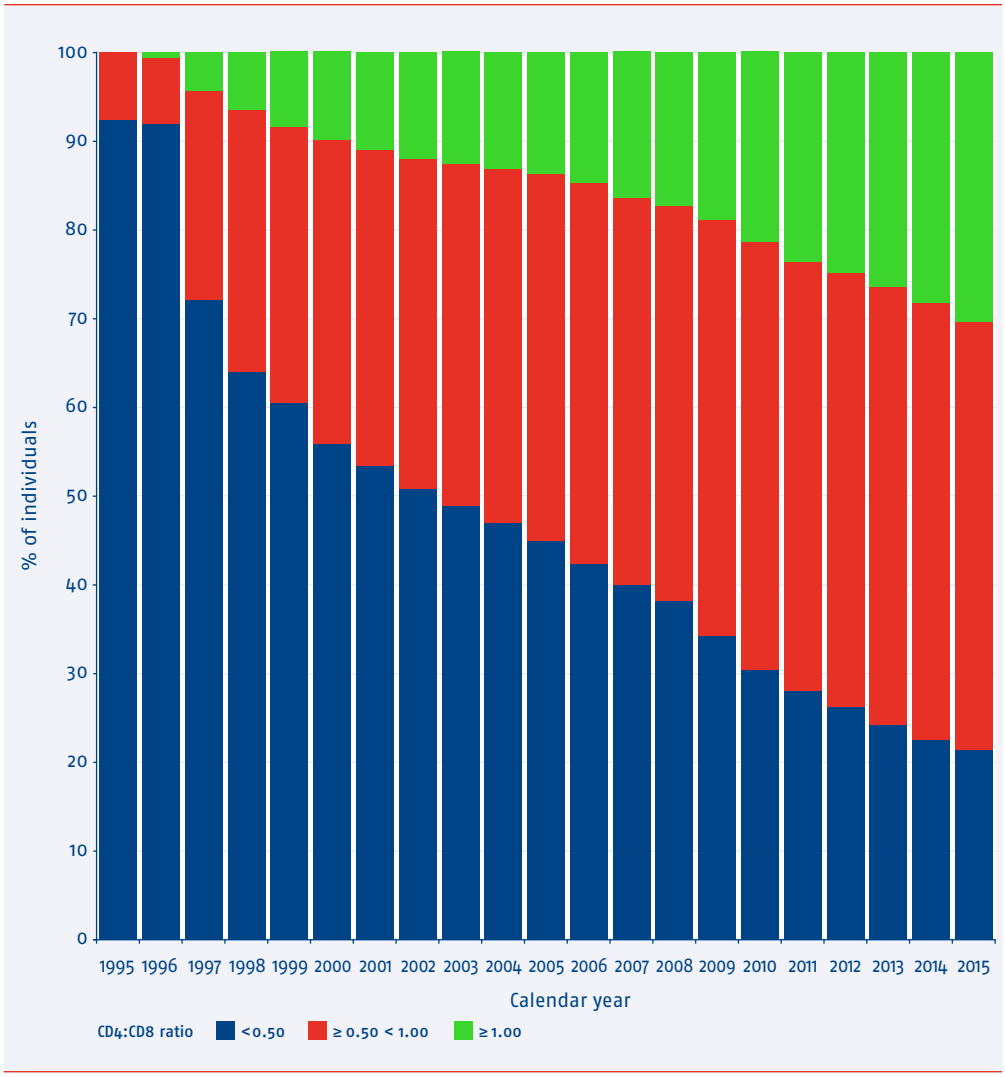


Figure 2.16: Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy (cART).



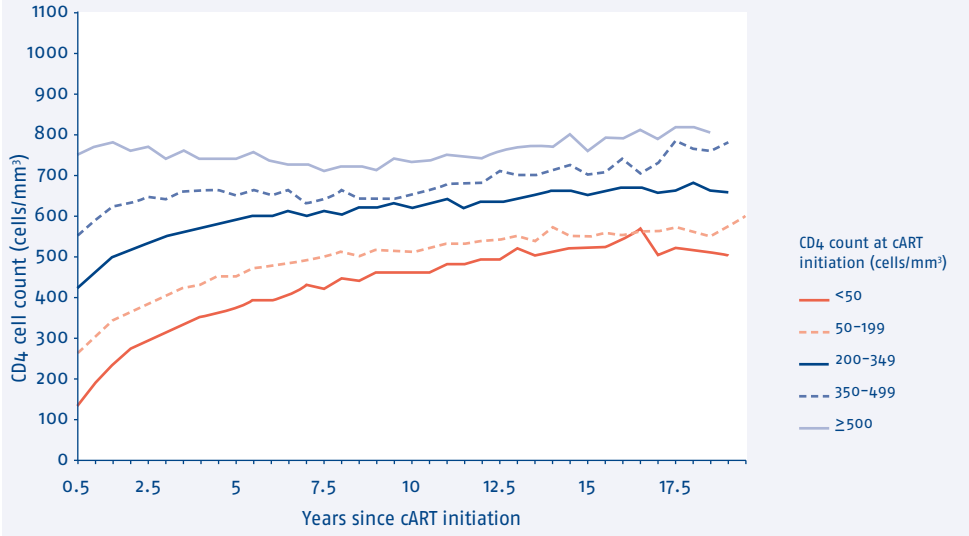
Of all CD4:CD8 ratio measurements ≥1, 15.4% had a CD4 count of less than 500 cells/mm^3, 35.3% had a CD4 count between 500-749 cells/mm^3 and 49.4% had a CD4 count of ≥750 cells/mm^3. When the CD4:CD8 ratio was ≥1, the median CD4 count was 740 cells/mm^3 (IQR 570-944). This number increased slightly over time, with a median of 710 cells/mm^3 (IQR 550-900) in 1995-1999, 730 cells/mm^3 (IQR 550-930) in 2000-2004, 730 cells/mm^3 (IQR 550-930) in 2005-2009 and 750 cells/mm^3 (IQR 590-950) in 2010-2015.

Immunological response – after cART initiation

Of the 21,377 individuals who were known to have initiated cART between January 1995 and December 2015, 17,747 were ART-naive at cART initiation and had immunology data available both at cART initiation and after it. At cART initiation, 2,274 (12.8%) had a CD4 count <50 cells/mm^3, 4,614 (26.0%) had a count between 50 and 199 cells/mm^3, 5,861 (33.0%) between 200 and 349 cells/mm^3, 2,915 (16.4%) between 350 and 499 cells/mm^3 and 2,083 (11.7%) had 500 or more cells/mm^3. In line with treatment guidelines, CD4 cell counts at cART initiation have increased over time, as described in Chapter 1.

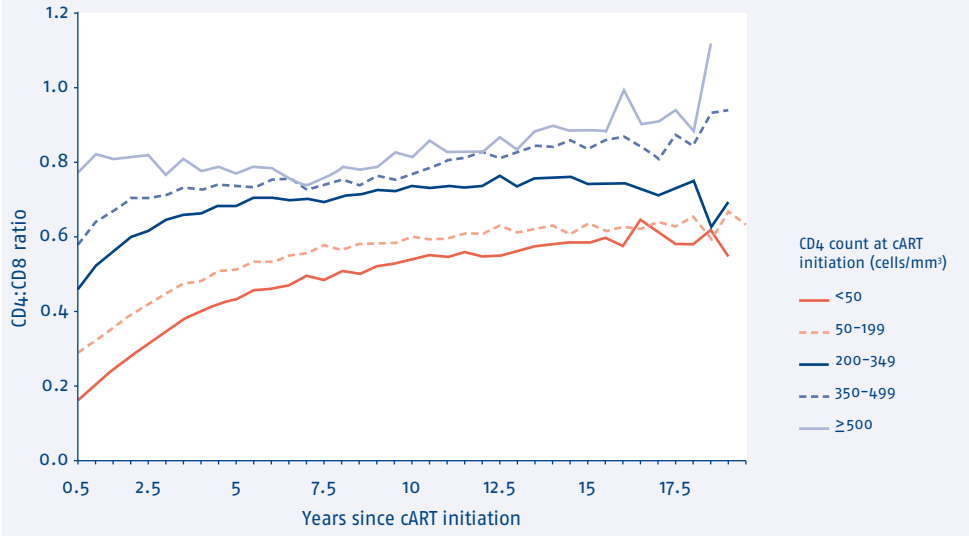
The CD4 trajectories after cART initiation are plotted in *Figure 2.17* by CD4 cell count at cART initiation and for all individuals who started cART. The level of viral suppression and treatment interruptions after initiating cART were not taken into account (CD4 cell count recovery among suppressed individuals is investigated in the next section). Although the median CD4 cell counts fluctuated over time and occasionally decreased, the trend over time reflects an increase in median CD4 cell count in the years after starting cART. Similar to the CD4 cell count response in ART-naive individuals, median CD4:CD8 ratios in the five baseline CD4 cell count strata did not seem to converge. Importantly, the ability to achieve a CD4:CD8 ratio of 1 or higher seemed to be strongly related to the CD4 cell count at the start of cART (*Figure 2.18*). In *Appendix Figures 2.9* and *2.10*, the CD4 count and CD4:CD8 ratio changes are plotted for individuals who had initiated cART since 2010.

Figure 2.17: CD4 cell count over time after the start of combination antiretroviral therapy (cART).



Legend: cART=combination antiretroviral therapy.

Figure 2.18: CD4:CD8 ratio over time after the start of combination antiretroviral therapy (cART).



Legend: cART=combination antiretroviral therapy.

Incomplete immunological recovery

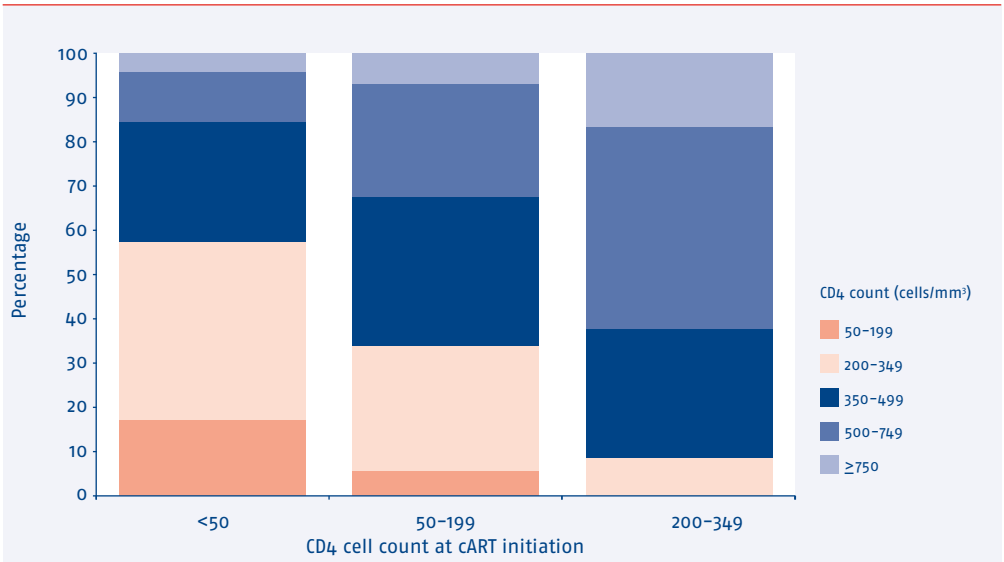
Incomplete CD4 cell count recovery, despite long-term viral suppression on cART, is associated with an increased risk of mortality, AIDS, and non-AIDS-related diseases[23, 49, 50]. We therefore investigated the CD4 cell count response after two and three years of cART, among ART-naive individuals who started cART with ≤350 cells/mm^3 and had sustained viral suppression. Sustained viral suppression was defined as initial virological success (HIV RNA <100 copies/ml after six months (±3 months) after starting cART), combined with no viral load >500 copies/ml thereafter (Box 2.3). 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.

We included 4,506 and 3,601 ART-naive individuals who started cART with ≤350 cells/mm^3 and had sustained viral suppression on cART for two and three years, respectively. Their median CD4 cell count was 440 (IQR 310-570) cells/mm^3 at two years and 470 (IQR 350-610) cells/mm^3 at three years of cART. At two and three years, 31% (1,404 out of 4,506 individuals) and 25% of individuals (894 out of 3,601 individuals) who started cART at <350 CD4 cells/mm^3 still had values <350 cells/mm^3, respectively, i.e., incomplete immunological recovery (*Table 2.5*). In line with findings described earlier in this chapter, we found an association between CD4 cell count at cART initiation and CD4 recovery (*Figure 2.19*).

Table 2.5: Immunological recovery among individuals with sustained viral suppression (see definition in Box 2.2), who started combination antiretroviral therapy at <350 CD4 cells/mm^3.

CD4 cell count (cells/mm^3)	2 years		3 years	
	n	%	n	%
<50	3	0.1	2	0.1
50–199	367	8.1	168	4.7
200–349	1,034	23.0	724	20.1
350–499	1,397	31.0	1,100	30.6
500–749	1,394	30.9	1,200	33.3
≥750	311	6.9	407	11.3
Total	**4,506**	**100.0**	**3,601**	**100.0**

Figure 2.19: Immunological recovery after three years of suppressive combination antiretroviral therapy, by CD4 cell count at therapy initiation.



Legend: cART=combination antiretroviral therapy.

We further assessed the demographic and clinical characteristics associated with immunological recovery after three years of suppressive cART. Using multivariable logistic regression analysis, we found several significant predictors for CD4 cell recovery. MSM, women infected through heterosexual contact, individuals with higher viral load and individuals with a higher CD4 cell count at cART initiation were more likely to achieve a CD4 cell count >350 cells per mm^3 after three years of suppressive cART. Individuals more than 50 years of age, men infected through heterosexual contact, individuals originating from sub-Saharan Africa, those who initiated cART before 2004, or had a hepatitis C infection at cART initiation were less likely to achieve a CD4 cell count >350 cells per mm^3 after three years of suppressive cART (*Table 2.6*). Although half the individuals experienced at least one HIV RNA blip (a detectable viral load <500 copies/ml), blips were not associated with CD4 cell recovery.

Chapter 3 further describes an analysis of the potential association between incomplete CD4 cell count recovery and the risk of mortality, AIDS, and non-AIDS-related diseases.

Table 2.6: Patient characteristics independently associated with CD4 recovery >350 cells/mm³ after three years of suppressive cART among ART-naive individuals who initiated cART with a CD4 cell count <350 cells/mm³.

	Adjusted odds ratio	95%CI	p-value
Sex, by transmission risk group			
Men who have sex with men	1 (reference)		
Heterosexual women	1.43	1.07-1.92	<.0001
Heterosexual men	0.75	0.59-0.95	<.0001
Age (years)			
<30	1 (reference)		
30-40	1.09	0.80-1.48	0.003
40-50	0.88	0.64-1.20	0.897
>50	0.60	0.42-0.84	<.0001
Region of origin			
The Netherlands-western Europe/North America/Australia	1 (reference)		
South America and the Caribbean	1.53	1.12-2.10	0.014
Other	1.44	1.0-2.02	0.074
Sub-Saharan Africa	0.78	0.58-1.06	0.001
Calendar year of cART initiation			
1995-2004	0.79	0.65-0.96	<.0001
2005-2009	1 (reference)		
2010-2015	1.36	1.05-1.77	0.001
CD4 cell count at cART initiation			
by 50 cells/mm³ higher	1.81	1.72-1.92	<.0001
Recent HIV infection (within 12 months)			
Yes	0.87	0.61-1.25	0.458
HIV viral load at cART initiation (log_{10})			
<4	1 (reference)		
4 to 5	1.31	0.92-1.87	0.299
≥5	2.19	1.53-3.13	<.0001
HIV viral load blips while on cART			
Always undetectable	1 (reference)		
Per blip	1.05	0.96-1.14	0.236
Hepatitis B status at cART initiation			
HBV negative	1 (reference)		
HBV positive	0.74	0.50-1.09	0.471
Unknown	0.78	0.42-1.46	0.774

Table 2.6: Continued.

	Adjusted odds ratio	95%CI	p-value
Hepatitis C status at cART initiation			
HCV negative	1 (reference)		
HCV Ab positive	1.28	0.46–3.54	0.517
HCV RNA positive	0.55	0.30–1.01	0.033
Unknown	1.34	0.72–2.47	0.289

Multivariable logistic regression analysis determines the factors associated with CD4 recovery. Odds ratios were adjusted for all variables listed in the table.

***Legend:** cART=combination antiviral therapy; HBV=hepatitis B virus; HCV=hepatitis C virus.*

Summary and conclusion

Rapid initiation of cART following a diagnosis of HIV infection is becoming increasingly common in the Netherlands. In 2015, the majority of individuals initiating cART did so within a month after diagnosis. INSTI-based cART has been implemented on a large scale in the Netherlands. Overall, INSTI-based cART was used by 23% of those in care in 2015. Because of the fixed-dose combination with dolutegravir, there has simultaneously been an increase in the use of abacavir-lamivudine. Of those who started cART in 2015, 75% were prescribed an INSTI-based regimen that was predominantly dolutegravir-based. Discontinuation of the initial regimen was mainly due to toxicity, associated with the central nervous system, gastrointestinal adverse events, rash (due to medication), and hepatic adverse events.

Overall, initial viral suppression on cART is successful and is being attained significantly more rapidly through the use of INSTI-based cART. Of those receiving cART who had a plasma HIV RNA measurement in 2015, 97% had a viral load <200 copies/ml. Although the overall viral suppression rate is high, young individuals, non-MSM, and migrants remain at increased risk of viral rebound. Finally, the proportion of high-level drug resistance among HIV-positive individuals in care is very low.

The CD4 cell count at cART initiation has increased over time; among HIV-positive individuals starting cART in 2015, the median CD4 cell count was 420 cells/mm^3 (IQR 240-610). This trend is important as the CD4 cell count at cART initiation is strongly associated with immunological recovery on cART, despite successful viral suppression, which underlines the importance of timely HIV diagnosis and cART initiation. Overall, current cART regimens are effective and provide high rates of viral suppression, but monitoring of long-term effects and toxicity is needed.

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

Ferdinand Wit and Peter Reiss

Introduction

Of the 24,055 adults and children infected with HIV-1 and ever registered in the Dutch national HIV registration and monitoring database up to 31 December 2015, 92.5% are currently on combination antiretroviral therapy (cART). Since the introduction of cART, the life expectancy of HIV-infected patients has markedly improved 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 [51].

Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased [52], 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 [53, 54, 55, 56, 57, 58].

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 [59, 60, 61]. For example, pulmonary hypertension [62], bone disease, and non-traumatic bone fractures [63, 64, 65] 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 [66, 67, 68]. Furthermore, as in uninfected individuals, traditional risk factors (e.g., tobacco use [69], alcohol abuse, and viral hepatitis co-infection [70]) are likely to also importantly contribute to the increased risk of certain non-AIDS comorbidities in people living with HIV.

One of the most prevalent comorbidities 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, such as 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 residual HIV-associated immune activation and inflammation, despite effective cART [45, 71].

< Back to page 90

In this chapter, we report on rates of mortality and causes of death for adult (18 years and older) HIV-1-infected patients using updated Stichting HIV Monitoring (SHM) data from 1 January 1996 until 31 December 2015: 23,399 adults at entry into care after being diagnosed with HIV-1 infection and 413 children (at the time of entry into care) who have since become adults, giving a total of 23,812 patients. In addition, we report on the incidence of AIDS and non-AIDS comorbidities, 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[72]). 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 entered care following an HIV-1 diagnosis 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 routinely collected renal laboratory data became available for analysis. 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 2011-2015, while standardising these according to the age distribution of the population during the period 2011-2015 (divided into age classes 18-29, 30-39, 40-49, 50-59, 60-69, and ≥70 years) using the indirect standardisation method[73]. Indirect standardisation compares the incidence rates in the study and reference (2011-2015) populations by applying the stratum-specific rates in the reference population to the study population. We investigated risk factors for AIDS and death and for each of the non-AIDS events, as well as a combined non-AIDS endpoint (defined as first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS malignancy). CKD was not included in this combined endpoint as serum 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 entry into care following HIV-1 diagnosis or January 2000, whichever occurred most recently. Subsequent follow-up time was divided into calendar quarters. 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

Overall mortality

From 1996 onwards, the overall mortality rate in all 23,812 HIV-1-infected adults ever registered in the SHM database was 16.5 (95% confidence interval [CI], 12.1-21.8) per 1,000 person years in 1996 and declined over time to 9.1 (7.7- 10.8) per 1,000 person years in 2015 (*Appendix Figure 3.1A*; *Appendix Table 3.1*). 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, 3.7 per 1,000 person years in 2015, when age and gender 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 are excluded, the mortality rate is 13.7 (13.2-14.3) per 1,000 person years overall (period 1996-2015) and 8.3 (6.8-10.0) per 1,000 person years in 2015. In the same group of 23,812 patients, the incidence of AIDS decreased sharply from 114.9 (103.0-127.9) in 1996 to 10.4 (8.8-12.2) cases per 1,000 patients per year in 2015 (*Appendix Figure 3.1B*).

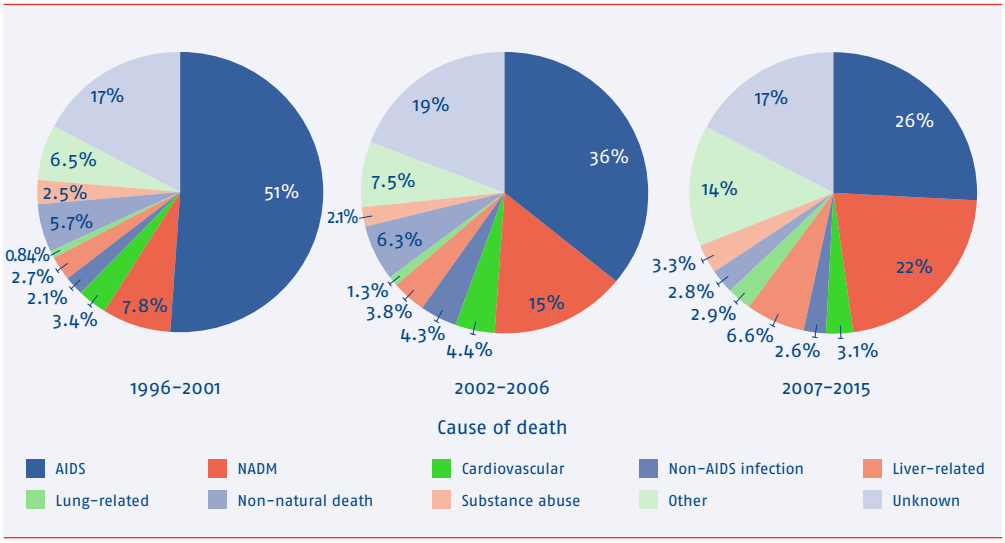
Mortality after start of cART

Likewise, the mortality rate after the start of cART has substantially decreased over calendar time to 9.1 (7.7-10.8) per 1,000 person years in 2015 (*Appendix Figure 3.1C*). Similarly, the incidence of AIDS after the start of cART has decreased dramatically and was 10.2 (8.6-12.0) per 1,000 person years in 2015 (*Appendix Figure 3.1D*). The incidence of AIDS after starting cART was lower with higher latest CD4 cell counts; it was 395.9 (95% CI 368.9-424.3) per 1,000 person years of follow up, 114.0 (108.1-120.1), 27.9 (26.0-29.9), 11.0 (10.0-12.1), 4.8 (4.3-5.4), and 3.0 (2.5-3.6) at latest CD4 cell counts of <50, 50-200, 200-350, 350-500, 500-750, and ≥750 cells/mm^3, respectively.

Cause of death

Observed underlying causes of death are presented in *Appendix Table 3.2*. Although the rate at which patients 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. In fact, 33% of all patients who died of AIDS between 2007 and 2015 had a CD4 cell count <50 cells/mm^3 when entering care. Moreover, patients who died of AIDS had lower CD4 counts (median 100 cells/mm^3; interquartile range (IQR) 30-320) when entering care compared with patients who died of another cause (median 250 cells/mm^3; IQR 90-456). Patients who entered care with more than 300 CD4 cells/mm^3 and who died of AIDS were relatively more likely to have an AIDS-related malignancy (34%) as the cause of death than patients who entered care with less than 50 CD4 cells/mm^3 (14%). The time between entry into care and death was significantly shorter in patients who died of AIDS (median 3.4 years; IQR 0.6-8.8) compared to patients who died of a non-AIDS cause (median 8.0 years; IQR 4.0-13.2, p<0.001). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figure 3.1*), partly as a consequence of the increasing average age of the Dutch HIV-infected population.

Figure 3.1: 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.

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 3.3*, including time-updated age, and time-updated lagged CD4 cell counts, the risk ratios for a number of possible risk factors are presented in *Appendix Table 3.3*. In general, men were more likely to die than women, and patients had an increased risk of death if they were older, belonged to the injecting drug use (IDU) HIV transmission risk group, had a current CD4 cell count less than 500 cells/mm^3 (even more marked with a CD4 cell count less than 200 cells/mm^3), had been pre-treated with nucleoside-analogue reverse transcriptase (RT) inhibitors at start of cART, had a prior AIDS diagnosis, were co-infected with hepatitis B virus (HBV) or hepatitis C virus (HCV), were underweight, were current or past smokers, 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 3.4*. Furthermore, the incidence of loss to follow up in individuals originating from sub-Saharan Africa and South-East Asia 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 individuals originating from

sub-Saharan Africa and South-East Asia impacts on mortality rates, at least to a higher degree than in individuals born in the Netherlands.

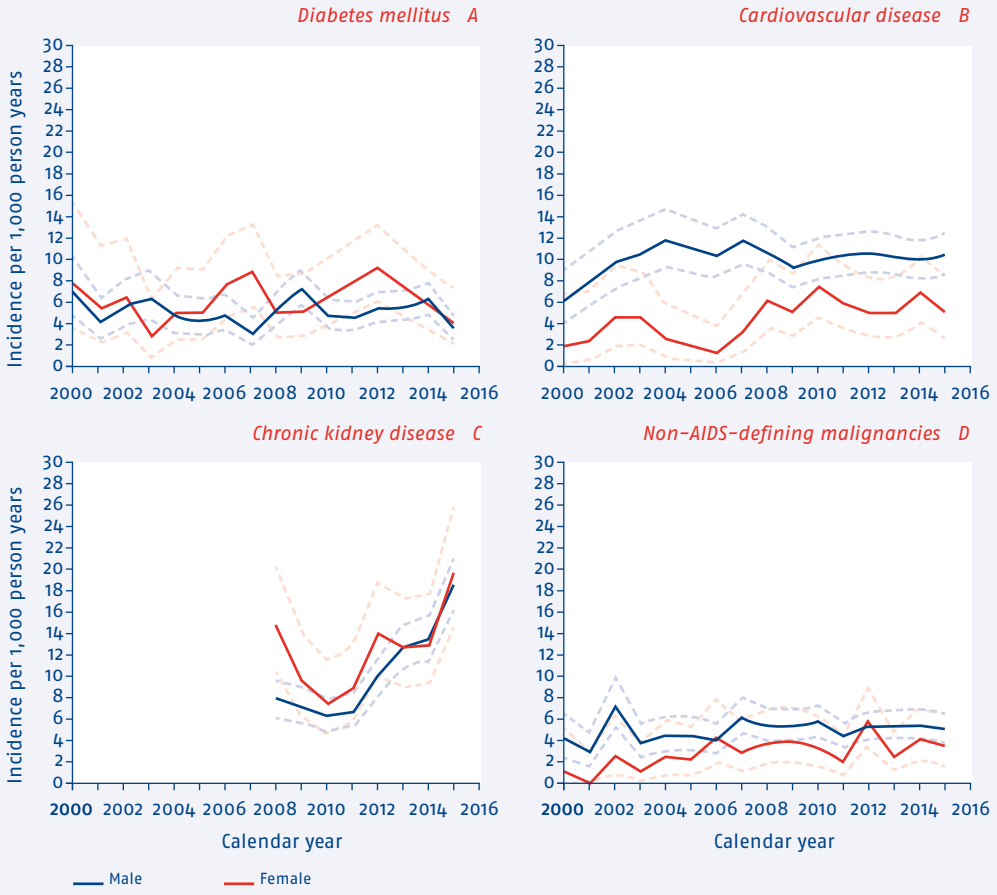
AIDS-defining events

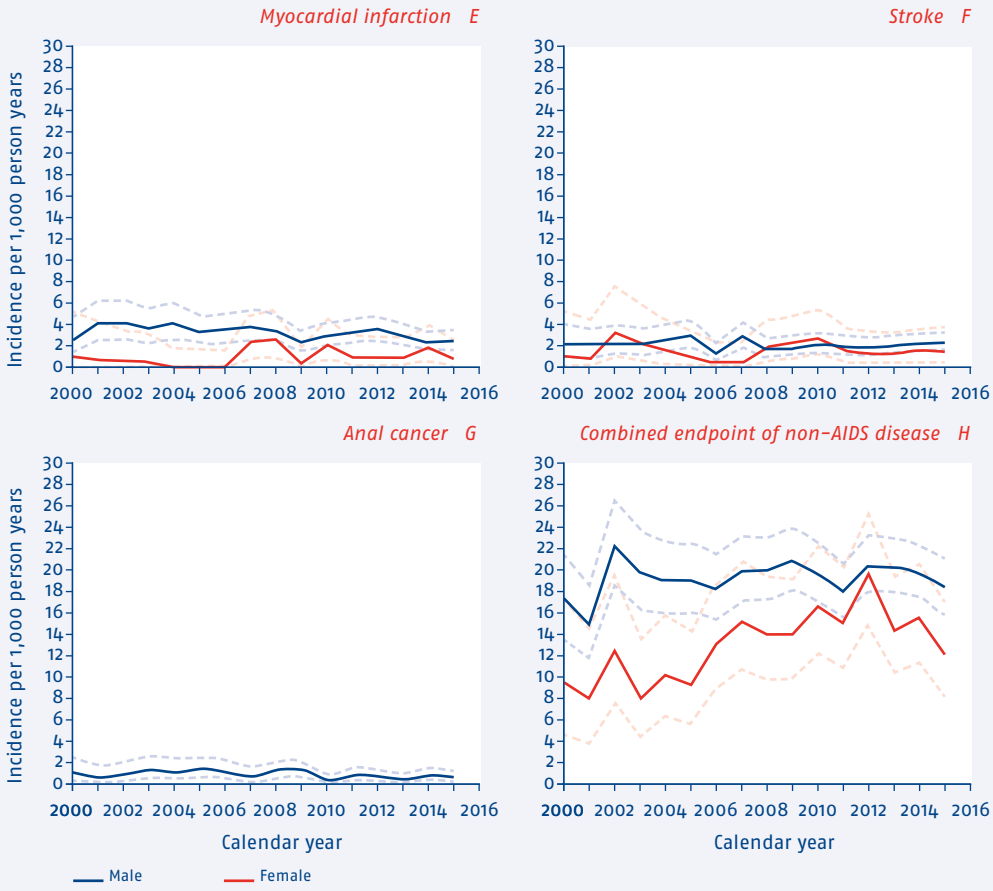
The incidence of the first occurrence of any AIDS-defining event after entering in care was 24.6 events per 1,000 person years of follow up. *Appendix Table 3.5* gives an overview of the AIDS events occurring between 1996 and 2015. The most common AIDS events occurring between 2007 and 2015 were pneumocystis pneumonia (21% of all events), oesophageal candidiasis (16%), Kaposi's sarcoma (11%), tuberculosis (pulmonary 8%, extrapulmonary 5%), lymphoma (6%), toxoplasmosis of the brain (5%), AIDS-related wasting (4%), AIDS dementia complex/HIV encephalopathy (3%) and cytomegalovirus-associated end organ disease (3%). Risk factors for AIDS-defining events are shown in *Appendix Table 3.3*. 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 older, had become HIV-1 positive through IDU, had a current CD4 cell count below 500 cells/mm^3 (but even more so when their CD4 cell count was below 200 or 50 cells/mm^3), or had more than 1000 HIV RNA copies/ml for a longer period of time. The same phenomenon of a lower rate in patients of non-Dutch origin was observed (similar to the apparently lower death rate in non-Dutch patients), and this is likely due to the larger proportion of sub-Saharan Africans becoming lost to follow up while having low CD4 counts (see above).

Non-AIDS-defining events

Of the 23,812 HIV-1-infected adults ever registered in the Dutch national HIV registration and monitoring database, 23,381 were aged 18 years or older while in follow up in or after January 2000. For these treated and untreated adults, 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 3.2*; *Appendix Table 3.6*).

Figure 3.2: Crude incidence rates per 1,000 person years of follow up and 95% confidence intervals (dotted lines) of (A) diabetes mellitus, (B) cardiovascular disease, (C) chronic kidney disease, (D) non-AIDS-defining malignancies, (E) myocardial infarction, (F) stroke, (G) anal cancer, and (H) combined endpoint of non-AIDS disease (diabetes mellitus, cardiovascular disease, and non-AIDS-defining malignancies), by gender, with exception of anal cancer, which is presented for males only.





Diabetes mellitus

Of the 23,381 individuals aged 18 years or more and in follow up in, or after, January 2000, a total of 1,020 (779 men and 241 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.2.A*) and, in 2015, was 7.0 (95% CI 4.8-9.9) per 1,000 person years of follow up in men and 7.6 (95% CI 2.2-11.3) per 1,000 person years in women. In both men and women, the incidence increased with older age (*Appendix Table 3.6.A*). In men,

the age-standardised incidence ratio declined over time and was significantly higher in 2000-2005 compared with 2011-2015. In women, the age standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2015 (*Table 3.1*).

Demographic and clinical factors independently associated with increased risk of new-onset diabetes mellitus were non-Dutch origin, older age, HIV acquisition through heterosexual or injecting drug use, a BMI greater than 25 kg/m^2 (and also a borderline significant association for a BMI below 18 kg/m^2), hypertension, a latest CD4 cell count below 50 cells/mm^3, pre-treatment with nucleoside-analogue RT inhibitors at start cART, and a prior AIDS diagnosis (*Appendix Table 3.7*). During the period 2000-2005, the risk was significantly higher than during 2011-2015. Having spent a longer time on stavudine, zidovudine, or didanosine was borderline significantly associated with an increased risk.

Table 3.1: *Crude incidence of diabetes mellitus per 1,000 years of follow up during 2000–2005, 2006–2010 and 2011–2015 and age-standardised incidence ratio (indirect method) with 95% confidence intervals.*

Calendar year	Male		Female	
	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)
2000–2005	5.4 (4.7–6.2)	1.31 (1.12–1.49)	5.3 (4.0–7.0)	0.84 (0.61–1.07)
2006–2010	5.3 (4.7–6.0)	1.13 (0.99–1.27)	6.5 (5.2–8.1)	0.99 (0.78–1.20)
2011–2015	5.2 (4.7–5.8)	1.00	7.0 (5.7–8.4)	1.00

**Standardised according to the observed age distribution between 2011–2015.*

Legend: *CI=confidence intervals.*

Cardiovascular disease

From January 2000 onwards, 898 individuals (800 men and 98 women) had a fatal or non-fatal cardiovascular event (461 myocardial infarction, 345 stroke, 75 coronary artery bypass graft, 312 coronary angioplasty or stenting, and 6 carotid endarterectomy). The crude incidence over time remained stable and was lower in women than in men (*Figure 3.2.B*). The incidence in both men and women increased with older age (*Appendix Table 3.6.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 2011-2015 (*Table 3.2*).

In the analysis of risk factors, those associated with cardiovascular disease were male gender, Dutch origin, older age, infection through heterosexual contact, a latest CD4 cell count <200 cells/mm^3, pre-treatment with nucleoside-analogue RT inhibitors at start of cART, use of abacavir (either currently or in the last 6 months), current and past smokers, and presence of hypertension. Cardiovascular risk was also higher during 2000-2005 than during 2011-2014, independent of other variables included in the analysis. A prior AIDS diagnosis was borderline significantly associated with an increased risk for CVD (*Appendix Table 3.7*).

From January 2000 onwards, 130 men and 12 women experienced a fatal or non-fatal secondary cardiovascular event (89 myocardial infarction, 60 stroke). The crude incidence per 1,000 years of follow up over the whole period between 2000 and 2015 in men and women with a prior cardiovascular event was 30.1 (95% CI 25.2-35.7) and 21.2 (95% CI 11.0-37.0), respectively. The crude rate and age-standardised incidence ratio (SIR) (indirect method) of secondary myocardial infarction and cerebrovascular accident per 1,000 years of follow up did not change significantly during 2000-2005 (crude rate 35.7 events per 1,000 years of follow up, SIR 1.28, 95% CI 0.86-1.69) and 2006-2010 (crude rate 27.3 events per 1,000 years of follow up, SIR 0.98, 95% CI 0.69-1.28) compared to the reference period 2011-2015 (crude rate 27.4 events per 1,000 years of follow up).

Table 3.2: *Crude incidence of cardiovascular disease per 1,000 years of follow up between 2000-2005, 2006-2010, and 2011-2015 and age-standardised incidence ratio with 95% confidence intervals.*

Calendar year	Male		Female	
	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)
2000-2005	9.8 (8.8-10.9)	1.36 (1.22-1.51)	3.0 (2.0-4.3)	0.79 (0.50-1.08)
2006-2010	10.4 (9.5-11.3)	1.20 (1.10-1.31)	5.0 (3.8-6.3)	1.09 (0.83-1.36)
2011-2015	10.3 (9.5-11.1)	1.00	5.6 (4.4-6.9)	1.00

**Standardised according to the observed age distribution between 2011-2015.*

Legend: *CI=confidence intervals.*

Trends in cardiovascular risk factors

The percentage of men with dyslipidaemia, defined as a cholesterol level of 6.2 mmol/l or higher, has decreased over time from 26% of those with an available cholesterol measurement in 2000 (regardless of whether statins were used) to 12% in 2015 (*Figure 3.3*). In women, this figure decreased from 19% in 2000 to 14% in 2005 and has fluctuated around that value ever since. *Appendix Figure 3.2* gives an overview of the absolute numbers of individuals in each cholesterol category over time.

Figure 3.4 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 2015, the percentage of overweight (25-30 kg/m^2) and obese (≥30 kg/m^2) men with an available BMI measurement was 32% and 8%, respectively. In women, these percentages were 30% and 25%, respectively. *Appendix Figure 3.3* 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 to ageing of the HIV-infected population. This revealed that the increase in BMI over time was at least partially driven by changes over time in demographic characteristics (age, region of origin, transmission risk group) and time since first starting cART, and that this effect was more marked in men than women.

Figure 3.5.A shows that, in 2015, 49% of those treated with antihypertensives still had grade 1 hypertension or higher. The figures above the bars show that, over time, the number of patients using antihypertensives has increased, while *Appendix Figure 3.4.A* shows that the number of patients on antihypertensive therapy with normal or high normal blood pressure has also increased. In 2015, 2,243 (25%) untreated individuals had grade 1-3 hypertension (*Figure 3.5.B*). For 2,140 of these 2,243 individuals, a 5-year CVD risk could be calculated with the recently recalibrated D:A:D study algorithm[74]. Of the 2,140 individuals, 6% 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[17]. *Figure 3.6* gives an overview of the cART-treated population's estimated risk of developing CVD over time. From 2004 until 2015, the percentage of individuals at high (5-10%) or very high risk (≥10%) increased only slightly from 16% and 9%, respectively, in 2004 to 19% and 12%, respectively, in 2015. The slight increase in the percentage of individuals at high or very high risk may reflect the ageing of the population under study.

Figure 3.3: Distribution of cholesterol levels (mmol/l) at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and the total number of women, respectively, with an available cholesterol measurement. For each individual, the last available measurement in each year was selected.

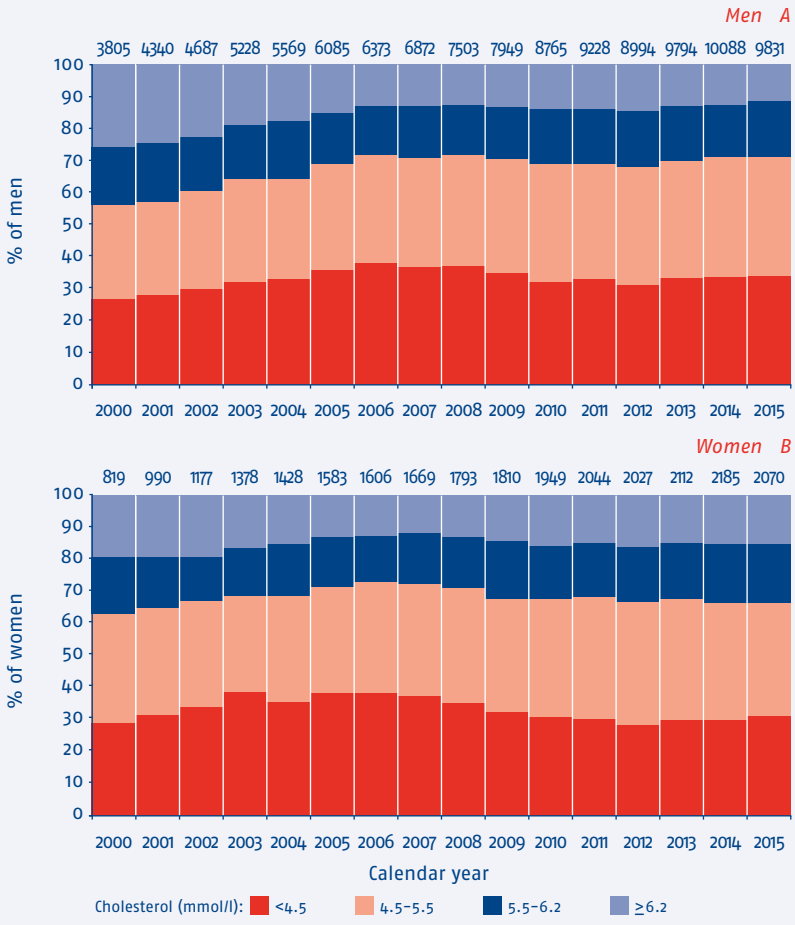
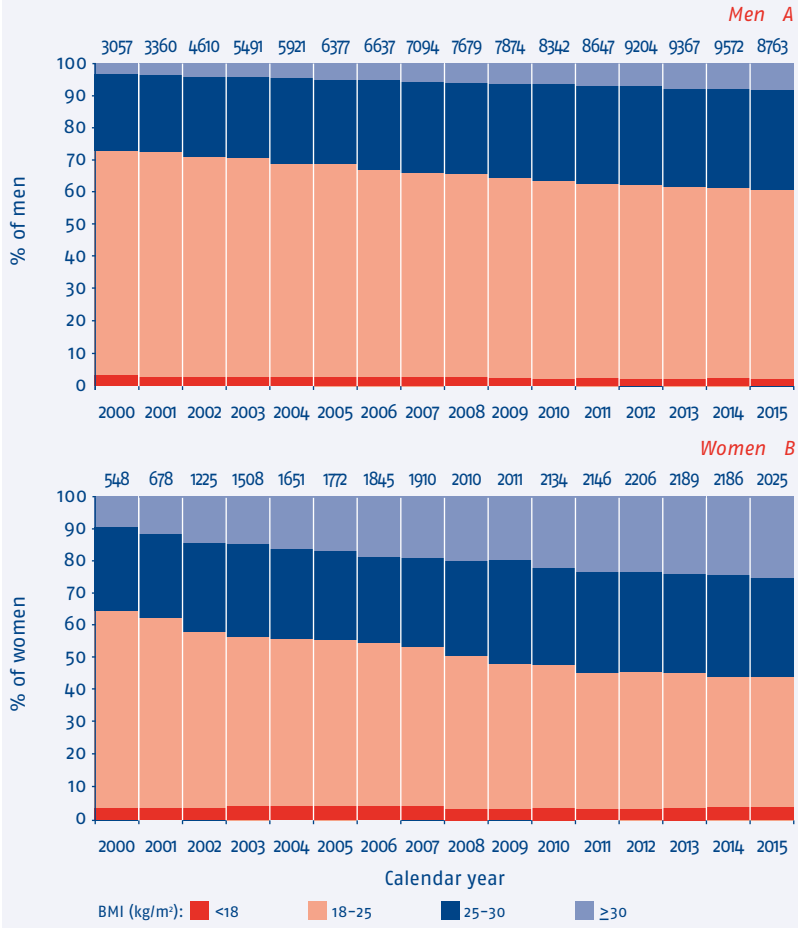
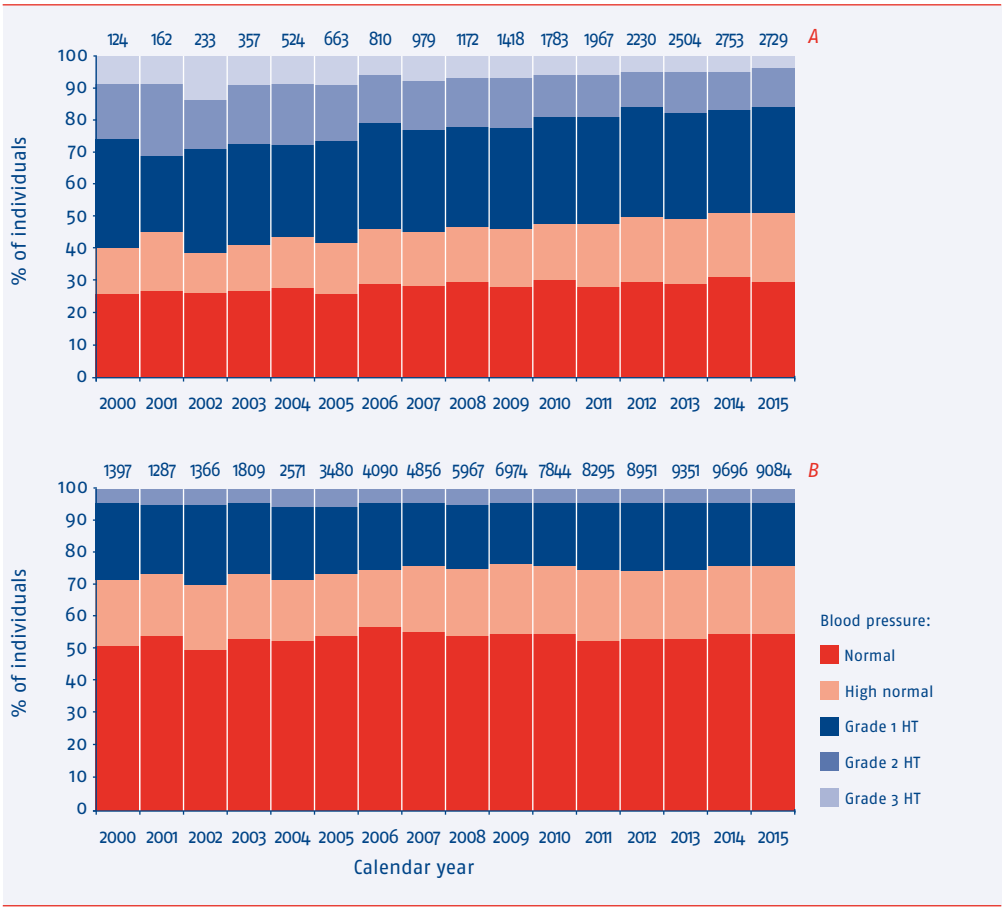


Figure 3.4: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and women with a known BMI in each year. For each patient, the last available weight measurement in each year was selected.



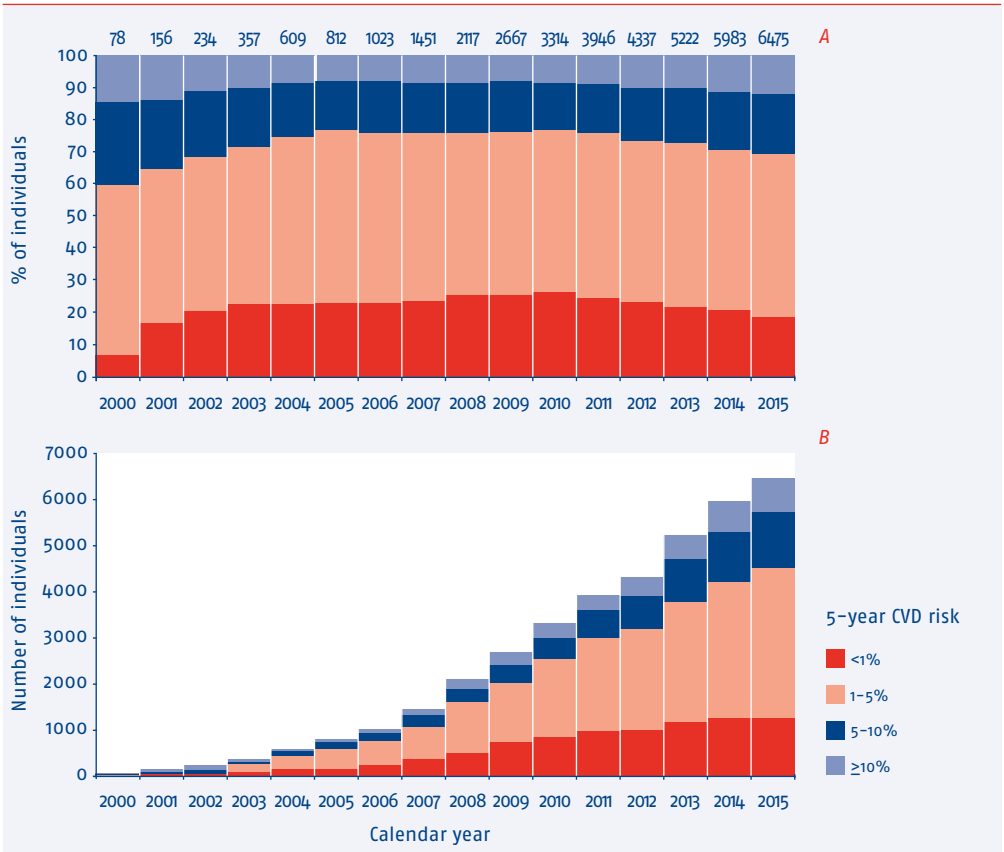
Legend: BMI=body mass index.

Figure 3.5: *Distribution of graded blood pressure at the end of each calendar year in (A) individuals known to be receiving antihypertensive treatment and (B) individuals not recorded as being treated for hypertension. 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 the European Society of Cardiology[175]). 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 3.6: *Estimated five-year risk of cardiovascular disease at the end of each calendar year according to the algorithm from the D:A:D: study[74]. 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. Panel A shows the percentage of patients and panel B shows 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 in younger individuals in particular because of missing data. Hence, the reported absolute number of individuals is much smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are overrepresented.*



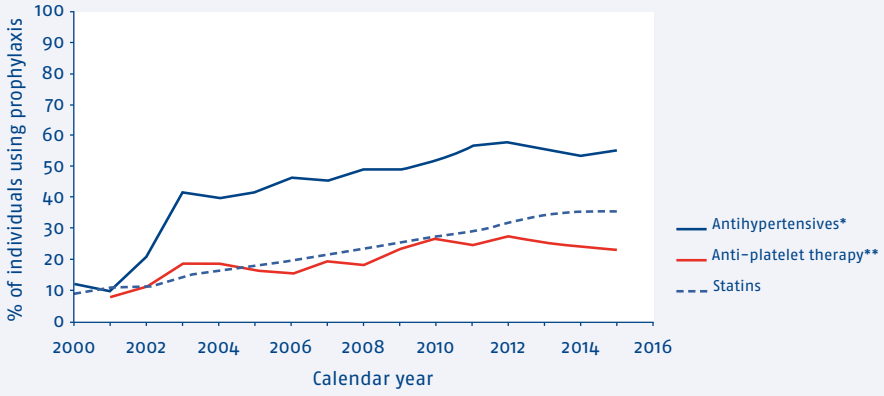
Legend: *CVD=cardiovascular risk.*

Use of primary or secondary prophylaxis for myocardial infarction or stroke

Primary prophylaxis

According to the 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/clopidogrel (anti-platelet therapy) should be offered to individuals aged 50 years or more with a 5-year CVD risk ≥10%[76]. *Figure 3.7* 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, but these percentages seem to have levelled off since 2012. Although there was also a slow increase up to 2012 in the percentage of individuals at high risk aged 50 years or older who use antiplatelet therapy as primary prevention, the overall proportion has remained minimal and might even have decreased somewhat during the last 3 years.

Figure 3.7: 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, anti-platelet therapy, or antihypertensives as primary prophylaxis for myocardial infarction or stroke.



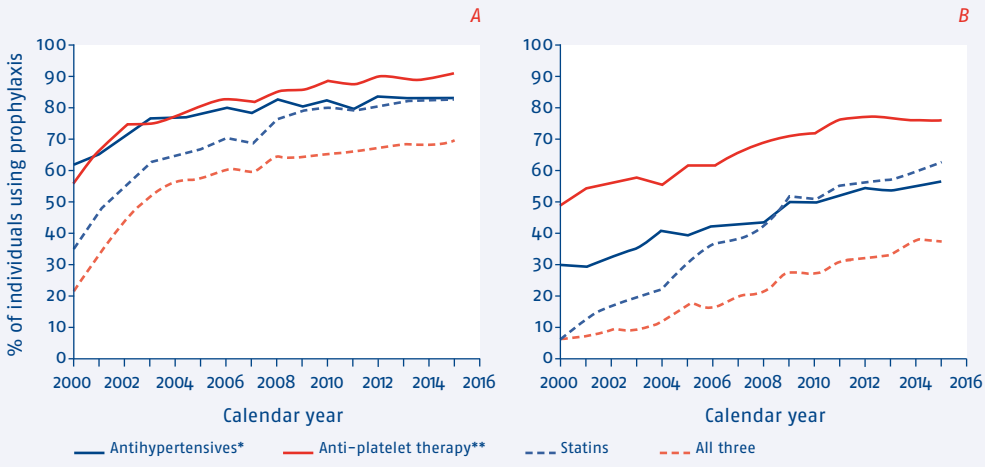
**Includes ACE inhibitors, beta-blockers, or angiotensin receptor blockers.*

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

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 (referred to here as anti-platelet therapy)[77, 78]. *Figure 3.8*.A shows that the percentage of individuals using statins, anti-platelet therapy, or antihypertensives after a myocardial infarction has increased between 2000 and 2015: in 2015, 83% of individuals with a prior myocardial infarction used statins, 83% used antihypertensives, and 91% used anti-platelet therapy. Although the use of statins and antihypertensives after an ischaemic stroke also increased over time, in 2015 they were used less frequently after stroke than after a myocardial infarction (63% for statins, 76% for anti-platelet therapy, and 56% for antihypertensives) (*Figure 3.8.B*).

Figure 3.8: *Percentage of individuals with (A) prior myocardial infarction or (B) prior ischaemic stroke using statin therapy, anti-platelet therapy, or antihypertensives.*



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

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

Chronic kidney disease

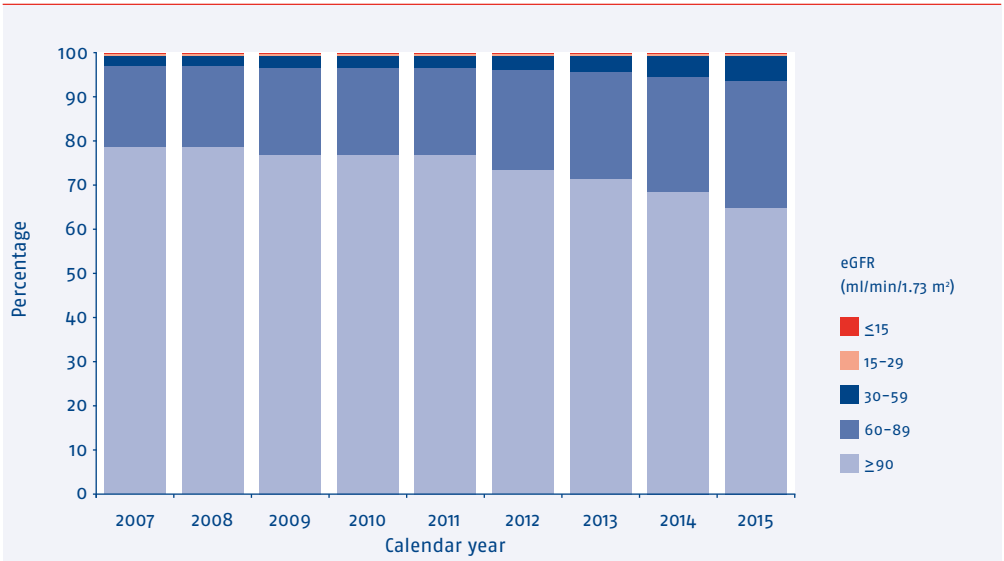
Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely, the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations[79]. As all three equations used to estimate 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[79, 80]. However, because the Cockcroft-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 3.9*. The percentage of patients with normal kidney function decreased over time from 79% in 2007 to 64% in 2015. This decrease was observed in both men and women (*Figure 3.10*). Typically, eGFR decreases with increased age, which is shown by *Figure 3.11*, 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/1.73m^2 at inclusion in the analyses and without previously confirmed CKD, the crude incidence of CKD, defined as eGFR <60ml/min/1.73m^2 confirmed by a second test at least 12 weeks later, varied over time (*Figure 3.2.C*). Routine collection of serum creatinine measurements commenced in 2007. To avoid misclassifying prevalent CKD as incident CKD we used serum creatinine levels measured in 2007 to distinguish between prevalent (CKD already present in 2007) versus new onset incident cases of CKD (no CKD observed in 2007) from 2008 onwards. In men, the incidence changed from 8.5 cases per 1,000 person years in the period 2008-2010 to 13.9 in 2011-2015, and in women the incidence went from 13.4 to 15.9 cases per 1,000 person years during the same periods (*Table 3.3.A*). The standardised incidence ratio in men, but not in women, increased significantly over time (*Table 3.3.A*).

Since creatinine levels were not collected in a standardised manner until 2007, eGFR could not be calculated before 2007, and, as explained above, the incidence of new onset CKD could not be reliably estimated before 2008. 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 2008 (*Table 3.3.B*), which showed the same pattern over time as the previous analysis. Risk factors for CKD included female gender, non-Dutch origin, low current CD4 cell count (<350 cells/mm^3), prior AIDS diagnosis, IDU HIV transmission risk group, older age, lower body mass index, diabetes mellitus, cardiovascular disease, and HCV co-infection (*Appendix Table 3.7*).

Figure 3.9: *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: *eGFR=estimated glomerular filtration; ≥90 ml/min/1.73m^2: normal kidney function; 60–89 ml/min/1.73m^2: mildly reduced; 30–59 ml/min/1.73m^2: moderately reduced; 15–29 ml/min/1.73m^2: severely reduced; <15 ml/min/1.73m^2: very severely reduced kidney function.*

Figure 3.10: Distribution of categories of estimated glomerular filtration rate (eGFR) at the end of each calendar year in (A) men and (B) women. For each patient, the last available measurement in each year was selected.

Legend: eGFR=estimated glomerular filtration; ≥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 3.3.A: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008–2010, and 2011–2015 and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)
2008–2010	8.5 (7.2–10.1)	0.67 (0.56–0.78)	13.4 (10.2–17.3)	0.99 (0.74–1.23)
2011–2015	13.9 (12.8–15.1)	1.00	15.9 (13.5–18.7)	1.00

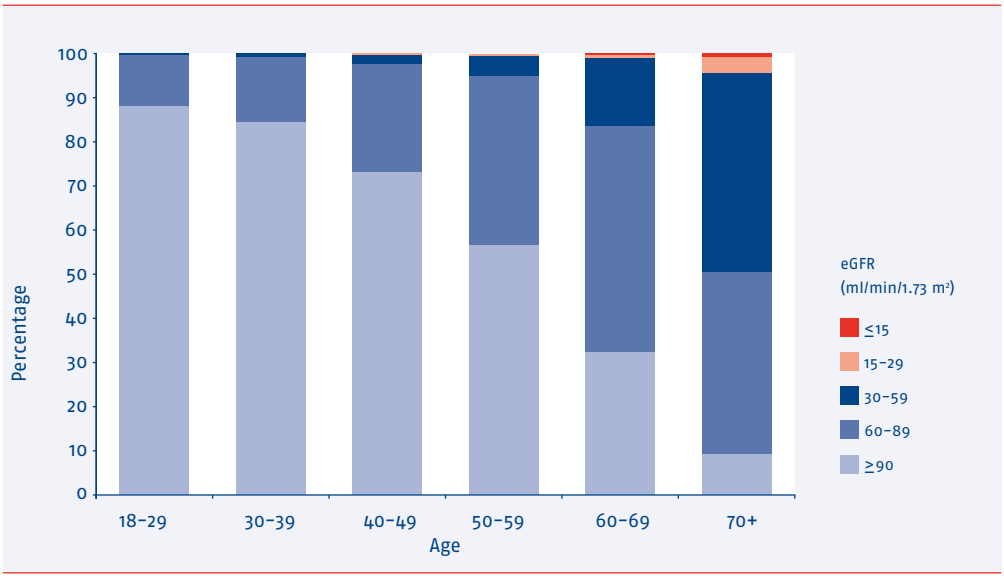
**Standardised according to the observed age distribution between 2011–2015.*
***Legend:** CI=confidence interval.*

Table 3.3.B: Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008–2010, and 2011–2015 and age-standardised incidence ratio with 95% confidence intervals in men and women with an HIV-1 diagnosis in or after January 2008.

Calendar year	Male		Female	
	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)
2008–2010	9.3 (6.5–12.8)	0.63 (0.43–0.84)	19.2 (10.2–32.8)	0.97 (0.44–1.50)
2011–2015	16.0 (14.3–17.8)	1.00	22.0 (17.4–27.5)	1.00

**Standardised according to the observed age distribution between 2011–2015.*
***Legend:** CI=confidence interval.*

Figure 3.11: Distribution of categories of estimated glomerular filtration rate (eGFR) in 2015 according to different age categories. For each patient, the last available measurement in 2015 was selected.



Legend: eGFR=estimated glomerular filtration; ≥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.

Non-AIDS-defining malignancies

Between 2000 and 2015, 1,141 patients in SHM's database had a recorded diagnosis of non-AIDS-defining malignancy. The most common types of non-AIDS-defining cancer were lung cancer (19%), invasive anal cancer (13%), Hodgkin's lymphoma (8%), and head and neck cancers (8%). *Figure 3.12* 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 3.13*, 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.

The crude incidence of non-AIDS-defining malignancies increased slightly from 6.1 cases per 1,000 person years in 2000-2005 to 6.5 cases per 1,000 person years in 2011-2015 in men and from 2.2 cases per 1,000 person years in 2000-2005 to 3.8 cases per 1,000 person years in 2011-2015 in women (*Figure 3.2.D*; *Appendix Table 3.6.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 3.4*). 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. In women, the age-standardised incidence was lower in the period 2011-2014 than in 2006-2010, but not 2000-2005.

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 (CD4 below 350 cells/mm^3), low body mass index, prior AIDS, chronic HBV co-infection, and current smoker (*Appendix Table 3.7*).

In total, 3 HIV-infected women and 146 HIV-infected men were diagnosed with anal cancer. Among HIV-infected men, the incidence of anal cancer slowly decreased over time from 1.1 cases per 1,000 person years in 2000 to 0.6 cases per 1,000 person years in 2015 (*Figure 3.2 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[81]. Furthermore, 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 2015 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[82]. 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.

Figure 3.12: Relative changes in non-AIDS-defining malignancies between 2000 and 2015 in HIV-1 infected patients in the Netherlands.

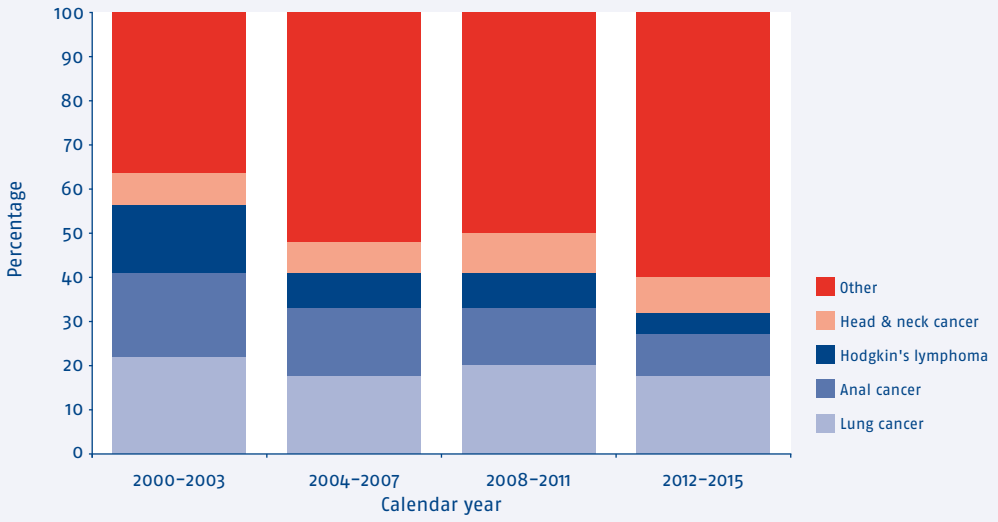


Figure 3.13: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1 infected patients in the Netherlands.

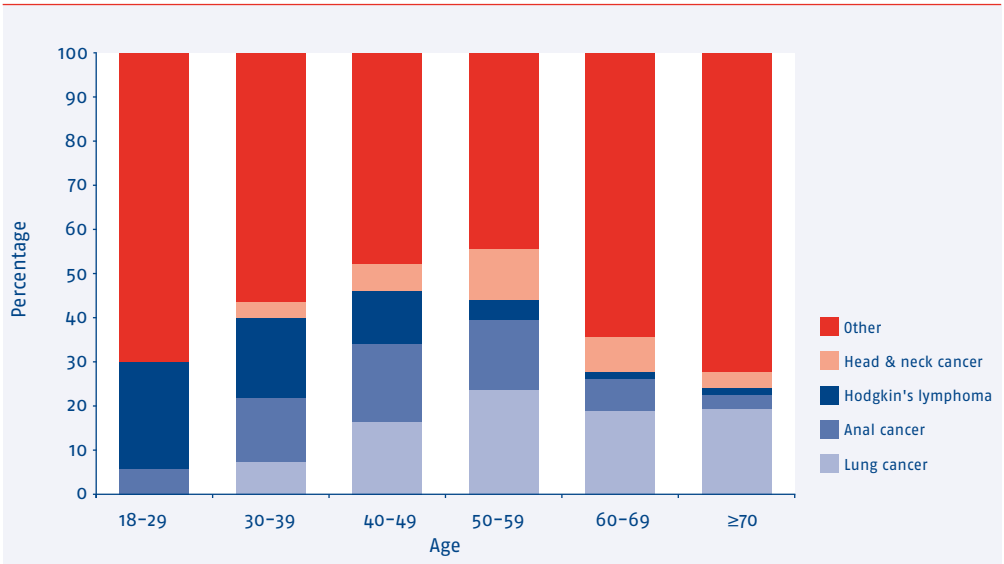


Table 3.4: Crude non-AIDS-defining malignancy incidence per 1,000 years of follow up between 2000-2005, 2006-2010, and 2011-2015, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)
2000-2005	6.0 (5.3-6.9)	1.34 (1.16-1.52)	2.2 (1.4-3.4)	0.96 (0.56-1.35)
2006-2010	6.8 (6.1-7.6)	1.26 (1.13-1.39)	4.3 (3.2-5.5)	1.45 (1.07-1.82)
2011-2015	6.5 (5.9-7.2)	1.00	3.8 (2.9-4.9)	1.00

**Standardised according to the observed age distribution between 2011-2015.*

***Legend:** CI=confidence intervals.*

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

In 5,716 therapy-naive individuals who started cART with less than 350 CD4 cells/mm^3 and who had 3 years of viral suppression on cART, 1,248 were classified as immunological nonresponders (defined as those having less than 350 CD4 cells/mm^3 after 3 years of viral suppression on cART) and 4,468 patients had a good immunological response (those having a CD4 cell count of 350 cells/mm^3 or higher after 3 years of viral suppression on cART). We analysed the association between immunological response and the risk of the following endpoints: death, AIDS, non-AIDS-defining malignancy, diabetes mellitus, and cardiovascular disease. We only considered first events; patients in whom a particular endpoint had already occurred prior to the start of observation of this analysis (mainly prior AIDS events) were excluded. For this analysis, the observation period started after 3 years of successful cART. Changes in immune status and/or plasma viraemia and/or use of cART after 3 years of cART have been ignored in this analysis, meaning that patients remained in their original category of immunological responder/non-responder. The number of events, crude incidence per 1,000 patient years of follow up, and age-standardised incidence ratio of these events are reported in *Table 3.5*. Although the crude incidences of death, AIDS, non-AIDS-defining malignancies and cardiovascular disease were higher in the immunological non-responders, the age-standardised incidence ratio only reached statistical significance for death. Similarly, after further adjustment for current age, region of origin, gender, and HBV and HCV status, immunological non-response remained only significantly associated with death (risk ratio (RR) 1.42, 95% CI 1.10-1.84, p=0.007), but not with AIDS (RR 1.12, 95% CI 0.69-1.82, p=0.66), non-AIDS-defining malignancy (RR 1.25, 95% CI 0.88-1.78, p=0.21), diabetes mellitus (RR 0.84, 95% CI 0.58-1.23, p=0.37), and cardiovascular disease (RR 1.13, 95% CI 0.81-1.57, p=0.48). However, as the number of endpoints is small, these results should be interpreted with caution.

Table 3.5: Crude incidence per 1,000 years of follow up, and age-standardised incidence ratio with 95% confidence intervals of various clinical endpoints. The study population consists of patients who started cART with a CD4 cell count below 350 cells/mm³ and after 3 years of virologically successful cART were either immunological responders (CD4 cell count >350 cells/mm³) or non-responders (CD4 cell count <350 cells/mm³).

Risk of various clinical endpoint	Total PY exposure	Total number of events	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)	p-value
Death					
Responder (CD4 ≥350)	26,887	161	5.99 (5.10-6.99)	1.000	0.01
Non-responder (CD4 <350)	8,538	95	11.13 (9.00-13.60)	1.374 (1.098-1.651)	
AIDS					
Responder (CD4 ≥350)	20,070	76	3.79 (2.98-4.74)	1.000	0.65
Non-responder (CD4 <350)	4,630	21	4.54 (2.81-6.93)	1.110 (0.635-1.585)	
Non-AIDS-defining malignancy					
Responder (CD4 ≥350)	26,391	95	3.60 (2.91-4.40)	1.000	0.17
Non-responder (CD4 <350)	8,316	48	5.77 (4.26-7.65)	1.249 (0.895-1.602)	
Diabetes mellitus					
Responder (CD4 ≥350)	25,689	115	4.48 (3.70-5.37)	1.000	0.45
Non-responder (CD4 <350)	8,080	37	4.58 (3.22-6.31)	0.890 (0.603-1.177)	
Cardiovascular disease					
Responder (CD4 ≥350)	26,496	113	4.26 (3.51-5.13)	1.000	0.40
Non-responder (CD4 <350)	8,307	52	6.26 (4.68-8.21)	1.132 (0.825-1.440)	

**Standardised according to the observed age distribution in the immunological responders.*

***Legend:** PY=person years; CI=95% confidence interval.*

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 those reported by studies from Spain[83], Denmark[84], several other European countries[85], and the USA[86]. 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[87]. Moreover, 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 mainly a reflection of the high proportion of patients continuing to present late for care and who already have advanced immunodeficiency, AIDS, or both.

Diabetes and cardiovascular disease

Whereas the crude incidence of diabetes mellitus and cardiovascular disease (CVD) in men and women was found to have remained relatively stable, the age-standardised incidence for both diseases has 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[88] and myocardial infarction[89, 90] to those that, to date, have not been associated with such risks), and increased attention to managing traditional risk factors for diabetes and CVD. Furthermore, the declining 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 at 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 diabetes and CVD, including age, hypertension, smoking and obesity, similar to what has been reported in other studies[88, 91, 92]. Several of these risk factors have been reported to be more prevalent among people living with HIV[69].

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 2000-2015. This suggests that cardiovascular risk management has improved over time, as illustrated by the increasing use of statins and antihypertensives over time and the shift away from the use of antiretrovirals which have been demonstrated to be

associated with increased cardiovascular risk, particularly in patients with high underlying risk[93] (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 slowly 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[94]. 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[95]. 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

Since 2008, the incidence of new onset chronic kidney disease (CKD) has been increasing steadily and, as expected, older individuals and those with traditional risk factors such as older age and 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[96, 97] and the use of tenofovir, atazanavir/ritonavir, and lopinavir/ritonavir to be additional independent predictors of chronic renal impairment[98]. Moreover, in the HIV-infected population, renal impairment is associated with an increased risk for cardiovascular disease[99].

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, current or past smokers and more likely to have lower CD4 counts (the effect was significant with CD4 cell counts below 350 cells/mm^3) and a prior AIDS diagnosis. Several cohorts, including the Swiss HIV cohort study, have previously reported an increased incidence of non-AIDS-defining malignancies with increasing age[100, 101, 102, 103]. Moreover, the effect of immunodeficiency may be stronger for

infection-related non-AIDS-defining malignancies[104]. 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 on 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 protease inhibitor-based cART regimen. This association was observed particularly for anal cancer[105]. 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 for 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 to be expected that this may also have a beneficial impact on the incidence of those comorbidities, such as non-AIDS-defining malignancies, for which advanced immunodeficiency is a contributing risk factor[11, 12, 13]. 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 comorbidities. Studies such as the ongoing 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 patho-physiological mechanisms[59, 106]. In addition, prolonged follow up of participants in such studies will demonstrate the extent to which comorbidity 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 comorbidities 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 perhaps 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[107].

Ageing, of course, strongly contributes to the risk of the development of comorbidity, 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 comorbidities, and the appropriate management of these risk factors offer considerable hope for lowering the comorbidity burden and ensuring healthy ageing in persons living with HIV.

4. Viral hepatitis

Colette Smit, Joop Arends, Peter Reiss and Clemens Richter

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 that 0.2 to 0.4% has ever been exposed to HBV[108]. In contrast, HCV and HBV co-infections are far more prevalent in HIV-infected individuals due to shared routes of transmission with HIV[109].

Individuals with chronic HCV and HBV infection are at risk for the development of liver fibrosis, which in time may lead to cirrhosis and can ultimately result in end-stage liver disease and hepatocellular carcinoma (HCC)[110, 111]. 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[112, 113]. However, 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[114, 115, 116, 117].

In the era when treatment for HIV infection was either unavailable or insufficiently effective to achieve sustained suppression of viral replication, most patients 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[118].

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). In the population with HIV and HCV and/or HBV co-infection, these

additional data allow increasingly reliable reporting of the demographic and clinical characteristics, progression to severe chronic liver disease and mortality, and responses to treatment, as summarised in this chapter. Importantly, this chapter also describes updated results of treatment of HCV co-infected patients with the direct-acting antivirals (DAAs) sofosbuvir, simeprevir, daclatasvir, dasabuvir, ledipasvir, ombitasvir and paritaprevir.

HCV

Demographic and clinical characteristics

In total, 2,616 (12%) of the 22,042 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 greater prevalence of HCV in the HIV-infected population than estimated for the general population in the Netherlands (*Figure 4.1*). In 194 of the 2,616 patients (7%), HCV RNA data were not documented. Of the remaining 2,422 patients with positive HCV RNA test results, 1,371 (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 441 (15%) were diagnosed with acute HCV infection (documented anti-HCV IgG seroconversion or HCV RNA conversion within 12 months). Another 407 (17%) patients had evidence of spontaneous clearance of HCV (documented positive test result for HCV antibody or HCV RNA followed by a subsequent negative HCV RNA test result, without having received HCV treatment); the demographic characteristics of these are shown in *Table 4.1*. The remaining 203 patients of the 2,422 patients with available HCV RNA data had one positive HCV RNA test result, but no registered follow-up results. This makes it impossible to determine whether their HCV infection was acute or chronic at the time of diagnosis, and, therefore, this group of patients was excluded from further analysis.

Table 4.1: Demographic characteristics of HIV/hepatitis C virus (HCV) co-infected patients registered in the SHM database, 1998-2016.

	Total	Chronic HCV	Acute HCV	Spontaneous clearance
Total number of patients screened for HCV	22,042	1,371	441	407
Male gender, n (%)	18,022 (82)	1,143 (83)	434 (98)	307 (75)
Region, n (%)				
Netherlands	12,674 (58)	845 (62)	349 (79)	203 (50)
Europe	1,456 (7)	209 (15)	27 (6)	57 (14)
Sub-Saharan Africa	3,101 (14)	46 (3)	7 (2)	48 (12)
Caribbean/South America	2,542 (12)	90 (7)	30 (7)	47 (12)
Southeast Asia	748 (3)	41 (3)	10 (2)	13 (3)
Other	1,521 (7)	140 (10)	18 (4)	39 (10)
HIV transmission route, n (%)				
HIV transmission route	13,351 (61)	656 (48)	414 (94)	165 (41)
Men who have sex with men	6,574 (30)	141 (10)	15 (3)	88 (23)
Heterosexual	712 (3)	423 (31)	6 (1)	95 (23)
Current and former injecting drug users	1,405 (6)	151 (11)	6 (1)	59 (15)
Other				
cART, n (%)	20,542 (93)		431 (98)	378 (93)
HCV genotype (GT), n (%*)				
Total determined		1,233	388	
GT 1		773 (63*)	267 (69*)	
1a		*478*	*218*	
1b		*90*	*7*	
1c, 1a/b or not further specified		*205*	*42*	
GT 2		62 (5*)	20 (5*)	
GT 3		174 (14*)	10 (3*)	
GT 4		195 (16*)	80 (21*)	
Other		29 (2*)	11 (3*)	
Not determined		138	53	
Deaths, n (%)	2,174 (10)	253 (18)	16 (4)	

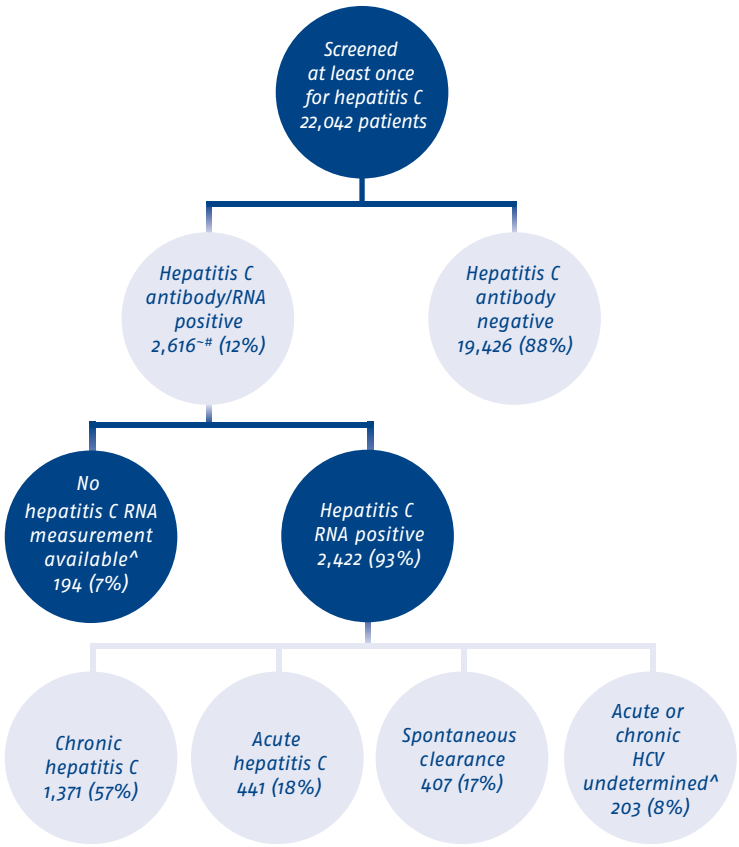
**Percentage of total number of individuals with an available HCV genotype.*

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

The analyses described in the remainder of this section on HCV are therefore limited to those patients who could be definitively classified as having either chronic (n=1,371) or acute (n=441) HCV infection. Most of these patients with chronic or acute HCV infection were male (83% and 98%, respectively). Most patients originated

from the Netherlands (chronic 845/1,371 [62%], acute 349/441 [79%]) *(Table 4.1)*. Fifty-nine percent of the patients ever registered and infected with HIV through injecting drug use (IDU) or former IDU had chronic HCV infection (423 of the total 712 [former] IDU), while 5% of men who have sex with men (MSM) had chronic HCV infection (656 of the total of 13,351 MSM) and 3% of MSM had experienced an acute HCV infection (414 of the total of 13,351 MSM). For 1,233 of the 1,371 patients (90%) with a chronic HCV infection, the HCV genotype was determined and documented in the clinical records. The majority of these patients (63%) were infected with HCV genotype 1 (n=773); of those with genotype 1, most were infected with genotype 1a (n=478). Five percent were infected with HCV genotype 2 (n=62), 14% were infected with genotype 3 (n=174), and 16% with genotype 4 (n=195). Two percent of the patients were either infected with genotype 5 or 6 or had been re-infected with another genotype. In 388 of the 441 patients (88%) with an acute HCV infection, an HCV genotype was available. In most of the cases, patients with an acute HCV infection were infected with either genotype 1 (69%) (n=267) or genotype 4 (21%, n=80). Of the 218 infected with genotype 1, 218 were infected with genotype 1a and 7 with genotype 1b.

Figure 4.1: 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*

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 4% of the patients in care had not been screened for HCV co-infection, and this total declined further to 0.4% in 2015 (*Figure 4.2*).

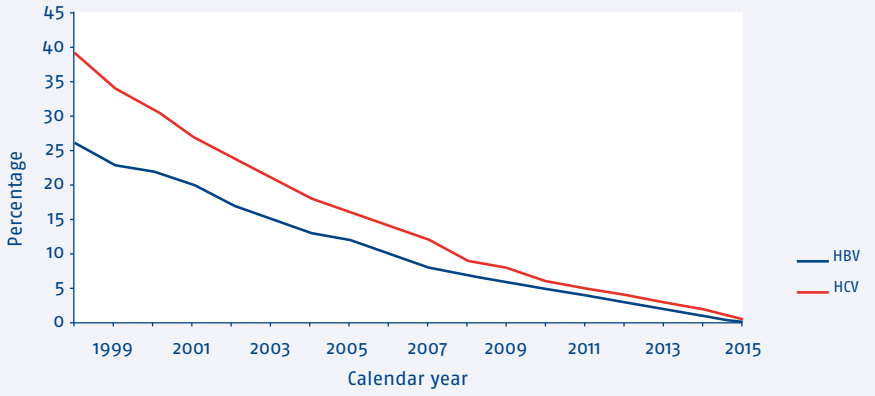
Prevalence of chronic HCV co-infected patients per calendar year

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 7% in 2015, 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 64% and 73% (*Figure 4.3*). The number of patients successfully treated for HCV was not taken into account when reporting the prevalence of chronic HCV.

Incidence of acute HCV infection over time

The incidence of acute HCV infection showed important differences between HIV transmission categories. The vast majority of acute HCV infections occurred in MSM (414/441 (94%)). For IDU or former IDU, the overall incidence was low (2.5/1,000 person years [PY], 95% confidence interval [CI] 0.8-5.9), 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 0.2/1000 PY (95% CI 0.10-0.34). *Figure 4.4* shows the incidence of acute HCV infection among MSM over time. The overall rate of acute HCV infection in this group was 3.5 per 1,000 PY of follow up (95% CI 3.2-3.9). This incidence increased from 0 diagnoses per 1,000 PY in 1998 to 5.9 diagnoses per 1,000 PY in 2015, with a peak in 2007 and 2008 of 7.2 acute HCV infections per 1,000 PY.

Figure 4.2: 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 4.3: Prevalence of chronic hepatitis C co-infection per calendar year.

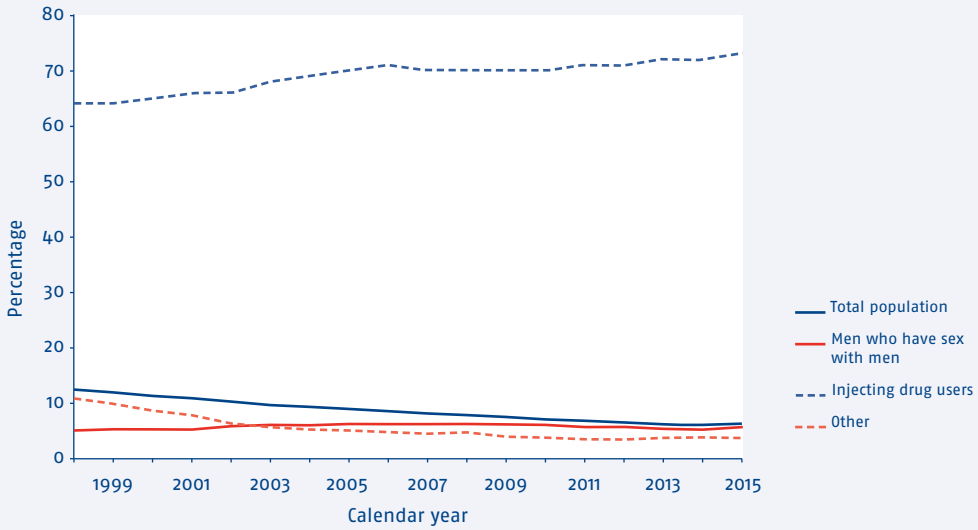
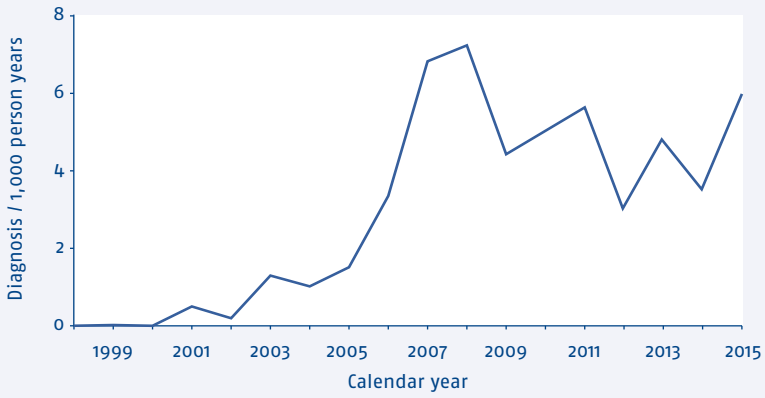


Figure 4.4: Incidence of acute hepatitis C infection among men who have sex with men, per calendar year.



Treatment for HCV infection

The primary aim of treatment for HCV is to achieve a sustained virological response (SVR)[17]. In the past, treatment 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 antivirals (DAAs) active against HCV genotype 1, became available in the Netherlands[119, 120]. These agents were subsequently used as part of triple therapy that included 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. Initially, as a consequence of government restrictions, the cost of sofosbuvir was reimbursed only for HCV-infected individuals with severe liver fibrosis or cirrhosis (metavir score F3-F4 or Fibroscan® stiffness ≥9.5), patients on the waiting list for, or having undergone, a liver transplant, or patients with extrahepatic manifestations such as porphyria cutanea tarda, leukocytoclastic vasculitis or vasculitis and/or renal insufficiency secondary to cryoglobulinaemia. In November 2015, sofosbuvir became available for all HCV-infected patients, regardless of their fibrosis status.

In addition to the introduction of sofosbuvir, additional novel DAAs, HCV NS3/4A protease inhibitors (PI) (simeprevir and paritaprevir), NS5A inhibitors (daclatasvir, ledipasvir and ombitasvir) and an NS5B polymerase inhibitor (dasabuvir) have also become available. *Table 4.2* gives an overview of all DAA-containing HCV treatment combinations currently available in the Netherlands[121].

Table 4.2: Overview of currently available treatment regimens, including direct-acting antivirals (DAAs) active against hepatitis C (HCV) in the Netherlands.

DAA/HCV treatment combination*	Available since	HCV genotypes covered	Treatment duration
Sofosbuvir+RBV+PEG-IFN	2014	All	12 weeks
Sofosbuvir+RBV	2014	2+3	12-24 weeks
Simeprevir+RBV+PEG-IFN	2014	1+4	24-48 weeks
Simeprevir+sofosbuvir +/- RBV	2014	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
Ledipasvir/sofosbuvir+/- RBV	2015	1, 3, 4	12-24 weeks
Paritaprevir/r/ombitasvir	2015	1,4	12-24 weeks
Paritaprevir/r/ombitasvir /dasabuvir	2015	1	12-24 weeks

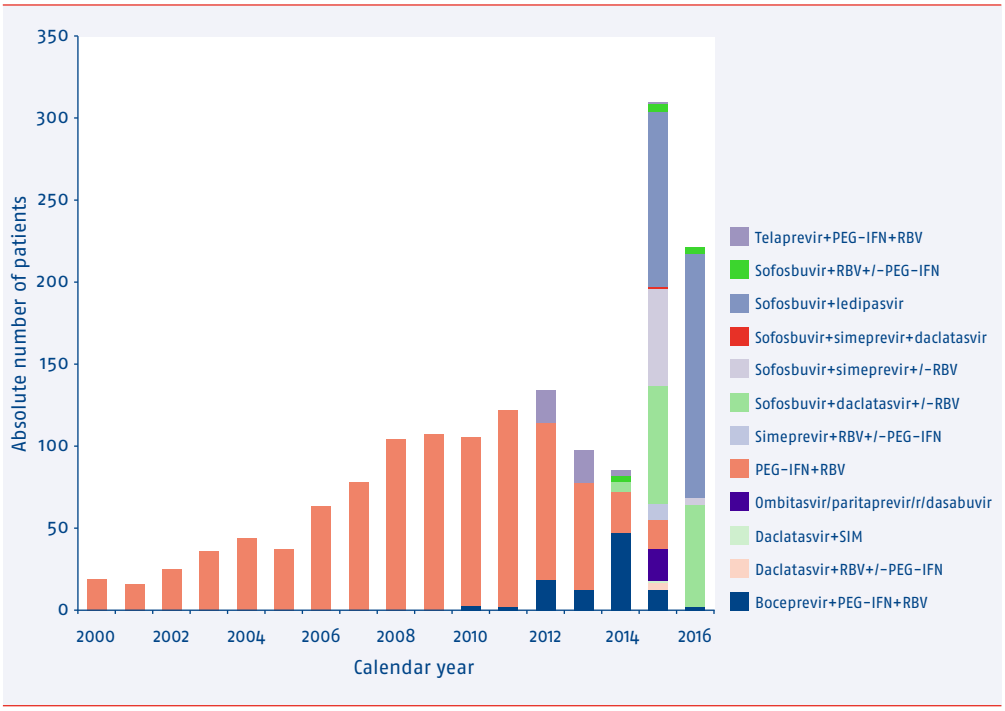
**Boceprevir and telaprevir were only temporarily available and therefore not included in this table.*
***Legend:** DAA=direct-acting antiviral agent; HCV=hepatitis C virus;; RBV=ribavirin; PEG-IFN=pegylated interferon; r=ritonavir.*

Figure 4.5 shows the absolute number of patients who have started HCV treatment per calendar year. In total, 1,256 patients have received HCV treatment; of those, 379 have received HCV treatment more than once, including patients who were unsuccessfully treated and those who became re-infected with HCV after previous successful treatment.

Treatment with IFN alpha/PEG-IFN alpha plus ribavirin

The number of patients per year starting IFN alpha/PEG-IFN alpha plus ribavirin (RBV) treatment increased from 19 in 2000 to 120 in 2011, followed by annual decreases to 17 in 2015 (*Figure 4.5*).

Figure 4.5: Number of co-infected patients starting hepatitis C treatment per calendar year.



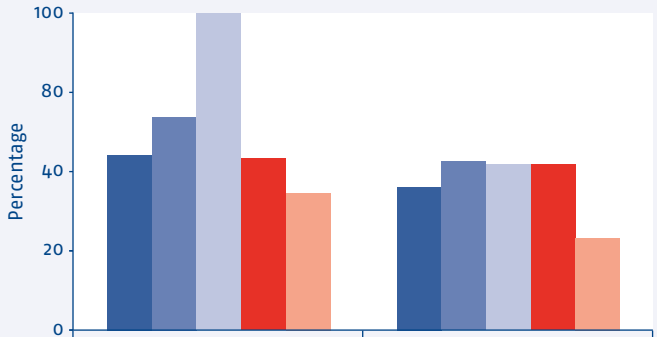
Legend: RBV=ribavirin; PEG-IFN=pegylated interferon; r=ritonavir.

Outcome of patients treated with IFN alpha/PEG-IFN alpha and RBV

Acute HCV

Of the 441 patients with an acute HCV infection, 283 had initiated treatment with IFN alpha/PEG-IFN alpha and RBV and, by the time of database closure, had completed a sufficient follow-up period to enable SVR24 (i.e., undetectable HCV RNA 24 weeks after treatment discontinuation) calculation. The median duration of treatment in these 283 patients was 24 weeks (interquartile range [IQR] 21-39). SVR rates are shown in *Figure 4.6*, stratified by HCV genotype. SVR24 rates were as high as 100% in patients with genotype 3, but ranged from only 43% to 67% for genotypes 1, 2, and 4. Of note, the number of patients with genotypes 2 and 3 receiving treatment was very small, limiting conclusions about treatment response for these genotypes.

Figure 4.6: Sustained virological response 24 (SVR24) achieved by pegylated interferon (PEG-IFN)+ribavirin (RBV) or IFN+RBV treatment in acute and chronic hepatitis C (HCV)-infected patients, stratified by HCV genotype.



	SVR acute HCV (%)	SVR chronic HCV (%)
Genotype 1	55% (n=105/191)	45% (n=178/399)
Genotype 2	67% (n=10/15)	53% (n=24/45)
Genotype 3	100% (n=4/4)	52% (n=49/95)
Genotype 4	54% (n=35/65)	52% (n=57/109)
Unknown/other	43% (n=3/7)	29% (n=2/7)

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

Chronic HCV infection

Of the 655 patients followed long enough to enable SVR24 calculation, the median duration of treatment with IFN alpha/PEG-IFN alpha plus RBV for chronic HCV infection was 25 weeks (IQR 16-47). *Figure 4.6* shows the SVR24 rate stratified by HCV genotype. Fifty-three percent of the patients with genotype 2 and 52% of patients with genotypes 3 and 4 achieved an SVR24, with lower rates for other genotypes (45% for genotype 1, and 29% for patients with an unknown or other genotype).

Treatment with boceprevir or telaprevir

Ninety-five patients started with boceprevir between 2010 and 2015, with treatment during the first two years provided as part of an international study and the national Dutch Acute HCV in HIV Study (DAHHS)[122, 123]. From 2012 onwards, 46 patients started telaprevir treatment[120] (*Figure 4.5*).

Outcome of treatment with boceprevir or telaprevir

Of the 141 patients starting either of these medications, 139 completed treatment with boceprevir (n=95) or telaprevir (n=44) 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 24 weeks (IQR 13-46) with telaprevir. Among those treated with telaprevir or boceprevir, 57% (79/139) achieved an SVR.

Treatment with novel DAAs

In total, 508 HIV co-infected patients have been treated with a regimen containing sofosbuvir, simeprevir, daclatasvir, ledipasvir, ombitasvir, paritaprevir or dasabuvir in a variety of combinations. Of these 508 patients, 9 started their treatment in 2014, 278 patients started in 2015, and the remaining 221 started in the first 4 months of 2016 (*Table 4.3*). 202 of these 508 patients had been pre-treated with PEG-IFN plus RBV before being treated with one of the novel DAAs. The most frequently-used regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=256), which was prescribed in 181 patients infected with genotype 1 and in 55 patients infected with genotype 4, and 2) sofosbuvir plus daclatasvir +/- RBV (n=139), which was prescribed in 84 patients infected with genotype 1 and in 26 infected with genotype 3. Two patients died after receiving treatment with sofosbuvir+ simeprevir and sofosbuvir+daclatasvir, one of a non-natural cause and the other of hepatic and renal failure by cirrhosis.

Table 4.3: Overview of responses to regimens containing novel direct-acting antivirals (DAAs) used by hepatitis C-HIV co-infected patients in care in the Netherlands, based on data available as of 15 August 2016.

Regimen	n	HCV genotype (GT)	HCV IFN/PEG-IFN+RBV pre-treated	Severe chronic liver disease (view definition)	Treatment completed and SVR12* data available	SVR12* (n/total no. patients with available HCV RNA test results)
Sofosbuvir+ledipasvir+/-RBV	256		97	77	198/256	196/198 (99%)
GT 1		181				
GT 2		3				
GT 3		5				
GT 4		55				
Other/unknown		12				
Sofosbuvir+daclatasvir+/-RBV	139		55	72	109/139	106/109 (97%)
GT 1		84				
GT 2		4				
GT 3		26				
GT 4		16				
Other/unknown		9				
Sofosbuvir+simeprevir +/-RBV	64		27	53	61/64	58/61 (95%)
GT 1		50				
GT 3		1				
GT 4		12				
Other/unknown		1				
Sofosbuvir + RBV +/- PEG-IFN	12		4	6	10/12	10/10 (100%)
GT 2		8				
GT 3		2				
GT 4		2				
Paritaprevir/r/ombitasvir/dasabuvir	21		8	6	19/21	18/19 (95%)
GT 1		10				
GT 4		1				
Other/unknown		10				
Simeprevir+PEG-IFN+RBV	10		7	2	10/10	10/10 (100%)
GT 1		4				
GT 4		5				
Other/unknown		1				

Regimen	n	HCV genotype (GT)	HCV IFN/PEG-IFN+RBV pre-treated	Severe chronic liver disease (view definition)	Treatment completed and SVR12* data available	SVR12* (n/total no. patients with available HCV RNA test results)
Daclatasvir+RBV +/- PEG-IFN	4		2	1	4/4	4/4 (100%)
GT 1		2				
GT 4		2				
Sofosbuvir+simeprevir+daclatasvir	1		0	0	1/1	1/1 (100%)
GT 4		1				
Simeprevir+daclatasvir	1		1/1	1	1/1	1/1 (100%)
GT 1		1				
Total	**508**		**201/508**	**218**	**413/508**	**404/413(98%)**

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

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

Outcome

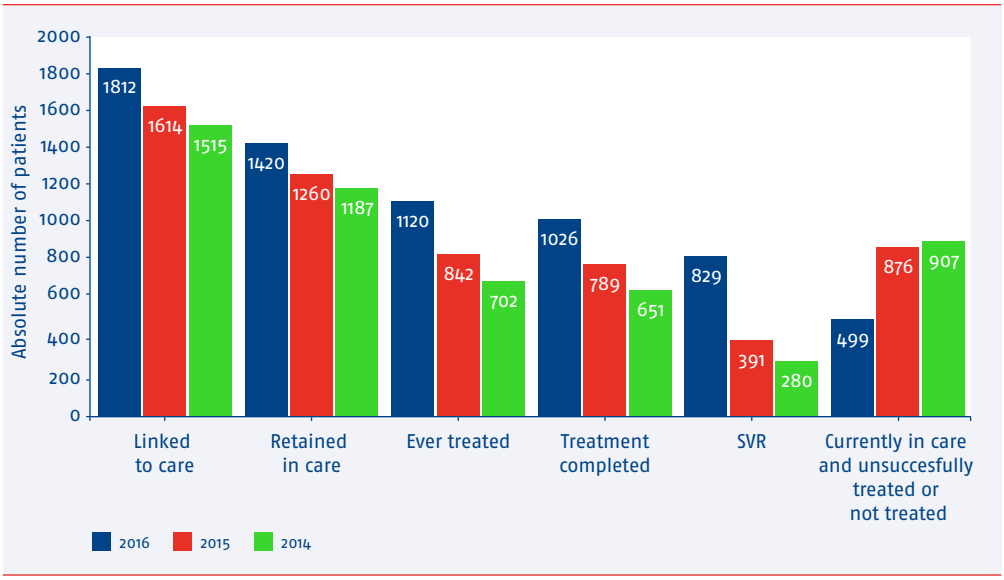
In total, at the time of database closure on 1 May 2016, 508 patients were known to have started a DAA regimen. HCV RNA data were collected up to 15 August 2016, at which point 413 patients had completed treatment with one of these regimens and had sufficient time since discontinuing treatment to enable calculation of the SVR12 rate (*Table 4.3*); 404 out of these 413 patients achieved an SVR12 (98%). In both treatment-naive patients and pre-treated patients the stratified SVR rate was 98%, and in patients with chronic liver disease the SVR rate was 97%. Nine patients failed to achieve an SVR. Although this group was not specifically different from the group that did achieve an SVR, it did have a slightly higher rate of chronic liver disease (5/9; 56% vs. 179/404; 44%). However, the small number of patients limits conclusions regarding failure to achieve an SVR in this group.

HCV treatment continuum of care

Figure 4.7 shows the continuum of care for patients with an HCV co-infection, based on the number known to be in care as of 1 May 2016, with data from the reports from 2014 (data cut-off 1 June 2014) and 2015 (data cut-off 15 September 2015) shown for comparison. Out of a total of 1,812 patients linked to HIV care and diagnosed with HCV, 1,420 patients (78%) were retained in care, and 1,120 (79%) of these 1,420 had ever received treatment for HCV. Of the 1,120 patients treated for HCV, 1,026 (92%) had completed HCV treatment and had data available to calculate

their HCV treatment response. Overall, 829 of the 1,026 (81%) patients who completed treatment had achieved an SVR. As a result, 591 of the 1,420 patients (42%) who were alive and in care as of 1 May 2016 in one of the Dutch HIV treatment centres remained untreated (n=300), not successfully treated (n=197), or were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation (n=94) for an active HCV infection. All 94 patients in whom SVR could not yet be calculated due to insufficient time since treatment discontinuation had been treated with novel DAA combinations. For that reason, we have extrapolated the DAA SVR rate of 98% observed so far and assumed that 98% of these 94 patients (n=92 patients) will be successfully treated, resulting in an estimated number of 591-92=499 HCV/HIV co-infected patients still alive and in care as of 1 May 2016 who remain untreated or unsuccessfully treated.

Figure 4.7: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

Compared with 2015, the continuum of care for 2016 shows that an additional 278 patients have received HCV treatment, resulting in an increase in HCV/HIV co-infected patients ever having been treated for HCV from 59% in 2014 and 67% in 2015 to 79% in 2016. Furthermore, an additional 438 patients have documented evidence of cure (including patients who had previously been unsuccessfully treated). Finally, despite the total number of patients retained in care with an

acute or chronic HCV infection having increased by 198 patients, the total number of patients who remain in need of HCV treatment has decreased from 876 to 499.

HCV reinfection

Re-infection with HCV following successful treatment has been reported mainly in HIV-infected MSM[124, 125, 126], with high rates of reinfections among MSM in the Netherlands, Germany[127] and the United Kingdom. To identify possible HCV re-infection among HCV co-infected patients, we selected the 525 patients who had initially achieved an SVR after receiving HCV treatment. Of these 525 patients, 114 (20%) had detectable HCV RNA levels more than 6 months after the end of treatment. This strongly suggests HCV re-infection. Moreover, for 28 of these 114 (25%) patients, an HCV genotype switch was reported, providing further evidence of HCV re-infection.

The majority of patients who became HCV RNA-positive after successful treatment for HCV (based on SVR) were MSM (100/114, 88%). A further four were injecting drug users (4/114, 4%) and one patient reported both injecting drug use and homosexual contact. For the remaining nine patients, five reported having been infected with HIV through heterosexual contact (one of whom had HCV re-infection confirmed by a reported genotype switch), two through blood-blood contact and two through an unknown route of transmission.

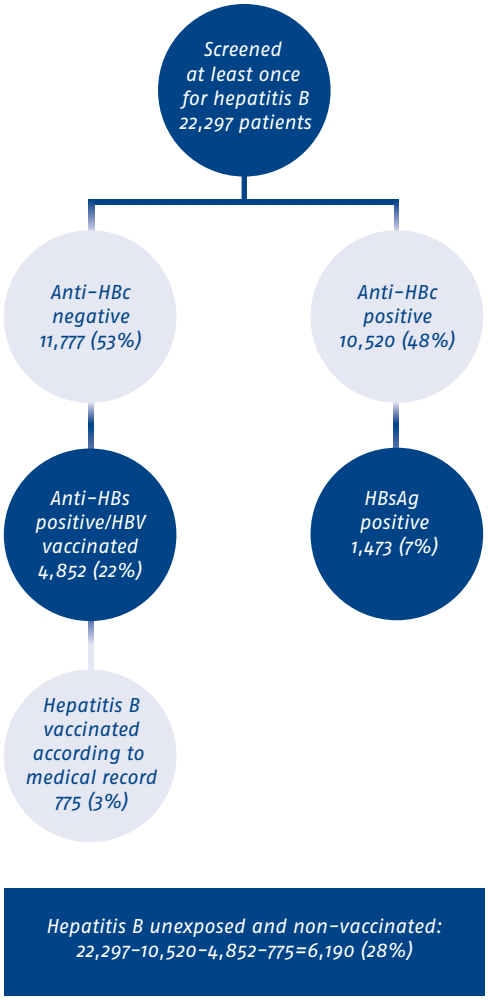
HBV

Forty-seven percent of the 22,297[(b)] 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, 11,777 (53%) HIV-infected patients tested negative for anti-HBc. Of those patients, 4,852 (22%) were anti-HBc-negative and hepatitis B surface antigen-positive (anti-HBs+), indicating that they had been successfully vaccinated against HBV (*Figure 4.8*). These proportions were 26% for MSM, 16% for heterosexuals and far lower (6%) for IDU and former IDU. For 775 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; 620 of these patients were MSM.

(b) 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 4.8: 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 28% 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% minus 47% exposed minus 22% with serological evidence of successful vaccination minus 3% former successful vaccination otherwise documented=28%). Furthermore, 20% of MSM remained at risk (100% minus 49% exposed minus 26% serological evidence of

successful vaccination minus 5% former successful vaccination otherwise documented=20%). Patients in these categories should be offered HBV vaccination, although they may be protected from HBV infection by the use of tenofovir as part of their cART regimen, as suggested by findings reported by an international study and by one of the Dutch HIV treatment centres[128, 129]. Of the patients with no exposure to HBV infection, 64% 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 period of at least 6 consecutive months) was found in 1,473 of the 22,297 (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 (1,267/1,473, 86%), in line with those co-infected with HCV (*Table 4.4*). 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 among IDUs and former IDUs.

Table 4.4: Demographic characteristics of HIV-infected patients with an active chronic hepatitis B virus (HBV) co-infection registered in the SHM database, 1998-2016.

	Total, n (%)	Hepatitis B surface antigen (HBsAg) positive, n (%)
Total number of patients screened for HBV	22,297	1,473 (7)
Male gender	18,103 (81)	1,267 (86)
Region		
Netherlands	12,755 (57)	736 (50)
Europe	1,460 (7)	90 (6)
Sub-Saharan Africa	3,232 (15)	329 (22)
Caribbean/South America	2,567 (12)	155 (11)
Southeast Asia	762 (3)	61 (4)
Other	1,521 (7)	102 (7)
HIV transmission group		
Men who have sex with men	13,341 (60)	871 (59)
Heterosexual	6,812 (31)	422 (29)
Injecting drug use	712 (3)	73 (5)
Other	1,432 (6)	107 (7)
cART	20,756 (93)	1,391 (94)
Deaths	2,308 (10)	250 (17)

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 in HIV-infected patients in care has improved over calendar time. In 1998, 26% of the patients were not screened for the presence of HBV infection (*Figure 4.2*). Since then, there has been a marked decrease in the proportion of HIV-infected patients with an unknown HBV status, with only 0.33% of all HIV-infected patients in care having an unknown HBV status in 2015 (*Figure 4.2*).

Prevalence

The overall prevalence of chronic HBV co-infection among HIV-infected patients in care decreased from 10% in 1998 to 6.4% in 2015. The highest prevalence was found in MSM: in 1998, 11% of MSM had chronic HBV co-infection, and this figure decreased to 6.6% in 2015 (*Figure 4.9*). This decreasing prevalence of chronic HBV co-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 4.10*).

Figure 4.9: Prevalence of chronic active hepatitis B co-infection per calendar year.

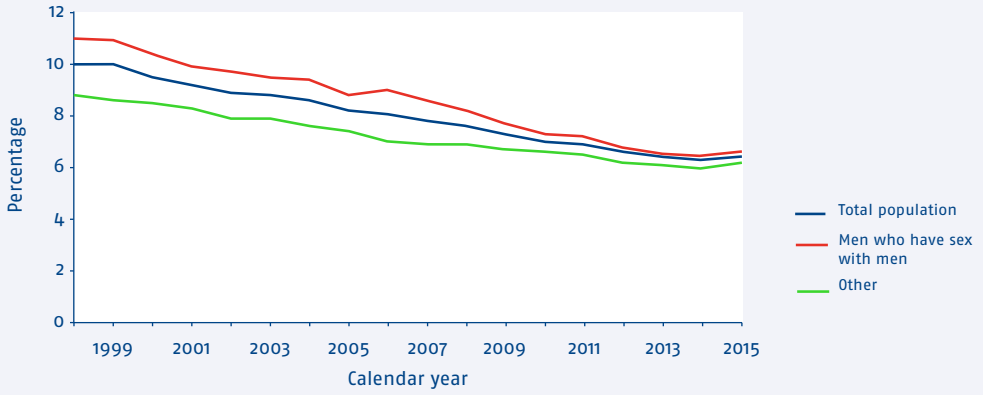
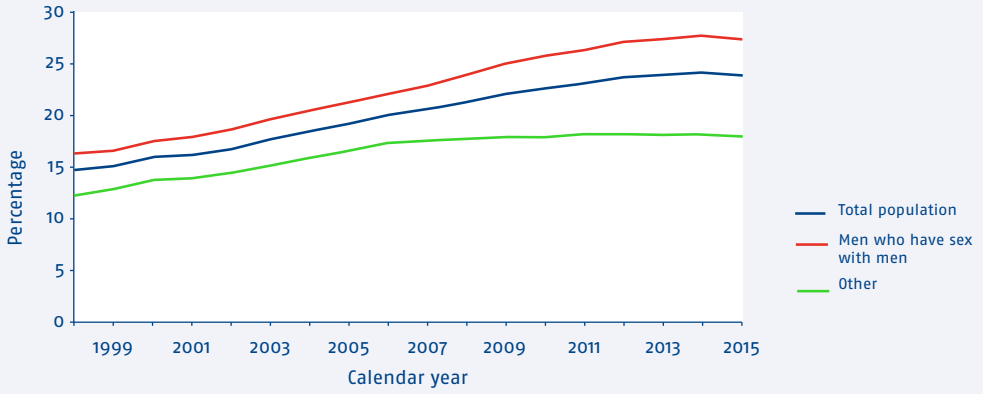


Figure 4.10: Prevalence of patients vaccinated against hepatitis B per calendar year.



Treatment for chronic HBV infection

Chronic HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg+). The aim of treatment is therefore to lower the level of HBV DNA which may cause HBsAg negativity in a subgroup of patients. Persistent HBsAg negativity, together with the development of anti-HBs antibodies, 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 sero-conversion 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, thereby lowering the risk of progression of liver fibrosis. 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 less than 20 IU/ml has been shown to delay progression of liver fibrosis to cirrhosis [130].

Several antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and particularly tenofovir, are also active against HBV. Of the 1,473 patients with HIV in the SHM database co-infected with chronic HBV, 1,391 (94%) have ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 82 patients not having received anti-HBV treatment included: death before being able to start treatment (n=16), recent entry into care (n=6), not receiving cART (most likely because of high CD4 counts) (n=16), lost to follow up (n=41) and lack of sufficient information (n=3).

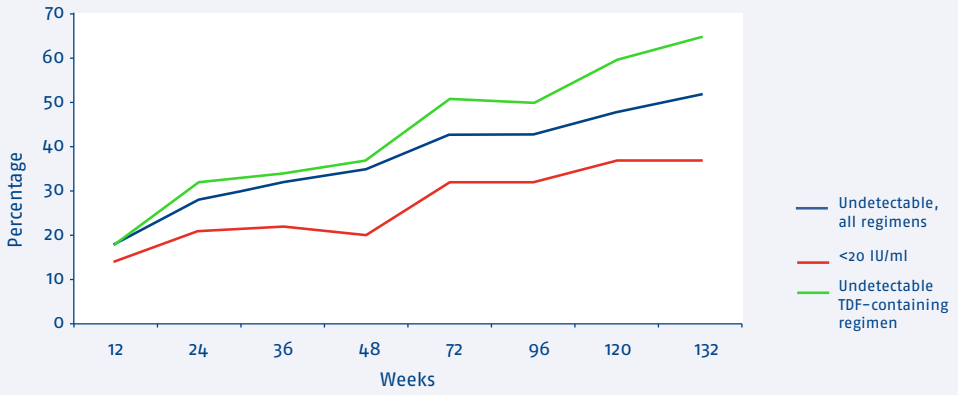
Most patients (n=755/1,391, 54%) initially received lamivudine against HBV. Of the patients treated for HBV with lamivudine, 295 (39%) switched to a regimen containing tenofovir plus lamivudine after a median of 1.7 years (IQR 0.5-4.1), and 221 (29%) switched to a regimen containing tenofovir plus emtricitabine after a median of 1.4 years (IQR 0.4-3.3) of prior exposure to lamivudine monotherapy for HBV. For 635 of 1,391 patients (46%), their initial cART regimen included tenofovir and one additional agent with activity against HBV; for 116 of these 635 patients (18%), the additional agent was lamivudine, and for 519 patients (82%) the additional agent was emtricitabine.

In most HBV mono-infected patients, a persistently inactive HBV carrier state with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC [131]. We therefore examined the HBV DNA levels in the population of individuals co-infected with HIV and HBV. *Figure 4.11* shows the proportion of patients who had an undetectable HBV DNA level less than 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 other than 20 IU/ml, 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, 18% of the patients had an undetectable HBV DNA level based on the detection limit of the assay used at the time of measurement, and 14% had an HBV DNA level less than 20 IU/ml. The percentage of patients with an undetectable HBV DNA level was 35% after

the first year of treatment, with an increase to 43% two years after the start of treatment and 52% three years after the start of treatment. The percentage of patients with an HBV DNA level less than 20 IU/ml was 20% one year after the start of treatment, 32% after two years, and 37% after three years. In terms of patients who were using a tenofovir-containing cART regimen, 65% of patients with HBV DNA follow-up data had an undetectable HBV DNA level after three years of receiving treatment (*Figure 4.11*).

Among the 1,391 patients whose cART regimen ever included one or more agents with activity against HBV, 514 of the 1,017 patients with an available test result (51%) had a documented positive test result for HBeAg. Of these 514 patients, 361 (70%) were retested, with 183 (51%) converting from HBeAg positivity to HBeAg negativity and 104 (29%) developing HBe antibodies.

Figure 4.11: *Percentage of patients with undetectable hepatitis B virus (HBV) DNA levels by assay with a detection limit of either <100, <200, <2000 IU/ml HBV DNA or <20 IU/ml since the start of HBV treatment.*



Legend: *TDF=tenofovir.*

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

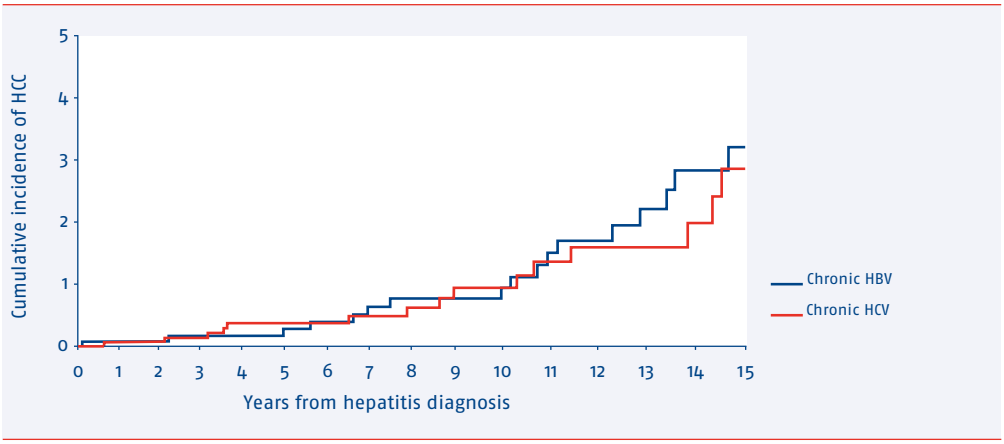
Liver-related morbidity

Additional data on pathology reports from liver biopsy or transient elastography (Fibroscan®), or both, were available for 1,514 of the 1,812 patients with chronic or acute HCV co-infection and for 1,087 of the 1,473 patients with an HBV co-infection. Review of these additional data showed that severe chronic liver disease according to our definition was considered to be present (presumptive and definitive

categories combined) in 648 of the 1,514 patients (43%) with HCV co-infection, and in 375 of the 1,087 (34%) patients with HBV co-infection. Definitive severe chronic liver disease was documented for 155 patients with an HCV co-infection and 61 with HBV co-infection.

HCC was diagnosed in 20 out of 1,371 patients (1.5%) with a chronic HCV co-infection, of whom 15 were born in the Netherlands. HCC was found in 23 patients (1.4%) with a chronic HBV co-infection, 14 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 4.12* shows the cumulative incidence of HCC. It should be noted, however, that the time between diagnosis of hepatitis co-infection and HCC was not significantly different between patients with an HCV co-infection and those with a hepatitis B co-infection. Ten years after a known diagnosis of viral hepatitis, HCC had developed in 1.2% (95% CI 0.7-2.6%) of patients with HCV co-infection and in 1.1% (95% CI 0.7-2.5%) of those with chronic HBV co-infection. It should be noted that the exact moment of hepatitis infection is unknown and that the infection with HBV or HCV could have existed for a longer period of time than was accounted for in these analyses.

Figure 4.12: *Cumulative incidence of hepatocellular carcinoma (HCC) among co-infected patients with HIV and hepatitis C (HCV) or hepatitis B (HBV) from date of hepatitis diagnosis onwards. The Kaplan-Meier estimate was used to determine the time to HCC. The follow-up time was measured from the date of hepatitis diagnosis to the date of last contact, diagnosis of HCC, or 1 January 2016.*



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 1,812 patients with an HCV infection (*Table 4.5*). The cumulative incidence of death from any cause was higher among patients who were diagnosed with HCV or HBV before 2000 compared with those who were diagnosed in later calendar years (*Figure 4.13*). 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 and time since HIV diagnosis), the overall risk of death was significantly higher in patients with HIV and HCV co-infection diagnosed before 2000 compared to HIV mono-infected patients. For patients with an HCV co-infection diagnosed after 2000, the overall risk of death was non-significantly higher than in HIV mono-infected patients.

Table 4.5: *Morbidity and mortality in HIV-infected patients with hepatitis C virus (HCV) and/or hepatitis B virus (HBV) co-infection registered in the SHM database.*

	HCV infection, n (%)	HBV infection, n (%)
Total	1,812	1,473
Severe chronic liver disease*	648 (36)	35 (25)
HCC	20 (1.1)	23 (1.6)
Deaths from any cause**	244 (15)	230 (16)
Liver-related deaths	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.*

For patients with a chronic HBV co-infection diagnosed both before and after 2000, the overall risk of death was higher than in HIV mono-infected patients (*Table 4.6*).

Table 4.6: Adjusted hazard ratios of time from start of combination antiretroviral therapy (cART) to all-cause mortality and liver-related mortality in HIV-infected patients with hepatitis co-infection compared with HIV mono-infected patients. 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. The 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 2016.

	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	<0.0001	1	<0.0001
HIV/chronic HCV, <2000	1.87 (1.50-2.33)		23.4 (10.9-50.1)	
HIV/chronic HCV, ≥2000	1.16 (0.90-1.50)		12.9 (6.62-25.2)	
HIV/chronic HBV, <2000	1.95 (1.62- 2.34)		36.0 (19.4-66.9)	
HIV/chronic HBV, ≥2000	1.26 (1.01-1.57)		5.91 (2.52-13.9)	

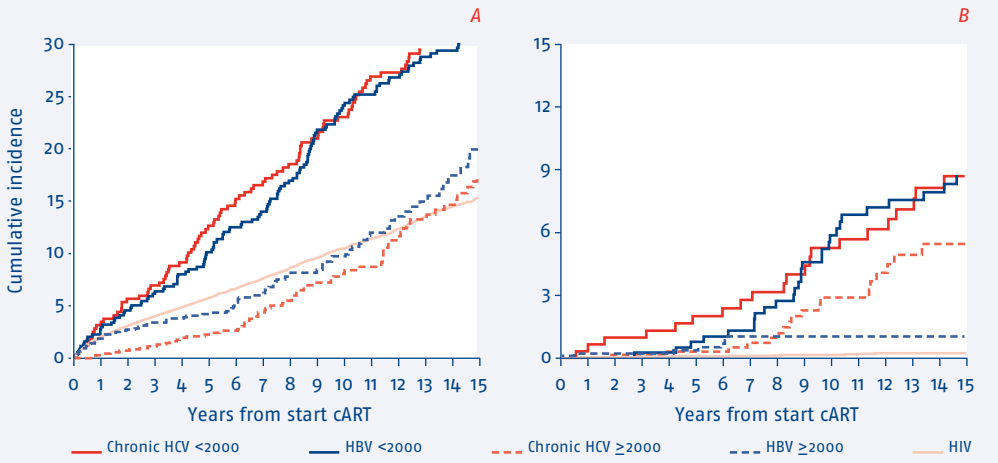
**adjusted for age, gender, region of origin, transmission risk group, calendar year of cART initiation, baseline CD4 and HIV RNA levels, alcohol use and smoking and duration of HIV infection.*
***Legend:** HBV=hepatitis B virus; HCV=hepatitis C virus; CI=confidence interval.*

Liver-related mortality

In total, 94 patients co-infected with hepatitis died of a liver-related cause (*Table 4.5*). Ten years after cART initiation, 6% (95% CI 3-9) of chronically HCV co-infected patients who were diagnosed with HCV before 2000 had 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, 7% of patients diagnosed before 2000 died of a liver-related cause (95% CI 5-10), which dropped to 1% (95% CI 0.5-2) in those diagnosed after 2000 (*Figure 4.13*).

After adjustment for demographic and clinical characteristics, HBV co-infected patients and HCV co-infected patients diagnosed both before and after 2000 remained more likely to have a liver-related cause of death than HIV mono-infected patients (*Table 4.6*). However, the risk of death from a liver-related cause strongly decreased in HBV co-infected patients from a hazard ratio (HR) of 19.8 (95% CI 10.9-36.1) in patients diagnosed with HBV before 2000 to an HR of 7.2 (95% CI 3.03-17.2) in patients diagnosed from 2000 onwards. This strong decrease in risk of death from a liver-related cause was thus far not observed in HCV co-infected patients.

Figure 4.13: Cumulative incidence of (A) all-cause mortality and (B) liver-related mortality, stratified by calendar year period. The Kaplan-Meier estimate was used to determine the time to death. The follow-up time was measured from the date of HIV diagnosis to the date of last contact, death or 1 January 2016.



Legend: cART=combination antiretroviral therapy; HCV=hepatitis C virus; HBV=hepatitis B virus.

Conclusion

Screening for HCV and HBV co-infection in the HIV-infected population in the Netherlands continues to improve over time. Although approximately 39% of the patients in care in 1998 had not been screened for HBV or HCV co-infection, by 2015 screening had become universal.

Six percent of HIV-infected patients registered in the SHM database were documented as being chronically infected with HCV, and 2.0% were documented as having had an acute HCV infection. Seven percent of the HIV-infected patients ever in care had chronic HBV co-infection. The prevalence of HBV has decreased over time, as the result of increased HBV vaccination rates, together with the HBV-prophylactic effect of tenofovir in cART-treated patients. Nonetheless, an estimated 28% of all HIV-infected patients and 20% of MSM either have not been exposed to HBV or have not been successfully vaccinated and may remain at risk of acquiring HBV. However, 64% of those patients still at risk of acquiring HBV infection use a cART regimen that includes tenofovir and may therefore be at a substantially lower risk due to sustained chemoprophylaxis. The remaining 36% of the patients remain unprotected against HBV, which represents an estimated 10% of the total population of HIV-infected patients.

In general, HIV-infected patients co-infected with HCV or HBV are at increased risk of progression to severe liver disease[110, 111]. In our study population, 36% 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 risk 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 largely being replaced in clinical practice by a variety of novel DAAs and more HIV-infected patients with HCV-co-infection are being treated for HCV infection. More than 500 patients have received or are currently receiving treatment with novel DAAs. Overall, 98% 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 IFN alpha/PEG-IFN alpha-containing regimens. This high cure rate has resulted in a lower number of HCV co-infected patients remaining in need of HCV treatment, despite an increase in the total number of patients currently in care compared with the numbers reported last year[8].

Overall, this could eventually contribute to a reduction in HCV prevalence. 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 probably limit the impact of HCV co-infection on liver-related morbidity and mortality. Successful treatment of HCV may also prevent onward transmission of HCV. However, in line with earlier reports[124, 126], an alarmingly high rate of detectable HCV RNA test results after successful treatment was observed, which strongly suggests HCV re-infection and ongoing transmission of HCV.

Recommendations

Continued efforts must be made to ensure that all patients with HIV are adequately assessed for the presence of HBV and HCV co-infection. In 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. In the long term, provision of the novel highly effective interferon-free regimens for all known HCV co-infected

HIV-positive patients 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, these novel regimens may have a beneficial impact on the risk of ongoing HCV transmission.

Nevertheless, regular screening for HCV RNA among patients who have been successfully treated is recommended for early detection of new HCV infections, in combination with preventive behavioural interventions aimed at MSM to reduce HCV reinfection after successful treatment of HCV. Continued monitoring of the population co-infected with HIV and hepatitis in the Netherlands will thus be key, not only to monitor the epidemiology of these infections and the response to existing and novel treatments, but also to assess 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 positive HCV RNA 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 test or a documented anti-HCV IgG seroconversion within the previous 12 months[189].

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 above criteria 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 period of at least 6 consecutive months.

SVR24

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.

SVR12

Sustained virological response, defined as a negative HCV RNA test result 12 weeks after treatment discontinuation in patients treated for prior documented acute or chronic HCV infection.

Severe (chronic) liver disease

Presumptive, based on 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 *definitive* 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 145

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

Colette Smit, Peter Reiss, Annemarie van Rossum

Background

Healthcare for HIV-1-positive 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 564 children aged up to 18 years at the time of their HIV-1 diagnosis, representing an increase of 30 children compared with last year's report.

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-1-infected children worldwide[132, 133, 134]. In particular, early initiation of cART in HIV-1-infected children has been proven to benefit the survival of these children[135, 136, 137, 138, 139]. In 2010, the World Health Organization (WHO) recommended starting cART in all HIV-infected children less than 2 years of age, regardless of their CD4 T-cell count or clinical status[140]. However, as of June 2013, this recommendation has been extended to include all HIV-infected children less than 5 years old[141]. Moreover, the Paediatric European Network for Treatment of AIDS (PENTA) 2015 guidelines for the treatment of paediatric HIV-1 infection also recommend treatment in all children younger than 1 year of age, and in children of all ages before the CD4 cell count reaches the age-specified CD4 treatment threshold[142].

Demonstrating an effect of age at initiation of cART on 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, with several studies having shown poorer immunological outcomes after initiating cART initiation in older children and in children with lower CD4 cell counts at time of cART initiation[143, 144].

Here we report the demographics, clinical characteristics, and long-term virological and immunological response to treatment in the 564 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 have become infected with HIV-1 through sexual transmission are predominantly under clinical observation in an adult HIV treatment centre (*Table 5.1*). All HIV-1 infected patients diagnosed before the age of 18 years and under clinical observation in a paediatric HIV treatment centre or in an adult HIV treatment centre are included in the analyses.

Table 5.1: Demographics and characteristics of 564 HIV-1-infected children in care in the Netherlands.

Characteristics	Vertically acquired HIV-1 infection*	Non-vertically acquired HIV-1 infection*	Route of transmission unknown*
Total	312 (55)	223 (40)	29 (5)
HIV-1 treatment centre			
Paediatric care	302 (97)	26 (12)	15 (52)
Adult care	10 (3)	197 (88)	14 (48)
Gender			
Male	154 (49)	94 (42)	16 (55)
Female	158 (51)	129 (58)	13 (45)
Country of origin child			
The Netherlands	107 (34)	56 (25)	3 (10)
Sub-Saharan Africa	163 (52)	117 (52)	18 (62)
Other	42 (13)	50 (22)	8 (28)
Country of origin mother			
The Netherlands	23 (7)	5 (2)	2 (7)
Sub-Saharan Africa	177 (57)	33 (15)	7 (24)
Other/unknown	112 (36)	185 (83)	20 (69)
Age at HIV-1 diagnosis	1.2 (0.3-4.1)	16.8 (15-18)	12.4 (4-17)
CDC** event at HIV-1 diagnosis			
CDC-b	30 (10)	9 (4)	2 (7)
CDC-c	57 (18)	12 (5)	5 (17)
Current age in years	14 (7-19)	30 (25-33)	22 (17-29)
cART-treated	298 (96)	203 (91)	28 (97)
Therapy-naive at cART initiation	256 (82)	163 (73)	27 (93)
CD4 at cART initiation	535 (272-1170)	282 (166-406)	310 (110-475)
VL (log copies/ml) at cART initiation	5.2 (4.5-5.8)	4.4 (3.6-5.1)	5.2 (4.8-5.5)
cART regimen			
NNRTI+≥2 NRTIs	93 (30)	84 (38)	12 (41)
PI+≥2 NRTIs	197 (63)	103 (46)	14 (48)
NNRTI+PI+2NRTIs	4 (1)	5(2)	1 (3)
3 NRTIs	4 (1)	11 (5)	1 (10)

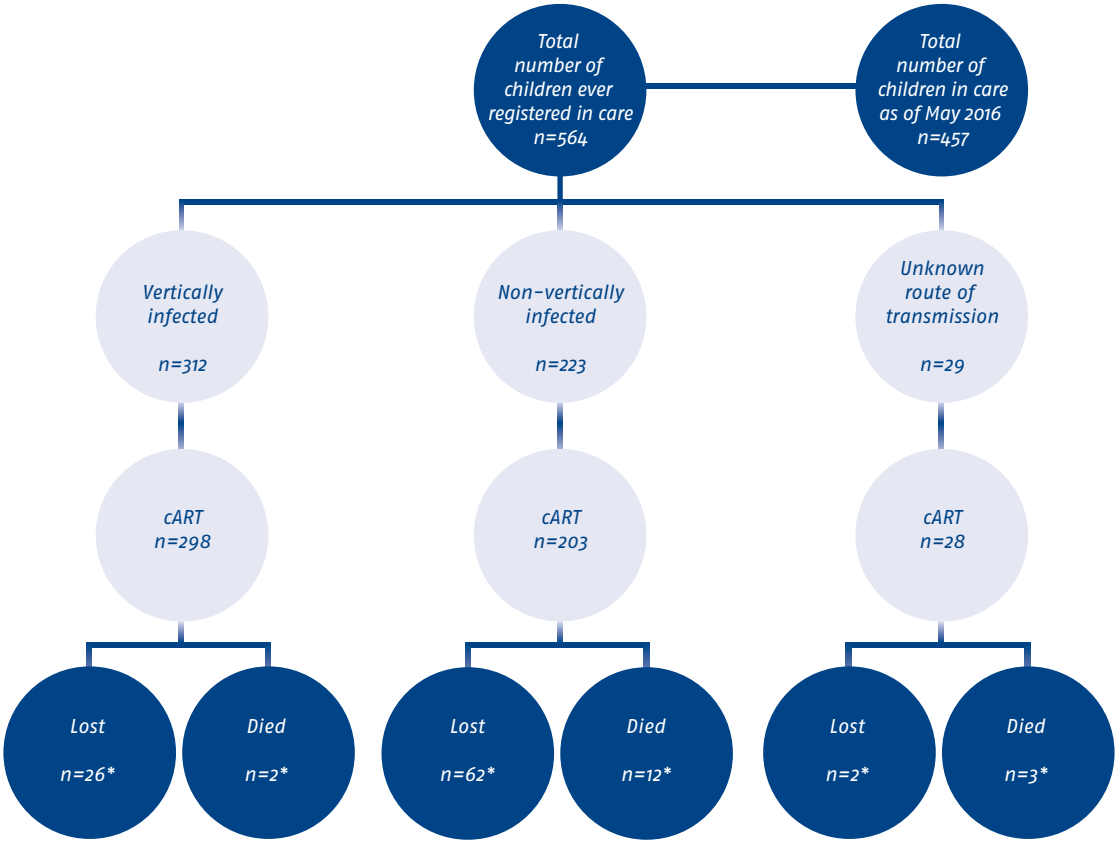
** Data are number (%) of children or median (interquartile range)*

*** Categories as defined by the Centers for Disease Control and Prevention.*

***Legend:** cART=combination antiretroviral therapy; VL=viral load; NNRTI=non-nucleoside reverse transcriptase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; PI=protease inhibitor.*

As of May 2016, 564 HIV-1-infected children have ever been registered by SHM. Of those, 312 were vertically infected with HIV-1, and 223 were non-vertically infected (*Figure 5.1*). For a small group of children, 29 in total, the route of HIV-1 transmission was unknown.

Figure 5.1: *Overview of HIV-infected children registered by Stichting HIV Monitoring as of May 2016.*



**of the total number of children vertically-infected, non-vertically infected or with unknown route of transmission.*

Vertically-infected children

A total of 312 children were vertically infected with HIV-1 (*Table 5.1*). The median age at HIV-1 diagnosis for the vertically-infected children was 1.2 years (interquartile range [IQR] 0.3-4.08 years). Although 34% of the children were born in the Netherlands, only 3% of these children (10 out of 312) had parents who both

originated from the Netherlands, whilst 58% (182 out of 312) had at least one parent who originated from sub-Saharan Africa. Of the 312 vertically-infected children, 97% received care in a paediatric HIV treatment centre, and 96% of these 312 children had started cART.

Non-vertically-infected children

Of the 564 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 16.8 years (IQR 15.5-17.5). The majority of the 223 non-vertically infected children received care in an adult HIV treatment centre (197/223, 88%). The main route of HIV-1-transmission was sexual contact. Of the non-vertically infected children, 134 out of 223 (60%) were infected through heterosexual contact, 36 (16%) were infected through homosexual contact and 44 (20%) by contaminated blood or blood product. The remaining 9 children were infected by injecting drug use or accidentally through contaminated needles. Fifty-two percent of the non-vertically infected children were born in sub-Saharan Africa. Of the 223 non-vertically infected children, 203 (91%) received cART (*Table 5.1*).

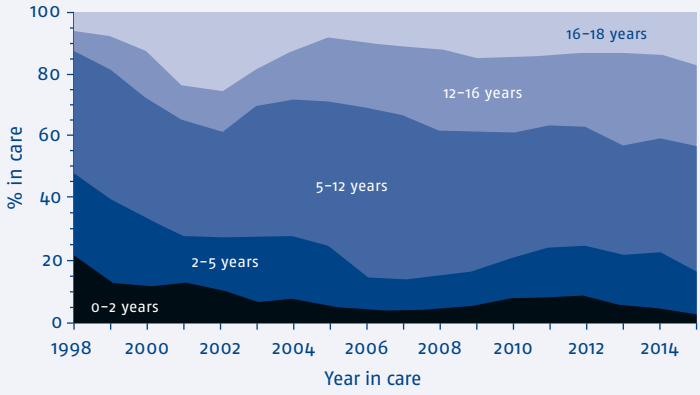
Unknown route of HV-1 transmission

For 29 of the 564 HIV-1-infected children, the route of transmission was unknown. Their median age at diagnosis was 12 years (IQR 4-17), 15 of these children were in care at a paediatric HIV treatment centre and 28 had started cART (*Table 5.1*).

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 5.2*). However, from 2010 onwards, the proportion of children aged between 2 and 5 years increased slightly. This small increase is probably due to an increase in adoption of HIV infected children in this age group (*Figure 5.3*).

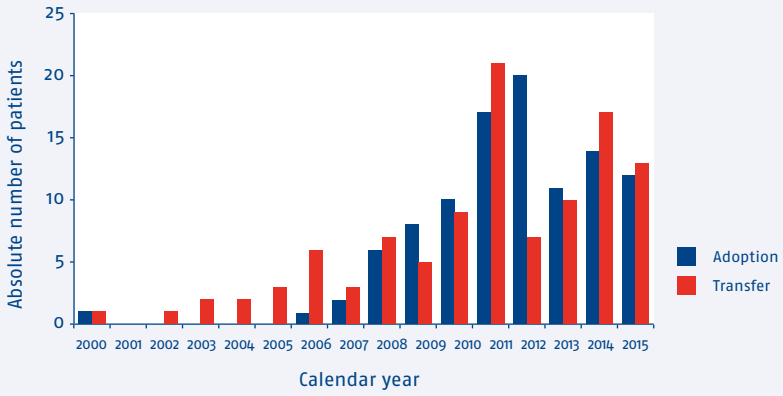
Figure 5.2: Time-dependent age distribution of HIV-infected children in care over time.



Adopted children

In total, 105 children in care for HIV-1 infection were adopted by Dutch parents. The majority of these children were born in sub-Saharan Africa (86%) and diagnosed with HIV-1 before the age of 2.5 years (83%). The number of children adopted varied between 1 and 20 per calendar year (*Figure 5.3*).

Figure 5.3: Number of HIV-infected children who came into paediatric care through adoption and number of HIV-infected children transferred to adult care, by calendar year.



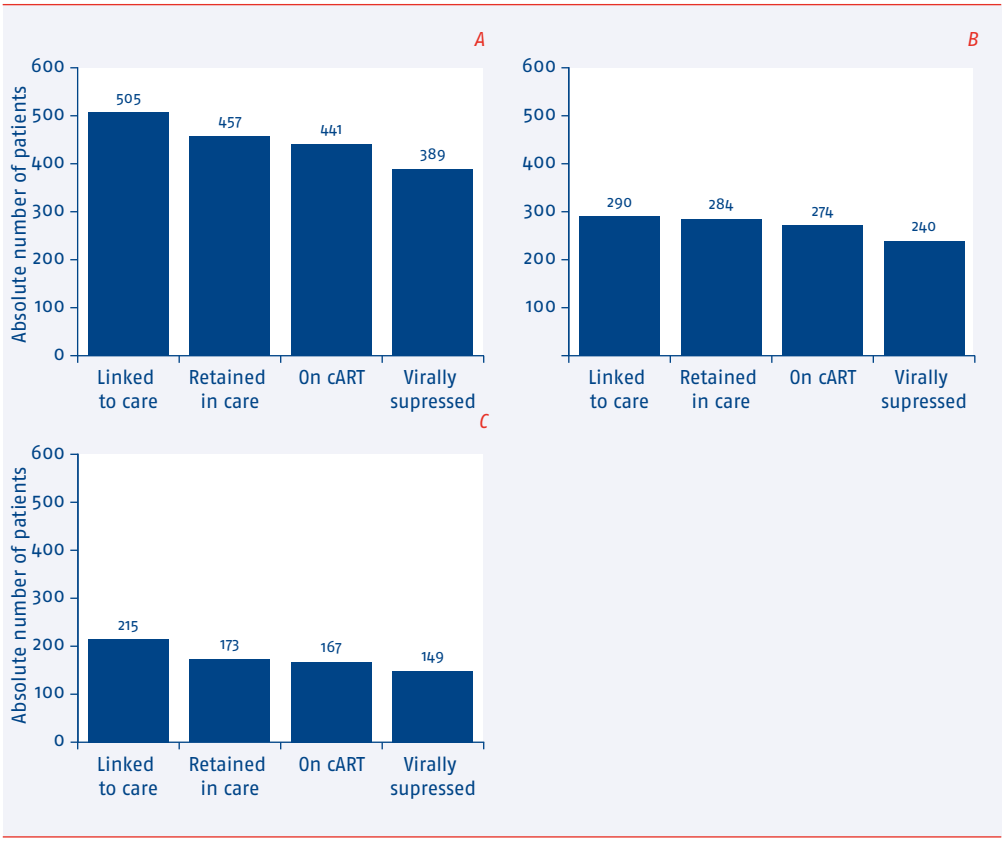
Children currently in clinical care

Of the 564 HIV-1-infected children ever registered by SHM, 457 (81%) currently remain in clinical care (*Figure 5.1*). Of these 457 children, 284 (62%) were vertically-infected, 149 (33%) were non-vertically infected, and 24 had an unknown mode of transmission. Of the 107 children who are no longer in clinical care, 17 (15%) have died, 14 of whom were 18 years or older at time of death, 42 patients have moved abroad and 48 (45%) have been lost to care. The median age at date of last contact for the patients who became lost to care was 21 years (IQR 19-25).

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 5.4A*). In total, 505 children were ever linked to care, registered by SHM, still alive, and not reported as having moved abroad. Seventeen children had died and 42 children were reported as having moved abroad. Of the 90% of children who were retained in care (457/505), 96% (441/457) had started cART. Overall, 88% of those starting cART had a most recent HIV RNA measurement below 100 copies/ml (389/441). In addition, a second continuum of care was constructed in the same way, but stratified by mode of HIV transmission (vertically infected, *Figure 5.4B*, and non-vertically or unknown mode of transmission, *Figure 5.4C*). In the group of vertically-infected children, 290 out of the 312 children were linked to care, 2 children had died and 20 had moved abroad. Of the 290 vertically-infected children, 284 (98%) were still in care as of 1 January 2016 (6 had been lost to follow up), 96% of those still in care (274/284) had started cART and 88% (240/274) 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, 215 out of the 252 children were linked to care, 15 had died and 22 had moved abroad. Of those linked to care, 80% (173/215) were retained in care and 42 patients were no longer in care as they had been lost to follow up. Among those who were still in care, 97% (167/173) had started cART and 89% (149/167) of those starting cART had a most recent HIV RNA measurement below 100 copies/ml.

Figure 5.4: Cascade of care for (A) all HIV-infected children, (B) vertically-infected children, and (C) non-vertically-infected children.



Legend: cART=combination antiretroviral therapy.

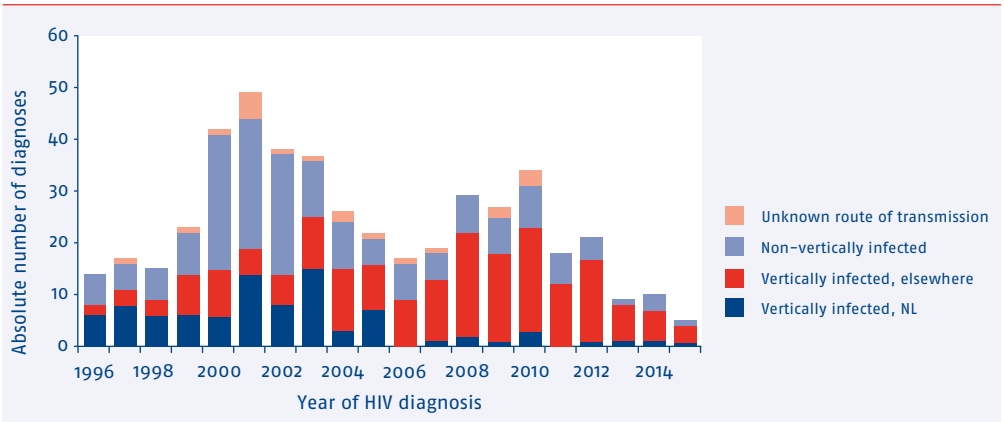
Registered HIV-1 diagnoses and vertical transmission of HIV-1 in the Netherlands

Figure 5.5 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 (15 cases in 2003), after which it markedly declined, with a single documented case of vertical transmission in the Netherlands in 2014. The decline of vertical transmission in the Netherlands is most likely due to HIV-1 screening among pregnant women, which was introduced nationally in 2004 [145, 146]. Since the introduction of the screening programme, 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 January 1 2004. Six children were born to mothers who first tested positive after giving birth; the mothers of four of these 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.

The majority of children with a newly-registered diagnosis of HIV-1 infection through vertical transmission in recent years were infected outside the Netherlands, and this number fluctuates each year (e.g., 20 cases in 2008 and 6 cases in 2014). The number of children who acquired HIV-1 infection by another mode of transmission ranged between 1 and 26 per calendar year.

Figure 5.5: Number of registered HIV-1 diagnoses among children, according to year of HIV diagnosis, route of transmission and region of origin.



***Note:** low numbers in 2015 may be due to a delay in registration.*

Mortality

During follow up, 3 out of 564 children (0.5%) died at less than 18 years of age. These were all boys born outside the Netherlands who died at the ages of 11, 12 and 17 years 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 before migrating to the Netherlands when he was 10 years old. He never received cART and died of multiple organ failure 1.5 years after the diagnosis and two months after being in care in the Netherlands. The boy who died in 1998 and

was 12 years of age at the time of death had been vertically infected with HIV-1. He was diagnosed when he was 9 years old. He died 3 years after the diagnosis from an AIDS-related event, having experienced severe issues with compliance during 14 months of cART, which had just become available for children in 1997. 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 2 months.

Treatment

In total, 529 of the 564 children had started cART; 387 started with a cART regimen before 2010, 92 started between 2010 and 2013, and 50 started cART from 2013 onwards.

The majority of HIV-1-infected children ever registered in the Netherlands have received cART (*Table 5.1*). Most children (59%) were treated with a first-line regimen including a protease inhibitor (PI) and 2 or more nucleoside reverse transcriptase inhibitors (NRTIs); 36% of the children received a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with 2 or more NRTIs. The protease inhibitors nelfinavir and (boosted) indinavir were used in the early years of cART[147] 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[148, 149, 150, 151].

The median time on first-line regimens was 17 months (IQR 4-48). Not taking into account weight-related dose changes, 440 children (83%) discontinued their first-line treatment regimen: 282/314 (90%) children who initially started with a PI-based regimen and 152/189 (80%) children who initially started with an NNRTI-based regimen. The most important reasons for changing first-line cART regimens included toxicity (13%), low drug plasma concentrations (9%), simplification (13%), and parental non-adherence (3%). Virological failure accounted for 7% of the reasons for changing first-line cART therapy. 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 with children who started before 2010 (*Table 5.2*), reflecting the implementation of more recent treatment guidelines.

Table 5.2: Median CD4 cell counts at treatment initiation of the 529 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	≥2010 and <2013	≥2013
0–1 year*	1,155 (490–1,890)		
1–3 years*	695 (310–1,520)		
3–5 years*	630 (420–1,030)		
0–2 years*		1,903 (631–2,216)	
2–5 years*		641 (406–860)	
<5 years*			1,240 (813–2,531)
≥5 years*	264 (120–390)	340 (275–460)	420 (290–594)

**Median (IQR)*

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

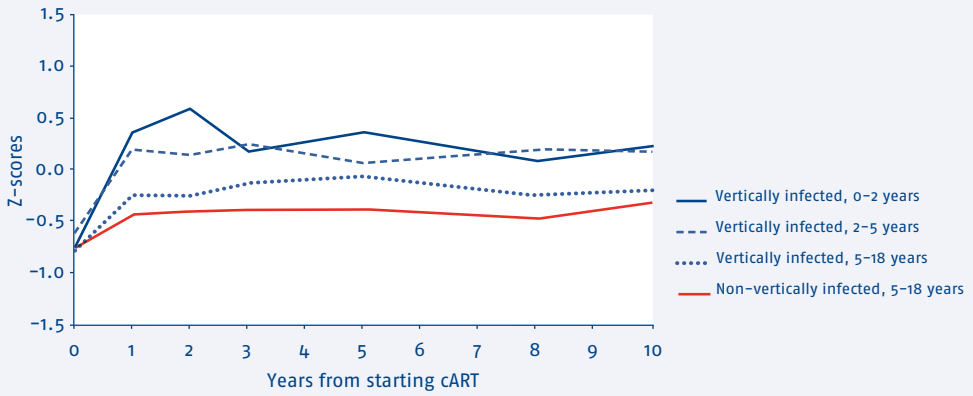
Immunological response

The clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers[53]. 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; (3) vertically infected, 5-18 years; and (4) non-vertically infected or unknown mode of HIV-1 transmission, 5-18 years[152]. 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 the same age distribution as those who were non-vertically infected. For these reasons, the children with an unknown route of HIV-1 transmission were included in the category of non-vertically infected. *Appendix Table 5.1* shows the differences in CD4 counts between younger and older HIV-1-infected children.

Given that normal CD4 cell counts in younger children are highly age-dependent, it is more appropriate to analyse time-dependent CD4 count trajectories whilst expressing CD4 counts as z-scores, in which counts are standardised in relation to age. 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[153] and dividing the outcome by the age-related standard deviation. A z-score of zero represents the age-appropriate median. A CD4 z-score of minus 1 indicates that a child's CD4 cell count[150] is 1 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 5.6*). This increase was lower in both vertically and non-vertically infected patients aged 5-18 years at cART initiation than vertically-infected children less than two years of age.

Figure 5.6: *Changes in Z-scores for CD4 T-cell counts among HIV-1 infected children stratified by age at initiation of combination antiretroviral therapy (cART).*



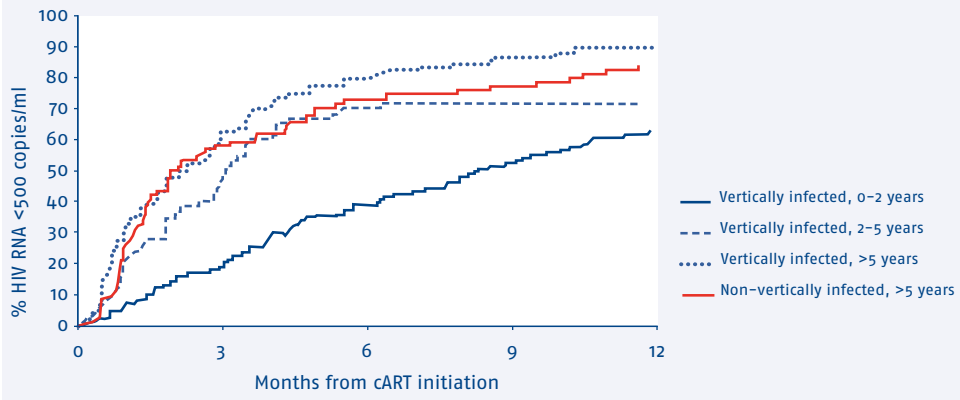
Legend: *cART=combination antiretroviral therapy.*

Virological response to cART

At the time of cART initiation, children less than two years of age had significantly higher HIV-1 RNA levels compared with older children, which is in line with findings from other studies[149] (*Appendix Table 5.1*). 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, 76% 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[149].

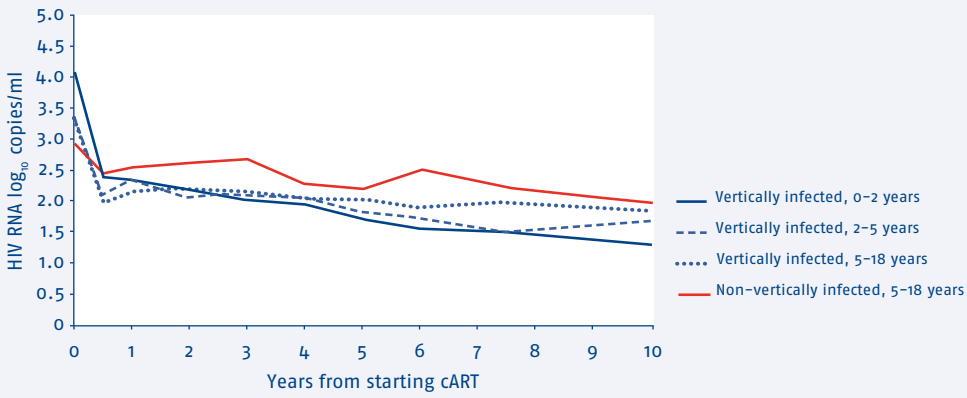
The poorest virological responses were observed among those less than two years of age (63% reached an undetectable HIV-1 RNA level 12 months after the start of cART) and those aged two to four years (75%). This less favourable initial virological response that has previously also been described by others[18] might be explained by difficulties in performing regular dosing adjustments in young children[19], but also could be explained by the higher pre-cART viral loads in younger children[20]. The best responses were among children aged five years or more who had been either vertically infected (91%) or non-vertically infected (84%) (*Figure 5.7*). *Figure 5.8* 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 non-vertically children aged five to eighteen years. However, two years after the start of cART, the decline in HIV RNA levels was no longer statistically significant, although median HIV-1 RNA levels were somewhat higher in non-vertically infected children aged 5 years or more.

Figure 5.7: *Kaplan-Meier estimates of the percentage 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 5.8: Changes in HIV RNA levels since the start of combination antiretroviral therapy (cART) among HIV-1 infected children stratified by age at initiation of 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

Of the 564 children, 105 children were adopted by Dutch parents and their median age was 2.8 years (IQR 1.8-4.5) at time of entering care in the Netherlands. Of these 105 adopted children, 101 received cART during follow up in clinical care in one of the Dutch HIV treatment centres, nine of whom had been treated with monotherapy or dual therapy before the start of cART. Although 80 children were receiving cART before being adopted, only 26 (25%) out of the 105 children had a viral load <100 copies/ml upon entry into care in the Netherlands. All 105 children are currently alive and in care, and their median current age is 7.3 years (IQR 4.7-9.1). All children who started cART currently remain on treatment, and 96/101 (95%) had an undetectable viral load at the last known time point.

Transfer to adult care

As of May 2016, 107 children who originally started care in a paediatric HIV-1 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 one child in 2001 to 21 in 2011 and 13 in 2015 (*Figure 5.3*). The median age at transfer was 19.3 years (IQR 18.6-20.1). At the time of transfer to an adult HIV treatment centre, 71 children (66%) had an HIV RNA level <100 copies/ml. The median time in care after transfer was 3.9 years (IQR 1.8-6.0). Of the children who transferred to adult care, nine were lost to follow up, four have since moved

abroad, and one patient had died at age 27. The remaining 93 are currently alive and in care. Eighty-four (90%) of these 93 patients are currently on a cART regimen, 12 of whom (14%) had a detectable viral load (median 3515, IQR 187-41,000) at the last known time point; their current median CD4 count is 405 cells/mm^3 (IQR 215-670). A recent study analysing virological and social outcomes of HIV-infected adolescents and young adults in the Netherlands before and after transition to adult care showed an increased risk of virological failure when aged between 18-19 years and this risk was concentrated around the time of, or shortly after, transitioning to adult care. Characteristics significantly associated with virological failure were low education and lack of autonomy of medication adherence at time of transitioning to adult care [154].

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.

Younger children below five years of age have 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 6 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 older. 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 (45%) of the children have survived into adulthood and are now in care in one of the adult HIV-1 treatment centres. The majority of these children are on cART. The high rate of detectable HIV-1 viral load in these children around the time of transitioning to adult care is, however, of concern.

The substantial decline in the occurrence of vertical transmission of HIV-1 in the Netherlands from 2004 onwards can be explained by the successful introduction of an HIV-1 screening programme in the first trimester of pregnancy[145]. This measure, however, has not completely prevented mother-to-child transmission from occurring. Paediatricians should therefore remain alert and continue to consider the possibility of an HIV infection if a child of a mother who tested HIV negative during pregnancy presents with symptoms compatible with HIV infection. Screening for HIV-1 during just 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%[146], a standard second nationwide 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. A large proportion of the children have survived into adulthood and transitioned to adult care. Special attention is needed for children transitioning to adult care, as this period seems to be associated with an increased risk of virological failure. HIV screening during pregnancy has very significantly reduced, but not fully abrogated, vertical HIV transmission.

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

Colette Smit, Liesbeth van Leeuwen

Introduction

Transmission of HIV from an infected mother to her child is the most common route of HIV transmission among children aged 0 to 15 years worldwide[155]. 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%[156]. However, since the introduction of combination antiretroviral therapy (cART) in pregnant women, the risk of MTCT has been dramatically reduced to less than 1%[157, 158].

Knowledge of a woman's HIV status during pregnancy is necessary for timely initiation of cART and, thus, to reduce the risk of MTCT. In January 2004, voluntary HIV antibody testing of pregnant women with the possibility of opting out was introduced in the Netherlands[159]. Since then, 299 women who were unaware of their HIV infection were diagnosed during their pregnancy and reported to SHM. By May 2016, a total of 2,254 pregnancies in 1,320 women had been registered among the total 5,185 HIV-infected women monitored by SHM. Overall, 55% of the pregnant women had been diagnosed with HIV before the onset of pregnancy.

Demographics

Maternal characteristics

Characteristics of HIV-infected women with a registered pregnancy are presented in *Table 6.1*. Of the 1,320 women with a documented pregnancy, 1,082 (82%) were of non-Dutch origin and 238 women (18%) originated from the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=736, 56%) or in the Caribbean/South American region (n=216, 16%). Women of Dutch origin were more often aware of their HIV infection before they became pregnant than those of non-Dutch origin (73% versus 52% respectively, $p<0.0001$). Furthermore, women of Dutch origin were older at the time of their first registered pregnancy, with a median age of 30 years (interquartile range [IQR] 27-35), compared with a median age of 29 years for non-Dutch women (IQR 25-34). Heterosexual contact was the most common route of HIV transmission in both groups of women (94%). However, women of Dutch origin were more likely to have been infected with HIV by another route than women of non-Dutch

origin (p<0.0001). Injecting drug use was reported as the route of transmission in 12 women of Dutch origin (5%); only one mother was diagnosed with HIV in 2010, all other HIV diagnoses occurred before 2001. Two mothers originating from sub-Saharan Africa were known to have become infected with HIV by MTCT. Thirty-four mothers were documented as having died during follow up, with a median time between the onset of pregnancy and death of 8.3 years (IQR 3.1-10.7). Two mothers died within 2 months of parturition: the cause of death was acidosis and rhabdomyolysis associated with sepsis in one woman and unknown in the other.

In total, 229 women were lost to follow up, which was more common in women of non-Dutch origin (20%) than in those of Dutch origin (6%).

Table 6.1: Characteristics of HIV-infected pregnant women registered and monitored by Stichting HIV Monitoring up to 1 May 2016.

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Maternal characteristics	1320	238 (18)	1082 (82)
HIV diagnosis before pregnancy	732 (55)	174 (73)	558 (52)
Age at start of first pregnancy occurring in HIV infection (years*)	29 (25-34)	30 (27-35)	29 (25-34)
HIV transmission route			
Heterosexual	1,240 (94)	210 (88)	1,030 (95)
Other	80 (6)	25 (28)	52 (5)
Ever CDC-c** event	235 (18)	38 (16)	200 (18)
Deaths	34 (3)	9 (4)	25 (2)
Lost to follow up	229 (17)	15 (6)	214 (20)
Total number of pregnancies	2,254	396	1,858
Maximum number of pregnancies after HIV diagnosis			
1	741 (56)	139 (58)	602 (55)
2	345 (26)	59 (25)	286 (26)
3	153 (12)	28 (12)	125 (12)
≥4	81 (6)	12 (5)	69 (6)
Pregnancy outcome			
Birth	1,675 (74)	299 (75)	1,376 (74)
Miscarriage	123 (5)	23 (6)	100 (5)
Abortion	255 (11)	42 (11)	213 (11)
Abortion, no additional data	181 (8)	32 (8)	149 (8)
Unknown	20 (1)	0	20 (1)

Table 6.1: Continued.

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
Mode of delivery			
Vaginal	988 (59)	210 (70)	778 (57)
Caesarean	639 (38)	82 (27)	5,557 (40)
Unknown	48 (3)	7 (2)	41 (3)
Pregnancy duration			
≥37 weeks	1,351 (60)	250 (63)	1,101 (59)
32-37 weeks	195 (9)	29 (7)	166 (9)
<32 weeks	129 (6)	28 (7)	101 (5)
Missing	579 (27)	89 (22)	490 (26)
Birth weight (grams, IQR*)	3,085 (2,680-3,405)	3,150 (2,720-3,455)	3,080 (2,650-3,390)
Gender			
Boy	869 (52)	151 (51)	718 (52)
Girl	790 (47)	146 (49)	644 (47)
Unknown	16 (1)	2 (1)	14 (1)
Perinatal deaths	58 (4)	11 (3)	47 (4)
First CD4 cell counts (cells/µl) in first pregnancy (median, IQR)	410 (264-564)	530 (360-740)	384 (250-530)
Start combination antiretroviral therapy (cART) in first pregnancy			
Before pregnancy	503 (38)	101 (42)	402 (37)
During pregnancy	707 (54)	110 (46)	597 (55)
No cART during pregnancy	110 (8)	27 (11)	83 (8)
HIV RNA plasma levels before delivery in first pregnancy			
HIV RNA available	1,191 (90)	222 (93)	969 (90)
Undetectable	1,008 (85)	188 (85)	820 (85)
Detectable	183 (15)	34 (15)	149 (15)
Unknown	125 (10)	15 (7)	108 (10)

**Median, Interquartile Range (IQR)*

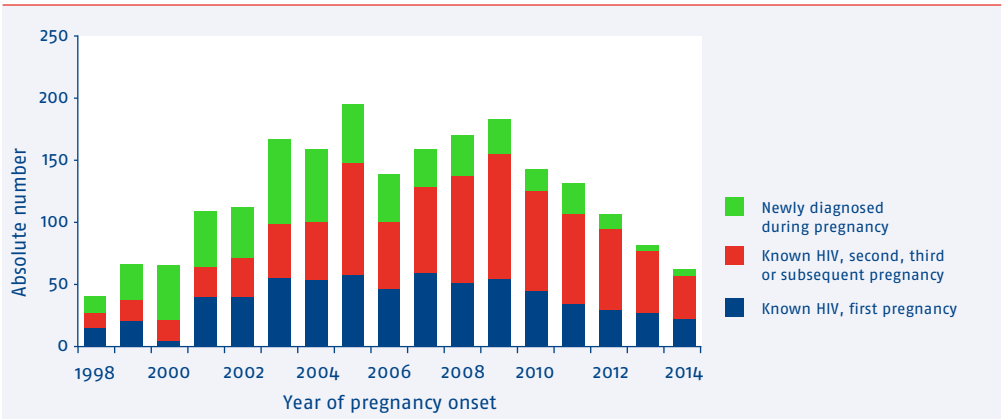
***CDC-c=US Centers for Disease Control and Prevention, category C.*

Trends in number of pregnancies amongst HIV-infected women

The absolute annual number of pregnancies varied between a minimum of 41 pregnancies in 1998 and a maximum of 195 in 2005 (*Figure 6.1*), with a decrease from 2009 onwards. The number of women who were diagnosed with HIV during pregnancy increased from 14 in 1998 to 68 in 2003, and varied between 4 and 59

from 2004 onwards. This increase in new HIV diagnoses during pregnancy in women who became pregnant in 2003 and 2004 may be the result of the introduction of HIV screening in the first trimester of the pregnancy in Amsterdam in 2003, which was subsequently expanded to a nationwide screening programme on 1 January 2004. The majority of women were already aware of their HIV infection at the time of their pregnancy. In 55% of the women, HIV was diagnosed before the onset of pregnancy. The number of second, third or subsequent pregnancies while known to be HIV-infected increased from 17 in 1998 to 156 in 2009 (*Figure 6.1*).

Figure 6.1: *Absolute number of pregnancies per year, stratified by known HIV infection at onset of pregnancy.*



Pregnancy-related characteristics

Overall, 1,320 women accounted for 2,254 registered pregnancies. Fifty-six percent of the women had one registered pregnancy, 26% had two registered pregnancies, and 18% of the women had three or more registered pregnancies (*Table 6.1*).

The 2,254 pregnancies resulted in 1,675 (74%) births. One hundred and twenty-three pregnancies (5%) ended in miscarriage, and 253 (11%) ended through abortion or ectopic pregnancy (n=2), with a known reason for abortion in 27 cases (4 medical, 23 non-medical). Another 181 (8%) pregnancies were recorded as having been terminated, but could not be defined as either a miscarriage or abortion owing to a lack of information. The outcome of the pregnancy was unknown for the remaining 20 pregnancies. In total, 869 (52%) boys and 790 (47%) girls were born, and, for 16 deliveries, the gender was not documented. Fifty-nine percent of the newborns were delivered vaginally; 70% of the women of Dutch origin delivered

vaginally compared to 57% of the women of non-Dutch origin (p<0.0001). A total of 639 newborns were delivered by Caesarean section. Elective Caesarean delivery is known to reduce the risk of MTCT if the maternal viral load is detectable, but such a delivery is less beneficial if viral load suppression is achieved following successful treatment with cART[160, 161]. The proportion of elective Caesarean deliveries in first pregnancies decreased over time from 36% in 2000 to 13% in 2014 (*Figure 6.2*), which is equivalent to the level seen in the non-HIV infected population[162]. In line with the decrease in elective Caesarean sections, the proportion of women with a viral load above 500 copies/ml at the time of delivery decreased over time (from 37% in 1998 to 7% in 2014, p<0.0001) (*Figure 6.3*). Although we observed a difference in the proportion of Caesarean deliveries between women of Dutch origin and those of non-Dutch origin, the proportion of women with a detectable HIV RNA load at the time of delivery did not differ significantly between these two groups (*Table 6.1*).

Figure 6.2: *Absolute number of pregnancies per year, stratified by mode of delivery.*

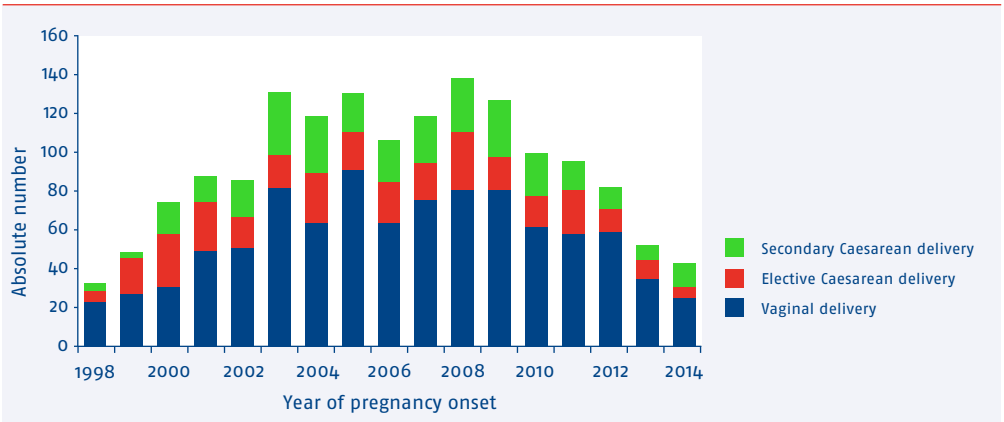
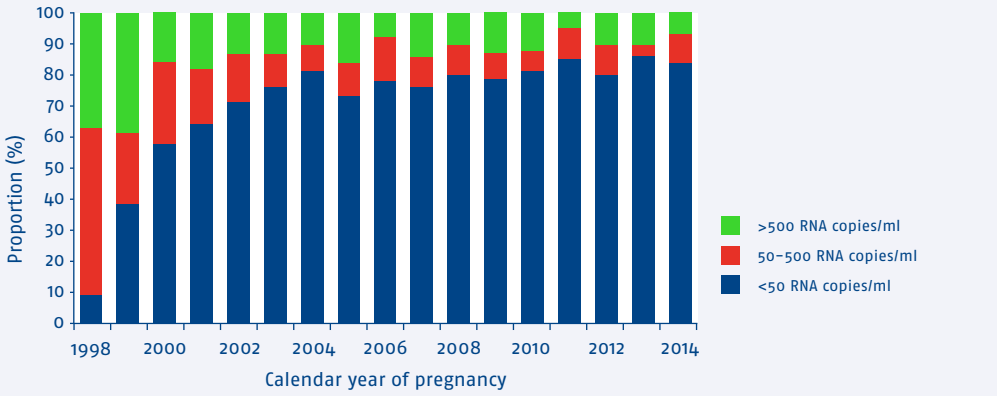


Figure 6.3: Distribution of women with HIV RNA level <50 copies/ml, 50-500 copies/ml, and >500 copies/ml at the time of delivery.



Overall, 81% of the pregnancies lasted at least 37 weeks. The median weight of newborns was 3,085 grams (IQR 2,680-3,405). Among newborns with a known birth weight and duration of pregnancy, a total of 322 (16%) were preterm births. The proportion of premature births varied from 27% in 1999 to 17% in 2012. In 1999, 6% were early-premature births (pregnancy duration less than 32 weeks), while in 2012 this figure was 1.5%.

After delivery, three infants were admitted to medium or intensive care, while another 82 children remained under clinical observation. Congenital disorders were registered for three infants, one of whom had died due to renal agenesis and cardiomyositis. Perinatal death occurred in 3.4% (n=58) of the births; 78% of these deaths occurred after a pregnancy duration of less than 32 weeks. No significant differences in pregnancy duration, birth weight, and perinatal death were found between women of Dutch and non-Dutch origin.

The earliest median CD4 count measured during pregnancy was significantly higher in women of Dutch origin (median 530, IQR 360-740) compared to women of non-Dutch origin (median 384, IQR 250-530, $p<0.0001$). The majority of women used cART during their pregnancy; 38% started cART before the onset of the pregnancy, and 54% started while pregnant. This proportion of women who were already receiving cART was somewhat higher in women from Dutch origin (42%) than in women from non-Dutch origin (37%).

Mother-to-child transmission

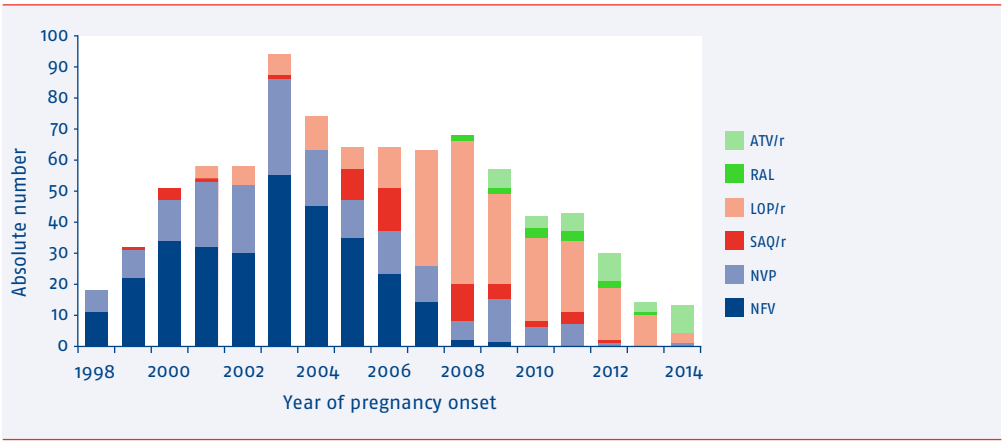
Of the 1,675 children born from registered pregnancies from 1996 onwards, 9 (0.5%) newborn infants were found to have become vertically infected with HIV. The mothers of seven of these 9 newborns had not received cART during pregnancy, in spite of five of these mothers having been diagnosed with HIV during pregnancy; it is unknown why these mothers did not start cART during pregnancy. Of the remaining 2 mothers who had not received cART during the pregnancy, one mother only tested positive for HIV infection on the day of delivery and the other mother first tested positive the day after delivery. The two remaining mothers who had transmitted HIV to their infants had started cART during pregnancy. One of these mothers had a detectable HIV RNA level during delivery, and the newborn was delivered spontaneously. The other mother had an undetectable HIV RNA load (<50 copies/ml) at the time of delivery and underwent a Caesarean section; her child was thought to have already become infected with HIV *in utero*.

Response to cART in pregnant women

Between 1998 and 2015, cART was used in 2,120 pregnancies out of a total of 2,254 (94%); cART was initiated before the start of pregnancy in 1,352 pregnancies and during the pregnancy in 768 pregnancies.

Figure 6.4 shows the most commonly used third-drug additions to the NRTI backbone as part of the cART regimens during the first registered pregnancy in women between 1998 and 2014. A nelfinavir-containing regimen was most commonly used between 1998 and 2006. Nevirapine was also often prescribed between 2001 and 2006. From 2007 onwards, a lopinavir/ritonavir-containing regimen became the most commonly used regimen among pregnant women. Subsequently, from 2008 onwards, raltegravir-containing and atazanavir-containing regimens were also prescribed for women during their pregnancy. Raltegravir has been shown to rapidly decrease time to virological suppression and is mainly added to a cART regimen in pregnant women whose HIV RNA level is not undetectable in the last trimester of the pregnancy[163].

Figure 6.4: The use of third-drug additions to the nucleoside reverse transcriptase inhibitor (NRTI) backbone as part of the combination antiretroviral therapy (cART) regimen during the first pregnancy.



Legend: cART=combination antiretroviral therapy; ATV/r=atazanavir plus ritonavir; RAL=raltegravir; LOP/r=lopinavir plus ritonavir; SAQ/r=saquinavir plus ritonavir; NVP=nevirapine; NFV=nelfinavir.

The combination of zidovudine and lamivudine as components of the NRTI backbone was used during 75% of the first registered pregnancies. However, the use of this combination decreased over time from 89% in 2002 to 0% in 2015. From 2011 onwards, emtricitabine in combination with tenofovir and abacavir in combination with lamivudine were also used as a backbone in 8% and 2%, respectively, of all first registered pregnancies.

As expected, CD4 counts at treatment initiation were significantly lower in women who started cART before pregnancy compared with those who started during their pregnancy ($p<0.0001$), because a proportion of women were treated only to prevent MTCT rather than for their own health. Furthermore, median pre-treatment HIV RNA levels were significantly lower in women who started cART during their pregnancy compared to women who started before they became pregnant ($p<0.0001$). (*Table 6.2*)

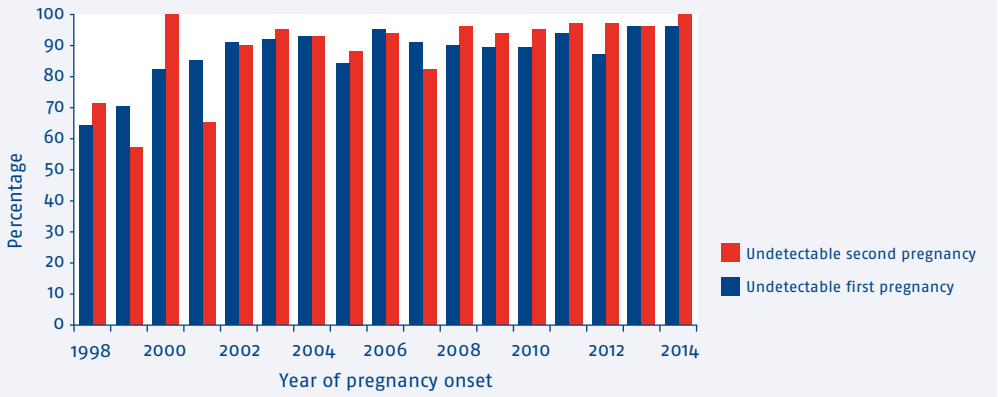
Table 6.2: Characteristics of 1,210 HIV-infected pregnant women who initiated combination antiretroviral therapy (cART) between 1 January 1998 and 1 May 2016.

	cART initiation	
	Before pregnancy	During pregnancy
Total women (n=1,127)	503 (42)	707 (58)
Age at start cART*	29 (25-32)	29 (25-33)
Region of origin		
Netherlands	101 (20)	110 (16)
Other	402 (80)	597 (84)
Calendar year of cART initiation		
<2000	162 (32)	104 (7)
2001-2006	215 (43)	362 (51)
≥2007	126 (25)	241 (34)
At start of cART		
CD4 cell counts (cells/mm^3)*	209 (100-310)	350 (211-510)
HIV RNA levels (log_{10} copies/ml)*	4.7 (4.0-5.3)	4.0 (3.4-4.6)
At parturition		
CD4 cell counts (cells/mm^3)*	445 (315-600)	460 (296-630)
HIV RNA levels (log_{10} copies/ml)*	1.7 (1.6-1.7)	1.7 (1.7-2.0)
Detectable HIV RNA levels	55 (11)	83 (12)

**Median, Interquartile Range (IQR).*

Figure 6.3 shows the percentage of women over time with an undetectable load at time of delivery; HIV RNA levels were categorised as <50 copies/ml, 50-500 copies/ml, and >500 copies/ml. Overall, 75% of the women had an HIV RNA level <50 copies/ml at the time of delivery, and 12% had an HIV RNA level between 50 and 500 copies/ml. The proportion of women with HIV RNA <500 copies/ml at the time of delivery increased from 63% in 1998 to 93% in 2014. One newborn became vertically infected with HIV, probably due to the presence of detectable maternal HIV RNA at the time of delivery. *Figure 6.5* shows the differences in having an undetectable HIV RNA level at time of delivery in the first and second registered pregnancies. In more recent years, there has been a statistically non-significant trend towards women being more likely to have an HIV RNA level <50 copies/ml at the time of delivery in a second pregnancy than in their first pregnancy.

Figure 6.5: Proportion of women with an undetectable load at the time of delivery in first or second pregnancy.

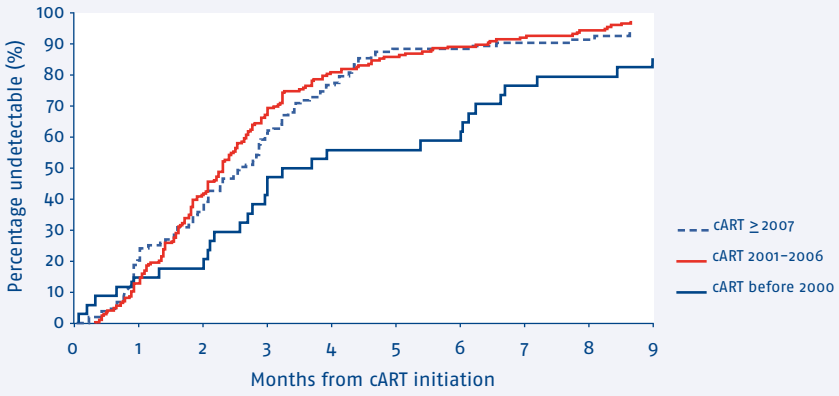


Time to initial virological success

Time from cART initiation to the first of two consecutive plasma HIV RNA concentrations of <50 copies/ml (or <500 copies/ml, depending on the detection limit of the HIV RNA assay used) in pregnant women who started cART during pregnancy was compared among women who started cART before the year 2000, between 2001 and 2006, and from 2007 onwards.

By four months after the start of cART, 77% of the women had achieved virological suppression with two consecutive HIV RNA levels <50 or <500 copies/ml. The most marked responses were observed in women who started cART during their pregnancy between 2001 and 2006 (82%, 95% confidence interval [CI] 76-87) and in women who started cART after 2007 (78%, 95%CI 69-86). Poorer response was seen in women who started cART during their pregnancy before 2000 (56%, 95% CI 41-73; p-value log rank test 0.01, *Figure 6.6*). By six months after the start of cART, 86% of the women had achieved virological suppression (77%, 95% CI 62-89, for those starting before 2001; 89%, 95% CI 84-93, for those who started between 2001 and 2006; and 89%, 95% CI 83-94, for those starting after 2007).

Figure 6.6: Time to initial suppression of HIV RNA to <50 (or <500) copies/ml after the start of combination antiretroviral therapy among pregnant women.



Virological responses after delivery

Among the 707 women who started cART during their pregnancy, 173 (24%) discontinued cART within one year after delivery. The proportion of women who discontinued cART after delivery decreased from 32% in 1998 to 0% in 2015. The remaining 534/707 women continued cART following delivery. Of these women, 134 (25%) with known prior HIV RNA suppression experienced virological failure (HIV RNA level >500 copies/ml) in the first year following delivery.

In the group of 503 women who received cART before the onset of their pregnancy, 43 (9%) discontinued treatment within one year of delivery, however, none of these women discontinued treatment in the more recent calendar years. None of the women who continued to use cART experienced virological failure.

Summary and conclusions

The absolute number of pregnancies in HIV-infected women in the Netherlands has declined over time. This is probably the result of the increasing age of women in follow up, and the declining overall birth rate in the Netherlands from 200,000 before 2007 to 170,000 in 2015, which is thought to be due to the economic crisis [164]. Viral load, the most important factor in preventing MTCT, was generally low near the time of delivery in women treated with cART. The proportion of cART-treated women with a detectable HIV RNA level at the time of delivery strongly decreased over time, which has resulted in vertical transmission of HIV becoming exceedingly rare. The MTCT rate was 0.5%, which is comparable to, or somewhat lower than,

that in other western European countries[165, 166, 167]. The proportion of women with non-suppressed HIV RNA levels at the time of delivery in our population was lower than in other reports[162]. In our population, time to virological suppression improved over calendar time. From 2000 onwards, time between the start of cART and viral suppression has become shorter. Factors associated with a detectable load at delivery are lower CD4 counts and higher HIV RNA levels at the start of pregnancy[168, 169]. Improvement in virological response may also be a result of the more effective and safer cART regimens that have become available over time. A higher proportion of women had an undetectable HIV RNA level at the time of delivery in their second pregnancy than in their first pregnancy.

Although earlier results on whether exposure to cART might increase the risk of preterm birth were conflicting[170], more recent studies have reported declines in preterm births in women infected with HIV[171, 172]. These declines were attributed to the reduction in Caesarean sections to prevent vertical transmission of HIV. In fact, from 1999 onwards, when Caesarean deliveries became less common, the number of preterm births has also declined. Nevertheless, the proportion of preterm births in HIV-1 infected women remains higher than that seen in the general population[162].

The percentage of HIV-infected women who delivered by Caesarean section in the Netherlands was comparable to the national rate of Caesarean sections, suggesting that the main reason for this type of delivery was not HIV, but rather obstetric indications, such as foetal distress or insufficient dilation or expulsion. On the other hand, in a large European cohort of HIV-infected pregnant women, the percentage of Caesarean deliveries was higher than that seen among the Dutch population of HIV-infected women[172]. This may be because, unlike other European countries, vaginal delivery has become widely accepted in HIV-infected women in the Netherlands[172].

Several studies have demonstrated that adherence to cART may deteriorate in the postpartum period[173, 174, 175, 176, 177]. A possible explanation for this phenomenon is that women may be more motivated during pregnancy to take medication to prevent vertical transmission than for their own health. We observed a marked difference in virological responses between women who started cART prior to the pregnancy and those who started during pregnancy. The women who were receiving cART before the onset of their pregnancy remained virologically suppressed during the first year after delivery, while those who started cART during their pregnancy had poorer virological responses during the first year after delivery.

Recommendations

Although the proportion of HIV-infected pregnant women with appropriately suppressed viraemia at the time of delivery has markedly increased over time, there remains room for improvement. As a result of changes in recent guidelines on HIV and pregnancy, cART will be given earlier in pregnancy. This may lead to a greater level of viral suppression at the time of delivery. Furthermore, earlier viral suppression should provide the opportunity to consider invasive procedures for genetic syndromes, such as amniocentesis in case of foetal anomalies on the 20 weeks ultrasound scan. However, to date, robust evidence is lacking to support the idea that starting cART at 12 weeks will lead to a greater proportion of women with suppressed viraemia at the time of delivery than starting cART at 20 weeks of pregnancy. Moreover, exposure to cART in the first trimester may be associated with a higher level of prematurity, and it is unknown whether longer exposure to cART is harmful to the foetus. Therefore, clinical trials and monitoring of pregnant women using cART during the first trimester of their pregnancy are needed to gain more insight into the impact of cART exposure on the foetus. Another factor to be considered when prescribing cART during the first trimester is that the severe nausea from which women may suffer, in particular during the first 12 weeks of pregnancy, may lead to poorer adherence and ultimately treatment failure. Finally, women infected with HIV who start cART during their pregnancy require a high level of clinical support, not only during pregnancy, but also after delivery. Continued monitoring of HIV-infected women after pregnancy is necessary to prevent decreased motivation to adhere to cART and to ensure early detection of virological failure.

Special reports

7. Quality of care

Colette Smit, Jan Prins, Kees Brinkman, Suzanne Geerlings, Frank Kroon, Sonia Boender, 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 pseudonymised data from HIV patients in care in the 26 officially acknowledged HIV treatment centres, 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, HIV treatment 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[178]. 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 HIV 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 United States Department of Health and Human Services (DHHS) HIV/AIDS practice guidelines[178]. These indicators were classified as volume, outcome or process indicators.

As noted in earlier studies, the number of patients in care (i.e., the hospital volume) may have an impact on the reported indicators[179, 180, 181]. In particular, the small number of patients in some HIV treatment centres could result in a wider range of scores for a given indicator. As such, in a low-volume treatment centre, a single patient with a deviating score will have a far greater impact on the centre's overall score than in larger-volume centres. For this reason, when reporting the results, we took treatment centre size into account, categorising centres according to the number of patients in care as follows: large: ≥600 patients, n=8 centres (red dots); medium-sized: 300-600 patients, n=11 centres (blue dots); small: <300 patients, n=7 centres (grey dots).

Volume indicator

To meet the national certification requirements set by the Foundation for Harmonisation of Healthcare Quality Review (Harmonisatie Kwaliteitsbeoordeling in de Zorgsector, HKZ), HIV treatment centres are expected to enrol a minimum number of approximately 20 new patients into care each year. Therefore, as a volume indicator, we calculated the number of patients newly entering care for the first time in 2012, 2013, 2014 and 2015 for each treatment centre.

Outcome indicators

The outcome indicators included retention in care, initiation of cART and achievement of viral suppression. For the purpose of the current analysis, retention in care was defined as the percentage of those patients who had either entered care for the first time after being diagnosed with HIV in one of the Dutch HIV treatment centres in 2012 and were still in care on 1 June 2014 or who had entered care in 2013 and were still in care on 1 June 2015. During this period, approximately 16% of patients switched treatment centres; these patients were considered to be retained in care, since they remained in care and were not lost to follow up. To avoid double counting, patients who switched centres were counted for the centre where they had their last visit and not for the centre where they initially entered care.

Initiation of cART describes the overall percentage of those patients who had entered care in 2012, 2013, and 2014 and who had started cART within 6 months of entry into care. This indicator was stratified by CD4 cell count at entry into care: CD4 ≥500 cells/mm^3, CD4 350-500 cells/mm^3 and CD4 <350 cells/mm^3.

Viral suppression was assessed by two indicators. The first indicator was defined as the percentage of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at 6 months after the start of cART. The HIV RNA measurement closest to 6 months after the start of cART was chosen, with a minimum of 3 months and a maximum 9 months. The target suppression rate was set at ≥90%. This indicator is part of the formal HKZ certification process for HIV treatment centres in the Netherlands. The indicator was developed jointly with the NVHB[182] during the foundation of the HKZ, using the Delphi method.

The second indicator for viral suppression was the percentage of all HIV-infected patients 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, 2014 and 2015.

Process indicators

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

To calculate the process indicators prior to cART initiation, we included all patients who had entered care in 2012, 2013 or 2014. Only patients who entered care for the first time were included; patients who had switched treatment centres were not counted as newly entering care, as they had been in care elsewhere. Accordingly, patients who had been in care and started cART outside the Netherlands were excluded. The indicators were defined as the percentage of patients newly entering care in 2012, 2013 or 2014 for whom the following measurements were available in the 12 months after entry into care: CD4, plasma HIV RNA, total cholesterol, screening for the presence of hepatitis B virus (HBV) and/or hepatitis C virus (HCV) co-infection, syphilis, alanine aminotransaminase (ALT) and creatinine.

To calculate the process indicators following cART initiation, we included patients who had started cART in 2012, 2013 or 2014. The indicators were defined as the percentage of patients in whom the following measurements were carried out at least once within 12 months after cART initiation: CD4 cell count, plasma HIV RNA, total cholesterol, ALT, and creatinine.

Additional process indicators were specifically defined for men who have sex with men (MSM), based on the national guideline recommendations to carry out annual HCV screening among MSM who report HCV-related risk-taking behaviour and to perform annual syphilis screening for all patients. The first of these indicators was calculated for MSM who were HCV-negative at entry into care in 2012 and 2013. We calculated the proportion with repeat HCV serology within three years after entering care (between 2012-2015 or 2013-2016 for MSM who entered care in 2012 and 2013, respectively).

The second of the MSM-specific indicators was derived for all MSM who entered care in 2012 and 2013, and the calculation of the proportion of men for whom syphilis serology was repeated within three years after entry into care (between 2012-2015 or 2013-2016 for men who entered care in 2012 and 2013, respectively).

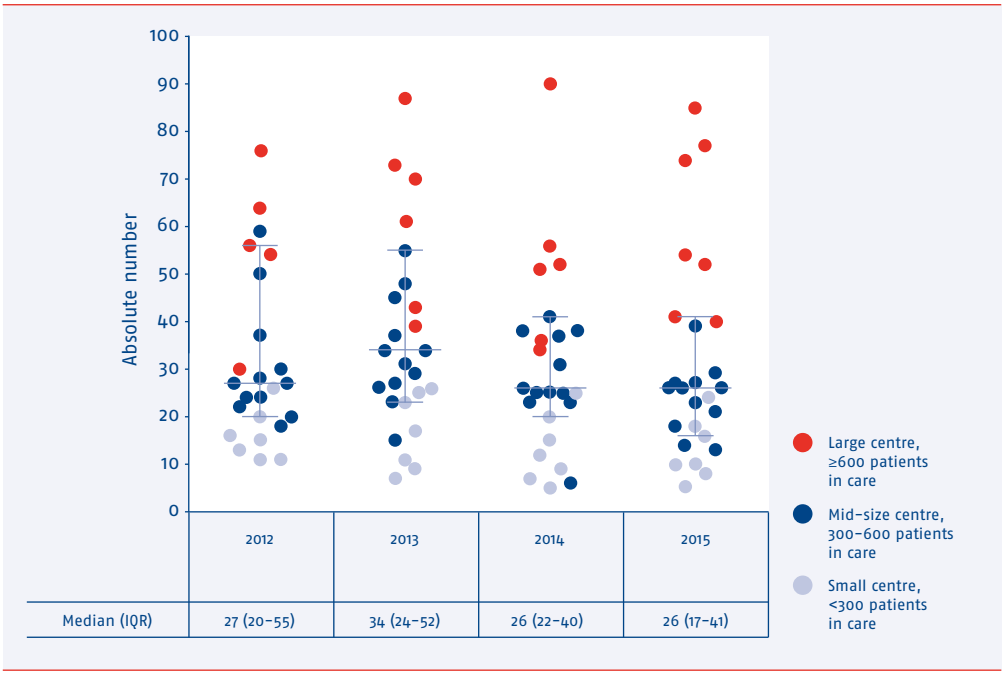
As smaller centres had a smaller number of MSM entering care in 2012 and 2013, we increased the sample size by using a wider range for repeat HCV and syphilis screening than recommended by the guidelines, calculating the proportion of repeat screening over a three-year period instead of within one year.

Results

Volume indicator

The numbers of patients who newly entered care in 2012-2015 across the HIV treatment centres are shown in *Figure 7.1*. The median number of patients entering care varied between a maximum of 34 in 2013 and a minimum of 26 in 2014 and 2015. The minimum number ranged from 5 in 2015 to 11 patients in 2012.

Figure 7.1: Numbers of patients entering care per HIV treatment centre in the Netherlands in 2012, 2013, 2014 and 2015.



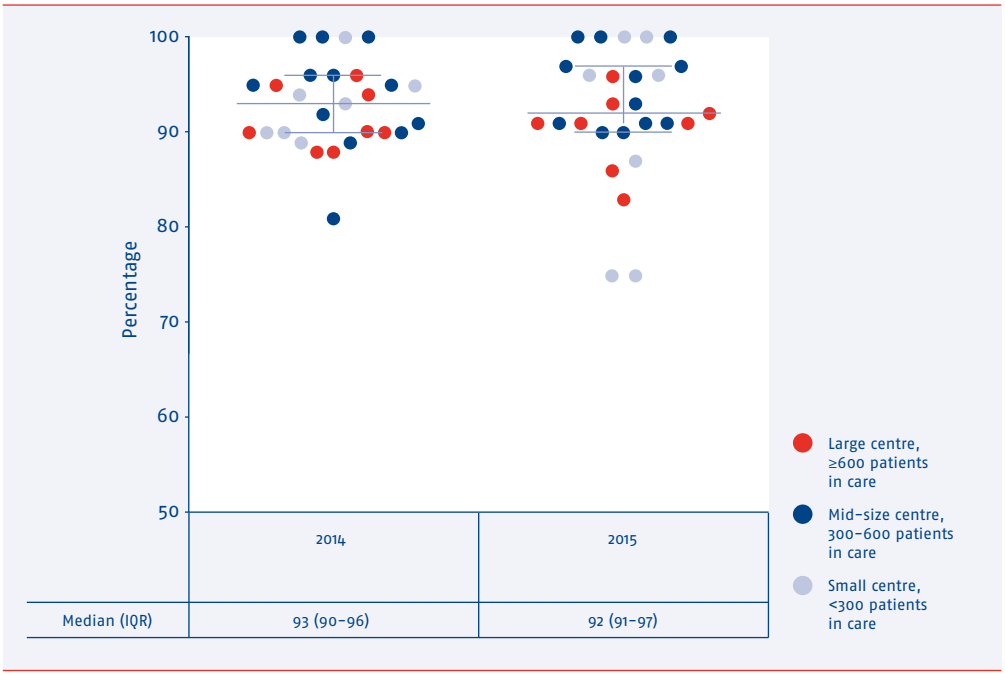
Legend: IQR: interquartile range.

Retention in care

In 2012, 1,174 patients newly entered care at one of the HIV treatment centres in the Netherlands. Overall, 1,076 of these 1,174 patients (92%) were documented as being retained in care after 1 June 2014. In 2013, 1,175 patients newly entered care, and 1,062 (92%) of those were retained in care after 1 June 2015. *Figure 7.2* shows the variation in retention rate across treatment centres for 2014 and 2015. The median

retention rate was 93% in 2014, with a minimum of 81% and a maximum of 100%. In 2015, the median retention rate was 92%, with a minimum of 75% and a maximum of 100%.

Figure 7.2: *Retention in care, defined as the percentage of patients who either newly entered care in 2012 and were still known to be in care after 1 June 2014 or who newly entered care in 2013 and were still known to be in care after 1 June 2015. Retention rates are presented as the median and interquartile range across all HIV treatment centres.*



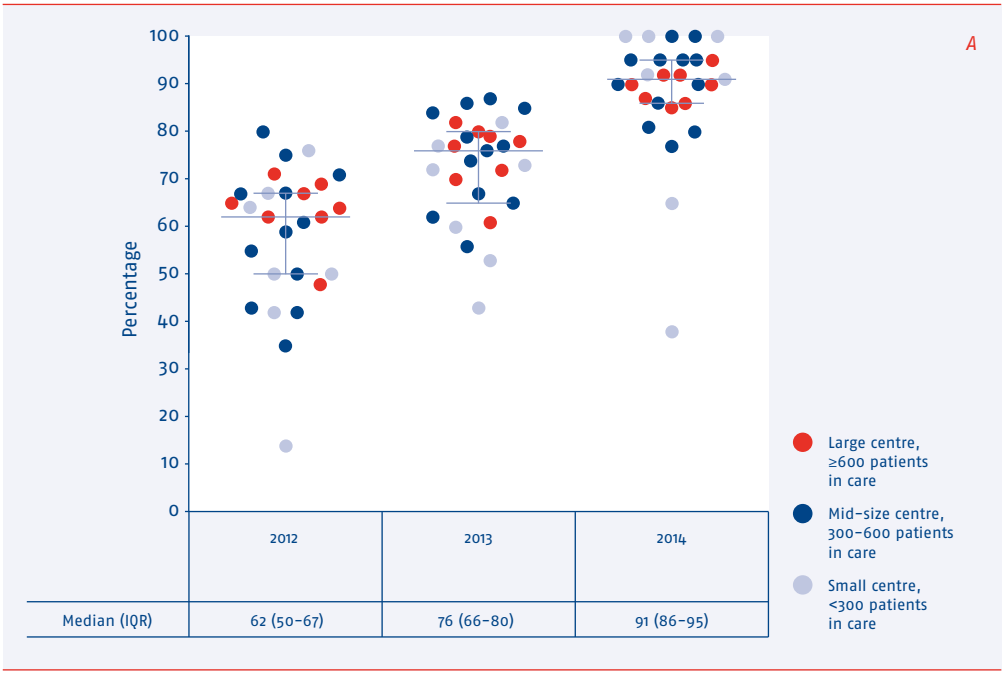
Legend: *IQR: interquartile range.*

Initiation of cART

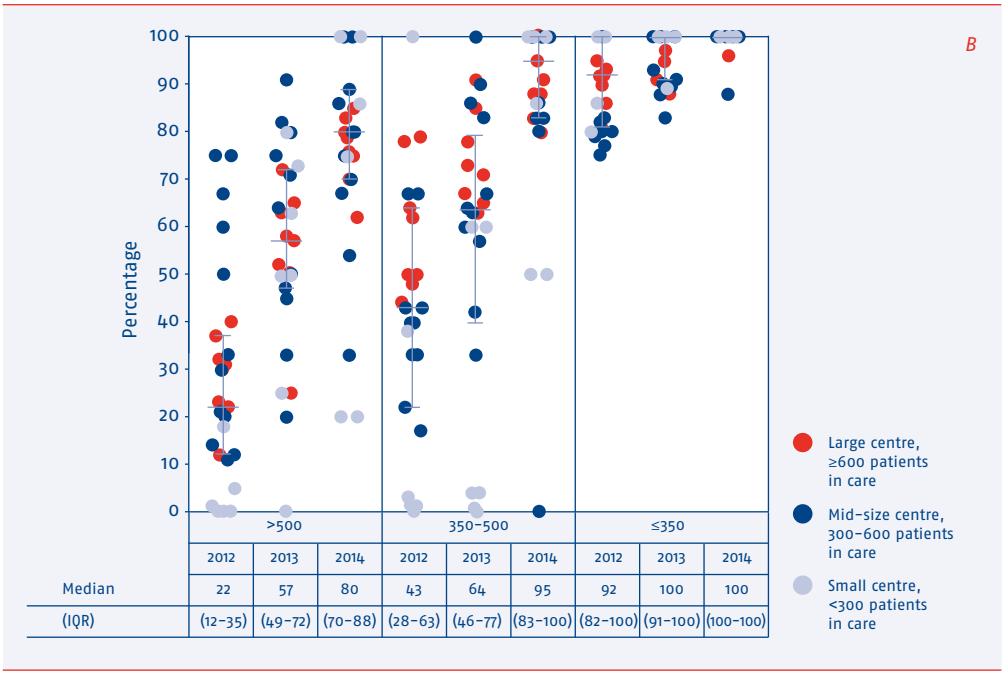
Figure 7.3 shows the percentages of patients starting cART within 6 months after entering care. Overall, a median of 62% of the patients who entered care in 2012 started cART within 6 months of entry, and this proportion increased to 91% among patients who entered care in 2014. In terms of variation across HIV treatment centres, the lowest percentage of patients starting cART within 6 months was 14% for 2012, 43% in 2013, 38% in 2014 and 20% in 2015. When stratified by CD4 cell

count, the percentage of patients starting cART within 6 months of entering care was lower for the CD4 cell categories >500 cells/mm^3 and 350-500 cells/mm^3, compared with the CD4 cell category of <350 cells/mm^3. This difference between CD4 cell categories decreased in 2014, as most of the patients entering care that year started treatment within 6 months (80%, 95% and 100% for the CD4 cell categories >500, 350-500 and <350 cells/mm^3, respectively); nonetheless, considerable variation remained between HIV treatment centres.

Figure 7.3: The percentage of patients who entered care between 2012-2014 and started combination antiretroviral therapy (cART) within 6 months after entry. (A) Overall percentages and (B) percentages categorised by CD4 cell count at entry are presented as the percentage of patients starting cART across all HIV treatment centres.



Legend: IQR: interquartile range.

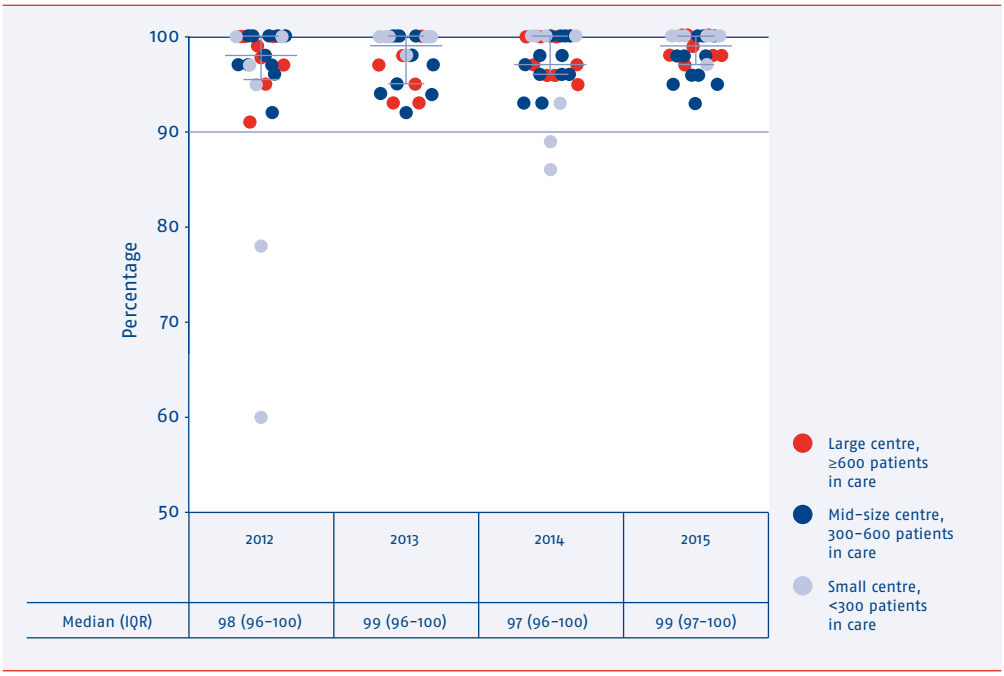


Legend: *IQR: interquartile range.*

Viral suppression

Viral suppression was assessed with 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. Percentages are shown for patients newly initiating treatment in the years 2012-2015 (*Figure 7.4*). The median percentage increased from 98% in 2012 to 99% in 2015. In 2012 and 2014, in two small treatment centres, less than 90% of the treatment-naive patients had achieved an HIV RNA <400 copies/ml within 6 (3-9) months after starting cART, while in 2013 and 2015 more than 90% of patients in all centres had achieved an HIV RNA <400 copies/ml within 6 (3-9) months after starting cART.

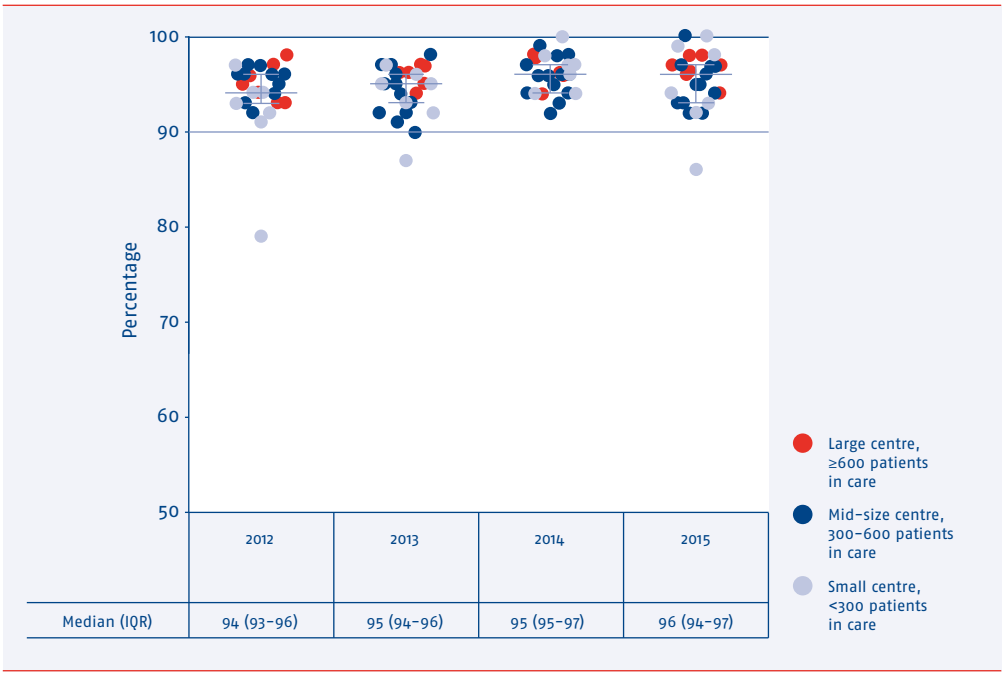
Figure 7.4: Percentages of treatment-naive patients with a plasma HIV RNA level <400 copies/ml at 6 months (minimum and maximum: 3-9 months) after the start of combination antiretroviral therapy (cART) across all HIV treatment centres.



Legend: *IQR: interquartile range.*

The second viral suppression indicator is the percentage of all HIV-infected patients in care who received cART for at least 6 months and had an HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2012-2015 (*Figure 7.5*). In all calendar years, the median percentage was more than 90%, with limited variation according to centre size.

Figure 7.5: The percentage of all HIV-infected patients in care who 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 2012-2015 and is presented as the percentage across all HIV treatment centres.



Legend: IQR: interquartile range.

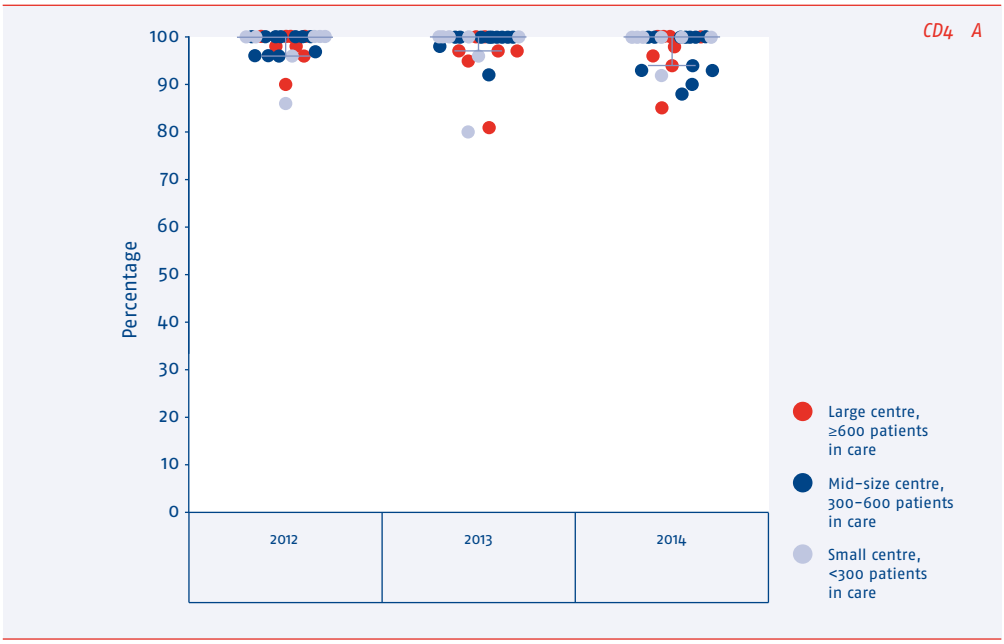
Process indicators

Prior to starting cART

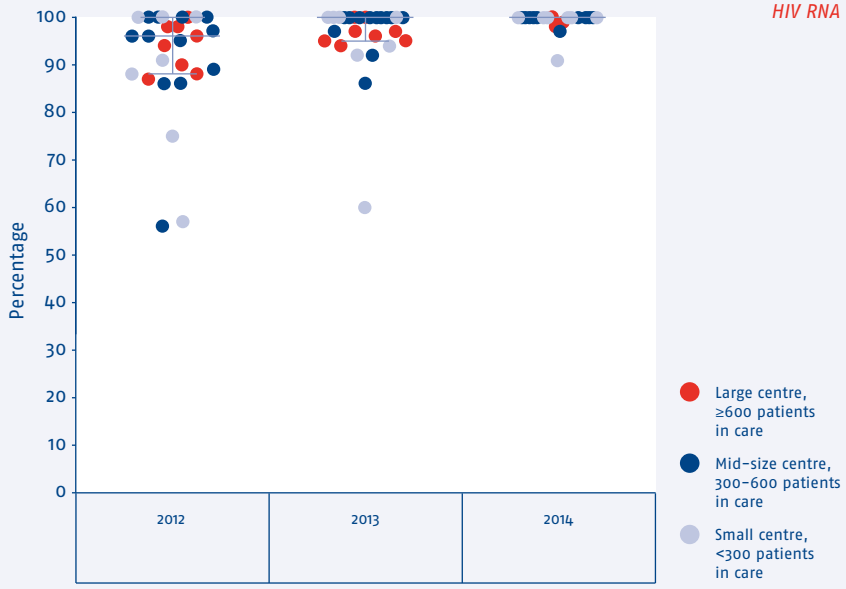
Figure 7.6 shows the variation in plasma HIV RNA, CD4 cell count, total cholesterol, ALT and creatinine measurements, as well as syphilis, HBV and HCV screening across the HIV treatment centres in the Netherlands in patients who had newly entered care in 2012-2014. The median percentages of patients tested for plasma HIV RNA, CD4 cell count, total cholesterol, ALT, creatinine and syphilis was greater than 90%. However, there was considerable inter-centre variation in the percentage of patients screened for the presence of HBV and HCV co-infection, cholesterol, syphilis, and HIV RNA. The maximum percentage of patients screened for HBV and HCV was 100%, while the minimum rates were 50% and 20%, respectively. In terms

of total cholesterol measurement, the maximum rate was 100% and the minimum rate 50%, and in terms of syphilis serology workup, these figures were 100% and 73%, respectively. HIV RNA assessment showed wide variation in 2012, with a maximum rate of 100% and a minimum rate of 53%. However, this variation improved, as shown by an increased minimum rate of HIV RNA assessment of 91% in 2014.

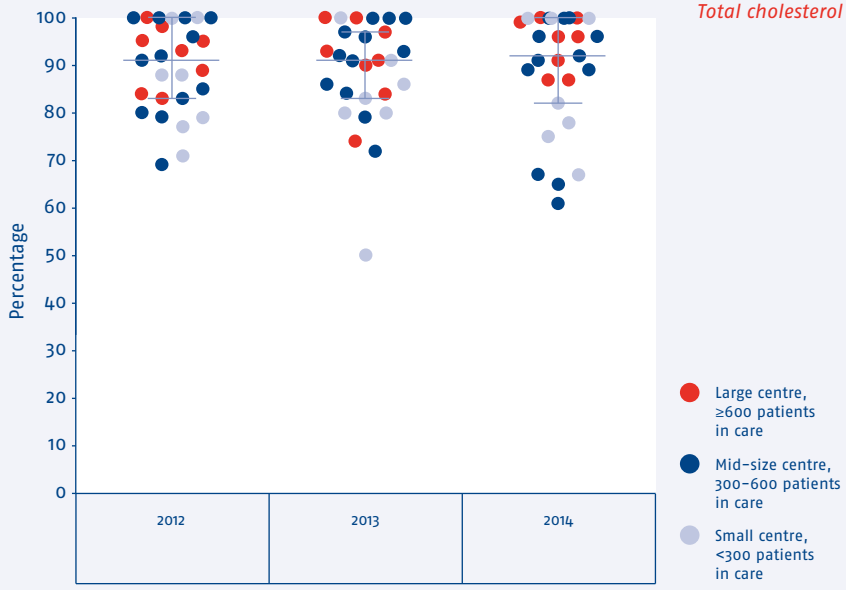
Figure 7.6: *Percentages of patients who newly entered care in Dutch HIV treatment centres in 2012–2014, with assessment of (A) plasma CD4 cell count, (B) HIV RNA, (C) total cholesterol, (D) hepatitis B, (E) syphilis, (F) hepatitis C, (G) alanine aminotransferase, and (H) creatinine.*



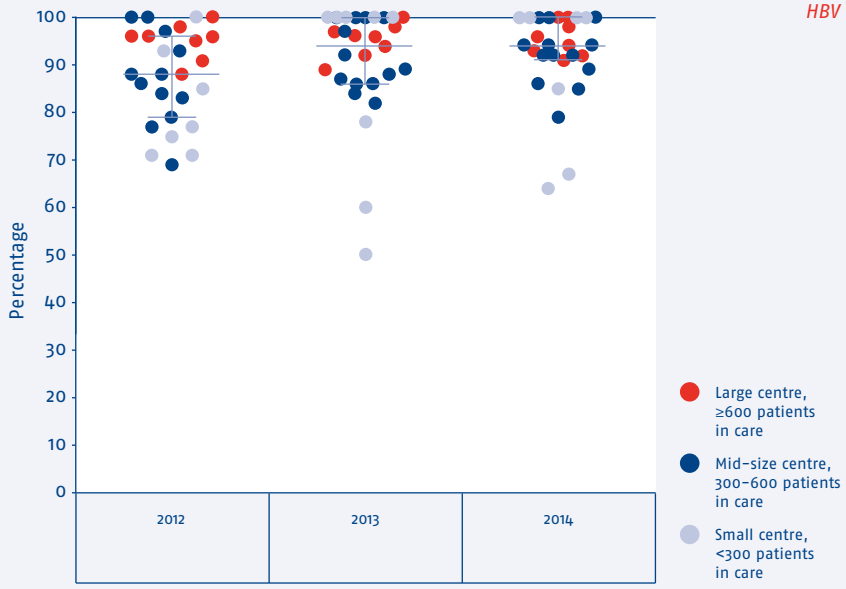
HIV RNA B



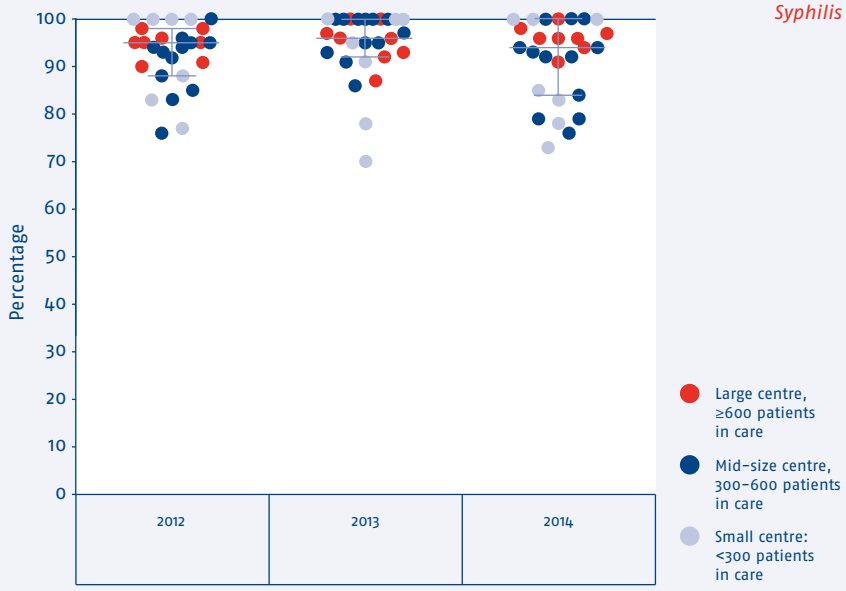
Total cholesterol C



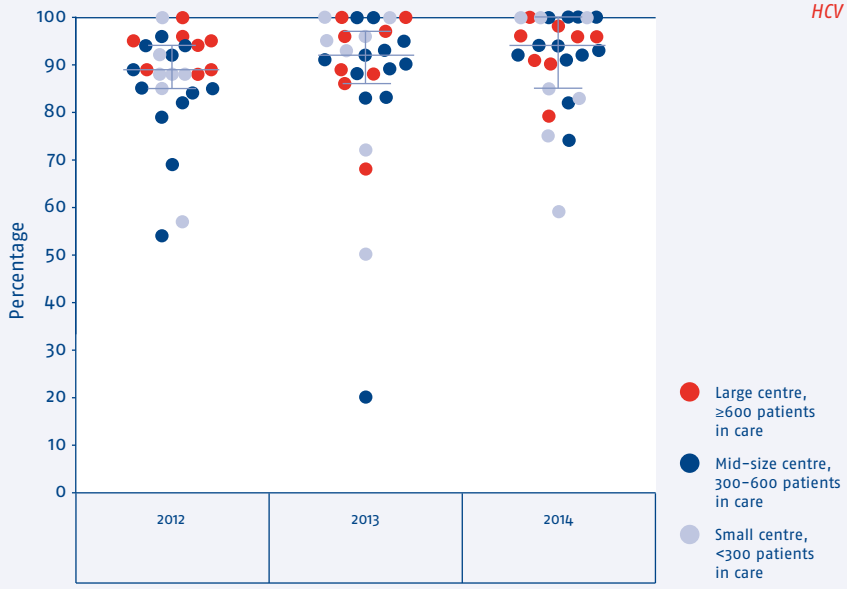
HBV D



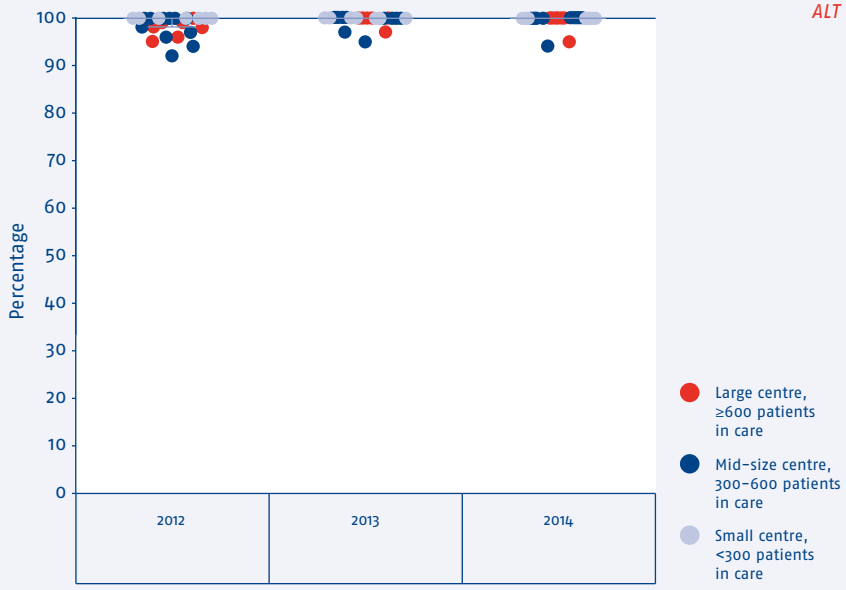
Syphilis E



HCV F


Percentage
100
90
80
70
60
50
40
30
20
10
0
2012
2013
2014
Large centre, ≥600 patients in care
Mid-size centre, 300–600 patients in care
Small centre, <300 patients in care

ALT G


Percentage
100
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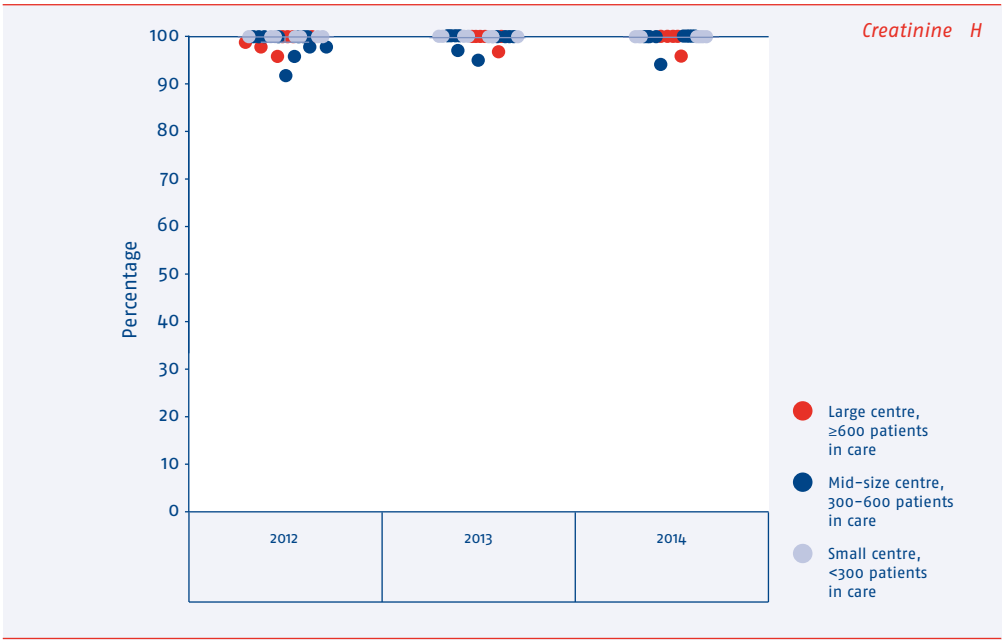
Large centre, ≥600 patients in care
Mid-size centre, 300–600 patients in care
Small centre, <300 patients in care

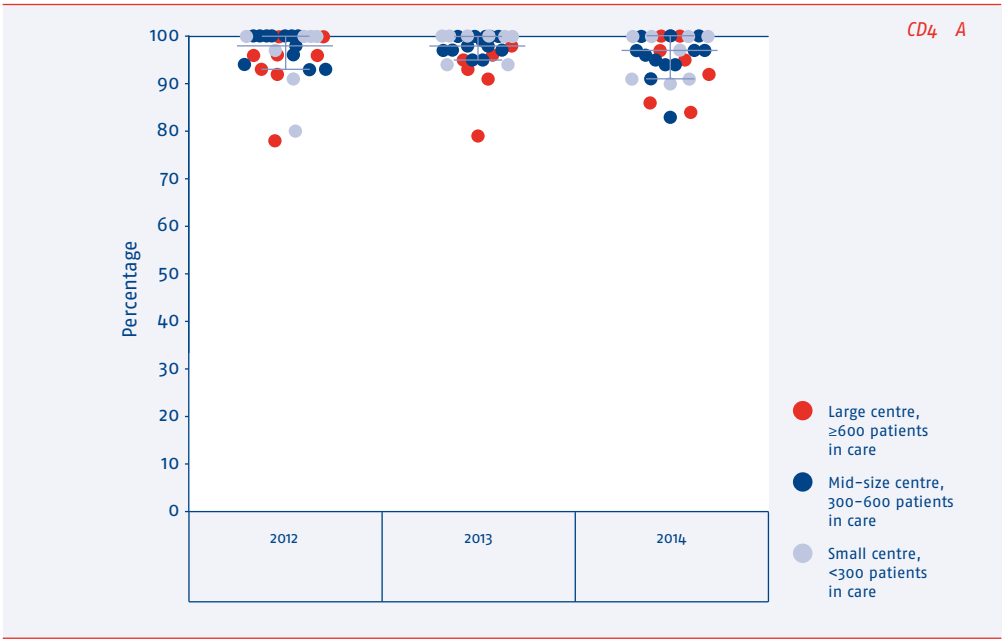


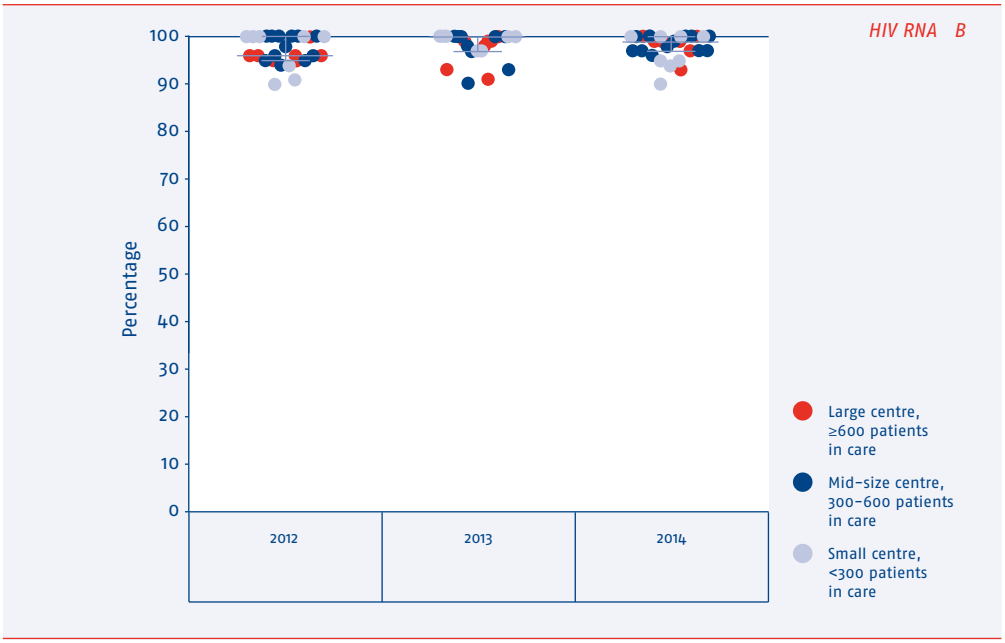
Legend: HBV=hepatitis B; HCV=hepatitis C; ALT= alanine aminotransferase.

Following the start of cART

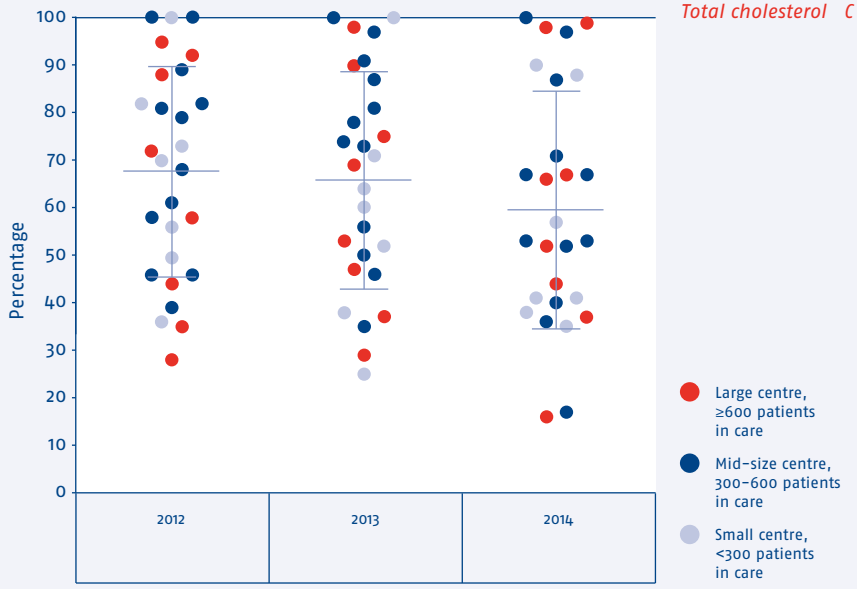
Figure 7.7 shows the variation between HIV treatment centres in the Netherlands in terms of assessing plasma HIV RNA, CD4 cell count, total cholesterol, ALT, and creatinine levels at least once within 12 months after cART initiation for all patients who initiated cART between 2012 and 2014 and who were still in care 12 months after starting cART. CD4 count, 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 78% 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, irrespective of centre size (*Figure 7.7C*).

Figure 7.7: Percentages of patients in HIV treatment centres in the Netherlands who initiated combination antiretroviral therapy (cART) in 2012–2014, with assessment of (A) plasma CD4 cell count, (B) HIV RNA, (C) total cholesterol, (D) alanine aminotransferase, and (E) creatinine within 12 months after start of cART.

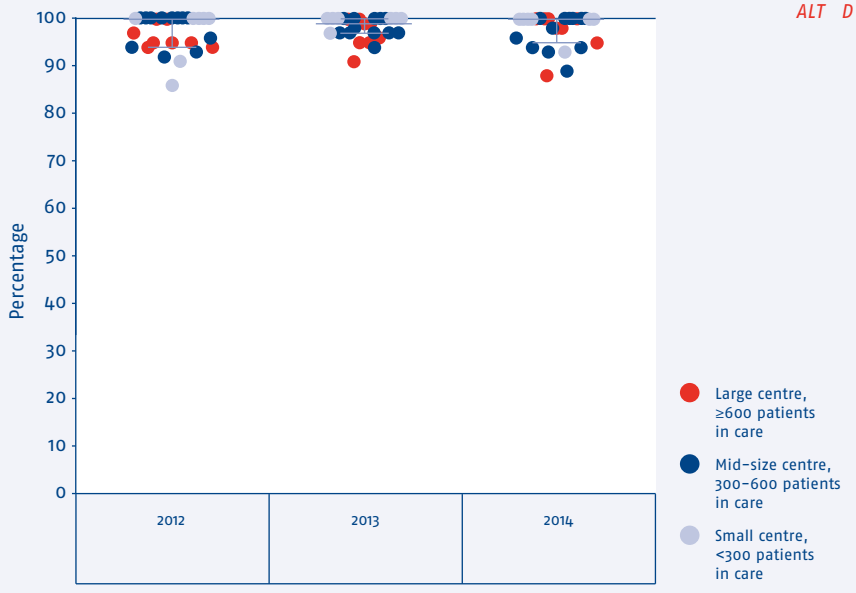


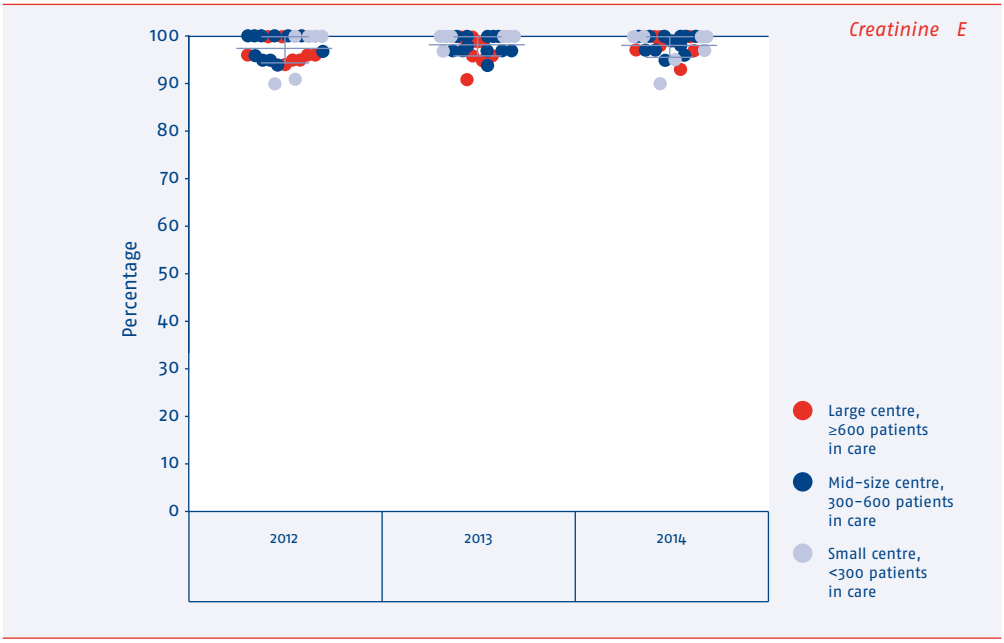


Total cholesterol C



ALT D



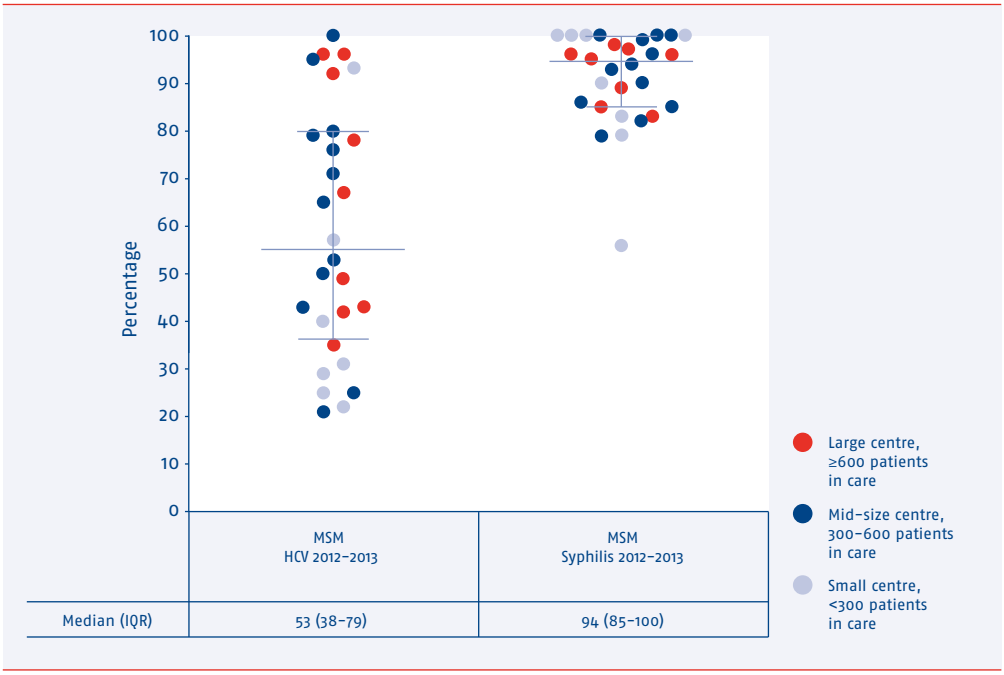


Legend: ALT= alanine aminotransferase.

Repeat screening for hepatitis C and syphilis in MSM

In 2012 and 2013, 1,444 MSM newly entered care; of those, 1,321 were screened for the presence of HCV in the first year after entering care. Thirty-one (2%) of these 1,321 MSM tested positive for HCV. The remaining 1,290 (98%) MSM were HCV-negative when they entered HIV care, and this group was included in the calculation of the repeat HCV screening rate. *Figure 7.8* depicts the rate of repeat screening for HCV among MSM who were HCV-negative at entry into care. This figure shows considerable variation in the rate of repeat HCV screening. The median rate of repeat HCV antibody or HCV RNA testing in MSM who were HCV-negative at entry into care was 53%; the maximum percentage was 100%, while one centre carried out repeat HCV tests in only 21% of MSM who were HCV-negative at entry into care. A large degree of variation was also observed between HIV treatment centres for repeat screening for syphilis among MSM during follow up, but this variation was smaller than that observed for HCV screening. The maximum percentage of patients undergoing repeat syphilis screening was 100%, and the minimum was 56%, with a median of 94%.

Figure 7.8: Percentages of repeat screening for hepatitis C virus (HCV) among men who have sex with men (MSM) who were HCV-negative at entry in care and for syphilis among all MSM who entered care in one of the HIV treatment centres in 2012 and 2013.



***Legend:** MSM=men who have sex with men, HCV=hepatitis C, IQR=interquartile range.*

Key findings

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

- Most HIV treatment centres see more than 20 new patients per year. However, a number of treatment centres did not meet the minimum of 20 new patients per year, as required by the HKZ standards for HIV treatment centres in the Netherlands.
- Median and treatment centre-specific retention-in-care rates are generally high.
- Large variation is observed in the percentage of patients starting cART within 6 months 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 [178], 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 CD4 cells/mm^3 started cART within 6 months of their first clinical visit. However, compared with 2012 and 2013, in 2014 there was a clear increase in the proportion of patients initiating cART and 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 2015, 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 85% in all but one HIV treatment centre in 2012, with a median of 95% in 2012 and 2013, and 96% in 2014.
- Large variation was observed in syphilis, total cholesterol, HBV and HCV screening before the start of cART, with HBV and HCV screening rates ranging from 50% to 100% and 20% to 100%, respectively.
- The measurement of total cholesterol in the first twelve months following cART initiation ranged from 16% to 100%.
- In MSM who entered care in 2012 and 2013 and were HCV-negative at entry into care, the rate of repeat HCV co-infection screening varied widely, from 21% to 100%. Although the guidelines recommend HCV screening in MSM who report behaviour that may increase their risk of acquiring HCV, we were unable to take this factor into account in our analyses, as data on risk-taking behaviour are not available to SHM.
- In MSM who entered care in 2012 and 2013, repeat syphilis screening varied considerably, from 56% 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, regardless of centre size. In addition, more patients who entered care in 2014 and 2015 started cART within six months after entry into care than those who had entered care in earlier calendar years. However, although the proportion of patients starting cART within 6 months after entering care has increased, the rate of starting treatment among patients who entered care with CD4 cell counts above 350 cells/mm^3 could be further improved in some centres. A large variation in the assessment of total cholesterol after cART initiation was also observed and may be attributed to centres that calculate cardiovascular risk profiles to identify patients with a low risk profile; in those patients less frequent assessment of lipids may be adequate. Finally, the variation in repeated HCV screening may, to some extent, be explained by physicians applying a policy of targeted screening only, guided by the presence of incident transaminase

elevations and/or by differences in the MSM population with respect to known risk-taking behaviour for HCV acquisition.

Quality of care covers several aspects of health care[183, 184]. As such, the wide range of indicators used in this analysis offers broad coverage of various aspects of HIV care to provide insight into the practise performance of the different treatment centres. Nonetheless, data reliability remains an important issue, and it should be recognised that, incidentally, some of the reported variation may have been introduced by missing data or delayed data collection in certain centres. Moreover, in smaller centres, indicator scores may be affected by the smaller numbers of patients, possibly rendering scores less stable and causing differences in patient populations to have a larger impact on scores than in treatment centres with a larger number of patients in care.

Finally, the variation between treatment centres may be used as a benchmark to compare centres and, accordingly, identify aspects that may be improved. Therefore, we invite treatment centres to enquire about their individual indicator results to potentially identify elements of care that may be improved.

8. The Amsterdam Cohort Studies on HIV infection: annual report 2015

Amy Matser 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 people who use drugs (PWUD) was initiated in 1985. In 2015, the cohorts reached 31 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 31 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 the past decade, research on the epidemiology of other blood-borne and sexually transmitted infections (STI) and their interaction with HIV has become an important component of the ACS research programme.

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.

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 Public Health Service of Amsterdam (Geneeskundige en Gezondheidsdienst Amsterdam; GGD Amsterdam) (Department of Infectious Diseases Research and Prevention), the Academic Medical Center (AMC) of the University of Amsterdam (Departments of Medical Microbiology, Experimental Immunology, and Internal Medicine (Division of Infectious Diseases), HIV treatment centre, Emma Kinderziekenhuis), 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 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).

Ethics statement

The ACS has been conducted in accordance with the ethical principles set out in the declaration of Helsinki. Participation in the ACS is voluntary and written informed consent is obtained from each participant. The most recent version was approved by the AMC Medical Ethics Committee in 2007 for the MSM cohort and in 2009 for the PWUD cohort.

The ACS in 2015

The cohort of men having sex with men

As of 31 December 2015, 2,713 MSM 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. Blood is collected for diagnostic tests and storage. Of the 2,713 MSM, 607 were HIV-positive at entry into the study, and 248 seroconverted during follow up. In total, the GGD Amsterdam was visited 56,184 times by MSM.

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. In line with the advice issued by the international scientific advisory committee in 2013, the cohort made additional efforts to recruit young HIV-negative MSM. 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 2015, 654 HIV-negative and 69 HIV-positive MSM were in active follow up within the ACS (6-monthly visits to the GGD Amsterdam for STI testing, including HIV); 66 of these 69 MSM filled in behavioural questionnaires. Apart from the HIV-positive MSM visiting the GGD Amsterdam, 269 HIV-positive MSM were followed outside the GGD Amsterdam via the Jan van Goyen Medical Centre or at a HIV Focus Centre in Amsterdam. Behavioural questionnaires were filled in by 39 of them. The median age of the total group of MSM was 43.6 years (interquartile range [IQR] 36.6-51.1), 8.4% were non-Dutch, and 73.4% had attained a high level of education. The majority of the participants (84.7%) were residents of Amsterdam. Additional efforts to expand the HIV-negative cohort resulted in 64 newly recruited HIV-negative participants in 2015. The median age in this group was 27.8 years (IQR 24.3-37.5).

The cohort of drug users

As of 31 December 2015, 1,680 people who use drugs (PWUD) were included in the ACS. Before 2014, participants visited the GGD Amsterdam every four to six months. They completed 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, HIV-positive participants and, in the past, HIV-negative participants, underwent a medical examination. Blood was collected for diagnostic tests and storage.

In 2014, PWUD included in the ACS were divided into two groups, in line with the advice of the international scientific advisory committee in 2013. Group 1 consists of PWUD who visit the GGD Amsterdam once a year to complete questionnaires with no testing and blood sampling. In 2015, there were 130 PWUD in active follow up in this group. Group 2, the focus group, consists of PWUD who are 1) HIV positive; 2) hepatitis C virus (HCV) seroconverters; 3) multiple-exposed, non-infected with HIV and HCV, or 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 2015, 61 PWUD were in active follow up in this focus group. The cohort was closed for new participants in January 2014. Therefore, no new participants were recruited in 2015.

Of the 1,680 PWUD, 323 were HIV-positive at entry, and 99 seroconverted during follow up. The last HIV seroconversion was seen in 2012. By 31 December 2015, 573 PWUD had died. In total, PWUD visited the GGD Amsterdam 28,002 times. The median age of the PWUD was 53.4 years (IQR 46.9-58.2), 7.1% had attained a high level of education, 11.5% were non-Dutch, and 182 (95.3%) 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 comorbidities and known risk factors for these comorbidities in HIV-infected patients aged ≥45 years, and to determine the extent to which comorbidities, their risk factors and their relation to quality of life differ between HIV-infected and uninfected groups. Participants undergo a comprehensive assessment for comorbidities 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 September 2015, 498 HIV-1-infected participants and 482 HIV-uninfected individuals had completed the second follow up visit. As of 31 December 2015, 368 HIV-1-infected participants and 226 HIV-uninfected participants had returned for their third visit. The third visiting round will continue until September 2016 and the fourth round of visits will commence in October 2016.

H2M Cohort Study

From 2010 to 2013, the H2M (HIV and human papillomavirus (HPV) in MSM) cohort study was conducted in a subset of the HIV-negative and HIV-positive ACS participants who were in active follow up and attending the STI clinic at GGD Amsterdam or the Jan van Goyen Medical Centre. The aim of the study was to compare the prevalence, incidence, and clearance of high-risk (hr) HPV infections between HIV-negative and HIV-infected MSM.

In 2015, a study based on the H2M cohort was initiated to identify potential predictors for high-grade anal intra-epithelial neoplasia in the HIV-infected MSM population. This study, the H2M2, is an Aids Fonds-supported project, and a collaboration between the GGD Amsterdam, HIV Focus Centre, the CIb-RIVM, VUmc, and the AMC. The study includes a subset of the HIV-positive ACS participants. Preliminary findings should be presented in 2016.

Since September 2014, collection of anal and genital swabs has been resumed in the ACS participants. The key aim of this second new study (the H2M3 study), which builds on the H2M study, is to study long-term incidence and clearance of anal and penile hrHPV infections. Samples at two time points (6 months apart) have been tested in the laboratory for HPV DNA and statistical analyses are underway. The study will investigate what proportion of MSM have long-term persistent hrHPV infections. This study is a collaboration between GGD Amsterdam, ACS, and Crucell.

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. In addition, the ACS biobank includes plasma/serum and PBMC 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 among 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 94 HIV-infected and HIV-exposed children at the Emma Kinderziekenhuis in the AMC until 2008. These are also stored at the AMC. In 2015, no new samples from children were collected within the ACS setting. All stored samples are available for ACS research.

The HIV epidemic

HIV incidence

In 2015, 2 MSM participating in the ACS seroconverted for HIV. The observed HIV incidence among MSM has remained relatively stable in recent years and was 0.34 per 100 person years in 2015. The HIV incidence in PWUD has been stable since 2008, with zero to less than one case per 100 person years. As follow up was restricted to a selection of PWUD in 2014 and inclusion of new PWUD

stopped, the yearly observed incidence of PWUD can only be presented until 2013. *Figures 8.1* and *8.2* show the yearly observed HIV incidence rates for MSM and PWUD from the start of the ACS through 2015 and 2013, respectively.

Figure 8.1: *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among men who have sex with men (MSM), 1984–2015.*

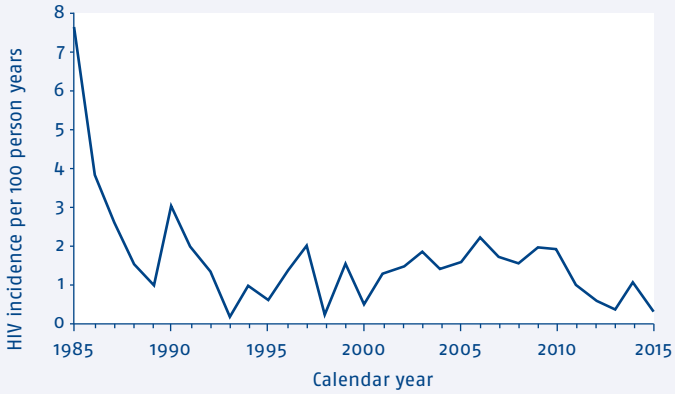
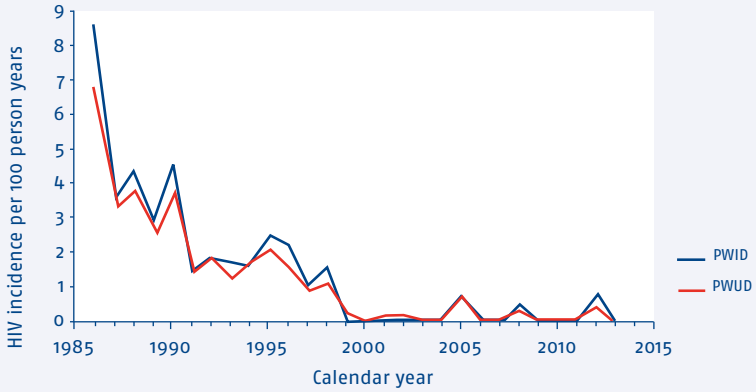


Figure 8.2: *HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among people who use drugs (PWUD), 1986–2013.*



Legend: *PWID=people who inject drugs; PWUD=people who use drugs (including injecting).*

Transmission of therapy-resistant HIV strains

In 2015, surveillance of transmission of drug-resistant HIV-1 strains was only performed between January and June. During this period there was one MSM seroconverter and one MSM who was positive at study entry. None of the individuals were infected with a virus harbouring resistance-associated mutations in the protease and reverse transcriptase genes. In both individuals, naturally occurring sequence variation was found in the protease gene. HIV-1 subtypes were determined by phylogenetic analysis: the seroconverter harboured a subtype B HIV-1 strain; the seropositive MSM had a mosaic virus containing subtype A and unknown sequences.

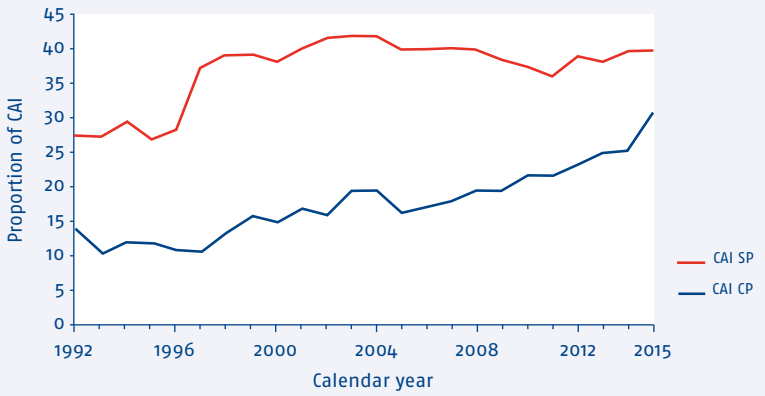
Combination antiretroviral therapy (cART) uptake

Of all 338 HIV-positive MSM from the ACS visiting the HIV Focus Centre, the Jan van Goyen Medical Centre or one of the other HIV treatment centres in the Netherlands in 2015, treatment data were available for 333 men. Of these, 328 (98%) received some form of antiretroviral therapy. Of the 330 MSM for whom viral load results were available in 2015, 306 (93%) had a viral load of <50 copies/ml (M2000rt assays). Of the 21 HIV-positive PWUD who visited the GGD Amsterdam in 2015 and for whom treatment data were available, 21 (100%) were receiving some combination of antiretroviral therapy. The 24 PWUD for whom viral load results were available all had an undetectable viral load (≤150 copies/ml [assay: M2000rt]) at their latest visit.

Risk behaviour of MSM in ACS

Information from the questionnaires completed by 654 HIV-negative MSM during cohort visits in 2015 showed higher proportions of condomless anal intercourse (CAI) with steady partners (39.6%) compared to casual partners (30.4%). Trends in CAI among HIV-negative MSM who are participants in the ACS, especially those with casual partners, continue to show a gradual increase from 1996 onwards. (*Figure 8.3*).

Figure 8.3: Trends shown by the Amsterdam Cohort Studies (ACS) in condomless anal intercourse (CAI) 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, 1992-2015.

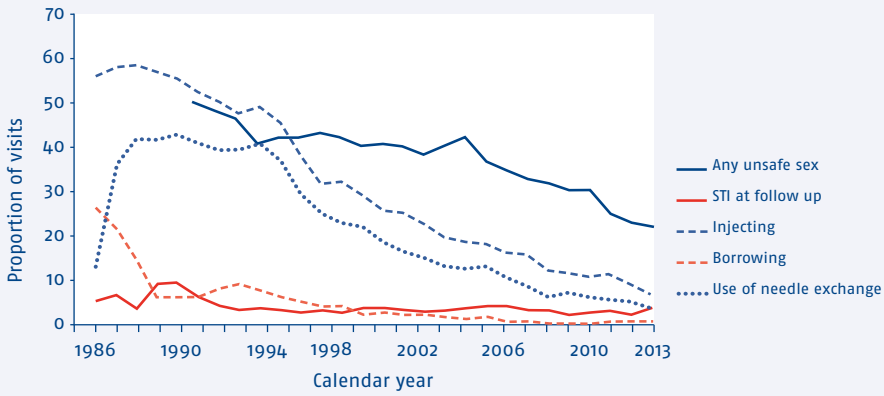


Legend: CAI=condomless anal intercourse; SP=steady partner; CP=casual partner.

Risk behaviour of PWUD in ACS

As follow up was restricted to a selection of PWUD in 2014 and inclusion of new PWUD has been halted, trends in risk behaviour of PWUD can only be presented until 2013. In HIV-negative PWUD, 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 8.4*).

Figure 8.4: Proportion of visits per calendar year at which injecting and high-risk sexual behaviour was reported among people who use drugs (PWUD) 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 2015, a total of 682 MSM from the ACS were screened for STI. The overall prevalence of any STI (i.e., chlamydia, gonorrhoea, and syphilis) was 10.2% (63/619) among HIV-negative MSM and 23.8% (15/63) among HIV-positive MSM.

ACS 2015 research highlights

Preexposure prophylaxis (PrEP) is a new biomedical approach that offers HIV-negative individuals a regime of lower-intensity antiretroviral therapy to reduce their risk of HIV infection. Although PrEP is not yet registered in the Netherlands, its approval and implementation are expected in the near future. The aim of the study was to gain insight into PrEP awareness, the intention to use PrEP, and to identify sociodemographic and psychological determinants of a higher intention to use PrEP among MSM in the ACS. The intentions to use PrEP were relatively low: 27% of the ACS participants had a low intention, 60% a medium intention, and 13% a high intention. High-risk MSM (i.e., men who reported receptive condomless anal sex with casual partners, had ≥5 casual partners, or had been diagnosed with gonorrhoea) were more likely to have a higher intention to use PrEP than low-risk

MSM. Approximately one-third of the participants anticipated a decrease in their condom use during anal sex while using PrEP. When PrEP implementation starts in the Netherlands, PrEP costs and psychological determinants will influence acceptability and uptake of PrEP and should therefore be addressed in targeted information campaigns. PrEP implementation should be combined with other HIV and STI prevention strategies[185].

The envelope glycoprotein (Env) trimer mediates HIV-1 entry into cells. The trimer is flexible, fluctuating between closed and more open conformations and sometimes encountered in the fully open, CD4-bound form. Such conformational flexibility and transient exposure of non-neutralizing, immunodominant epitopes could hinder the induction of broadly neutralising antibodies. Researchers from the Laboratory of Experimental Virology (AMC) have therefore modified soluble Env trimers to stabilize the closed, ground states. These closed trimers may be useful components of vaccines aimed at inducing broadly neutralizing antibodies[186].

HIV-1 exploits the cellular machinery for replication and therefore several interactions with cellular factors take place, some of which are yet unknown. We identified GTPase-activating protein-(SH3 domain)-binding protein 1 (G3BP1) as a cellular factor that restricts HIV-1, by analysing transcriptome profiles of *in vitro* cytokine-activated macrophages that are non-permissive to HIV-1 replication. Silencing of G3BP1 by RNA interference resulted in increased HIV-1 replication in primary T-cells and macrophages, but did not affect replication of other retroviruses. G3BP1 specifically interacted with HIV-1 RNA in the cytoplasm, suggesting that it sequesters viral transcripts, thus preventing translation or packaging. G3BP1 was highly expressed in resting naive or memory T-cells from healthy donors and HIV-1 infected patients, but significantly lower in interleukin 2 (IL-2)-activated T-cells. These results strongly suggest that G3BP1 captures HIV-1 RNA transcripts and thereby restricts mRNA translation, viral protein production and virus particle formation[187].

Steering committee

In 2015, the steering committee met four times. Seven proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: four from the AMC Medical Microbiology department, three from the GGD Amsterdam. All requests were approved, some after revision. Two of the approved proposals were collaborations with groups outside the ACS. Finally, a new ACS advisory board was installed in 2015 and a first meeting with this board took place in December 2015 and focused on future ACS data collection.

Publications in 2015 that included ACS data

1. van Aalderen MC, Remmerswaal EB, Verstegen NJ, Hombrink P, ten Brinke A, et al. **Infection history determines the differentiation state of human CD8+ T cells.** *J Virol. 2015;89(9):5110-5123*.

2. Bil JP, Davidovich U, van der Veldt WM, Prins M, de Vries HJ, et al. **What do Dutch MSM think of preexposure prophylaxis to prevent HIV-infection? A cross-sectional study.** *AIDS. 2015;29(8):955-964*.

3. Cobos Jiménez V, Martinez FO, Booiman T, van Dort KA, van de Klundert MA, et al. **G3BP1 restricts HIV-1 replication in macrophages and T-cells by sequestering viral RNA.** *Virology. 2015;486:94-104*.

4. Costa AI, Koning D, Ladell K, McLaren JE, Grady BP, et al. **Complex T-cell receptor repertoire dynamics underlie the CD8+ T-cell response to HIV-1.** *J Virol. 2015;89(1):110-119*.

5. De Taeye S, Ozorowski G, Torrents de la Peña A, Guttman M, Julien JP, et al. **Immunogenicity of stabilized HIV-1 envelope trimers with reduced exposure of non-neutralizing epitopes.** *Cell. 2015;163:1702-1715*.

6. Grady BP, Prins M, Rebers S, Molenkamp R, Geskus RB, Schinkel J. **BMI, male sex and IL28B genotype associated with persistently high hepatitis C virus RNA levels among chronically infected drug users up to 23 years following seroconversion.** *J Viral Hepat. 2015;22(3):263-271*.

7. Hajarizadeh B, Grady B, Page K, Kim AY, McGovern BH, et al. **Patterns of Hepatitis C virus RNA levels during acute infection: The InC3 Study.** *InC3 Study Group. PLoS One. 2015;10(4):e0122232*.

8. Hajarizadeh B, Grady B, Page K, Kim AY, McGovern BH, et al. **Factors associated with hepatitis C virus RNA levels in early chronic infection: the InC(3) study.** *The InC3 Study. J Viral Hepat. 2015;22(9):708-717*.

9. Jarrin I, Pantazis N, Dalmau J, Phillips AN, Olson A, et al. **Does rapid HIV disease progression prior to combination antiretroviral therapy hinder optimal CD4+ T-cell recovery once HIV-1 suppression is achieved? CASCADE Collaboration in EuroCoord.** *AIDS. 2015;29(17):2323-2333*.

10. Letko M, Booiman T, Kootstra N, Simon V, Ooms M. **Identification of the HIV-1 Vif and Human APOBEC3G Protein Interface.** *Cell Rep. 2015;13(9):1789-99*.

11. Marzolini C, Sabin C, Raffi F, Siccardi M, Mussini C, et al. **Impact of body weight on virological and immunological responses to efavirenz-**

containing regimens in HIV-infected, treatment-naive adults. *Obesity Project Team on behalf of Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord. AIDS. 2015;29(2):193-200.*

12. McLaren PJ, Coulonges C, Bartha I, Lenz TL, Deutsch AJ, et al. **Polymorphisms of large effect explain the majority of the host genetic contribution to variation of HIV-1 virus load.** *Proc Natl Acad Sci U S A. 2015;112(47):14658-14663.*

13. Mocroft A, Lundgren J, Antinori A, Monforte Ad, Brännström J, et al. **Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) study, 2010 to 2013.** *Euro Surveill. 2015;20(47).*

14. Monge S, Jarrín I, Mocroft A, Sabin CA, Touloumi G, et al. **Mortality in migrants living with HIV in western Europe (1997–2013): a collaborative cohort study.** *The Migrants Working Group on behalf of COHERE in EuroCoord. Lancet HIV. 2015;2(12):e540-549.*

15. Oude Munnink BB, Cotten M, Deijs M, Jebbink MF, Bakker M, et al. **A novel genus in the order Picornavirales detected in human stool.** *J Gen Virol. 2015;96(11):3440-3443.*

16. Sacks-Davis R, Grebely J, Dore GJ, Osburn W, Cox AL, et al. **Hepatitis C virus reinfection and spontaneous clearance of reinfection – the InC3 Study.** *InC3 study group. J Infect Dis. 2015; 212(9):1407-1419.*

17. Setiawan LC, Gijsbers EF, van Nuenen AC, Kootstra NA. **Viral evolution in HLA-B27-restricted CTL epitopes in human immunodeficiency virus type 1-infected individuals.** *J Gen Virol. 2015;96(8):2372-2380.*

18. Sloot R, Schim van der Loeff MF, van Zwet EW, Haks MC, Keizer ST, et al. **Biomarkers can identify pulmonary tuberculosis in HIV-infected drug users months prior to clinical diagnosis.** *EBioMedicine. 2014;2(2):172-179.*

19. Spits HB, Grijsen ML, Steingrover R, Nanlohy NM, Kootstra N, et al. **A lower viral set point but little immunological impact after early treatment during primary HIV infection.** *Viral Immunol. 2015;28(3):134-144.*

20. Welling CA, Mooij SH, van der Sande MA, van Rooijen MS, Vermeulen-Oost WF, et al. **Association of HIV infection with anal and penile low-risk human papillomavirus infections among men who have sex with men in Amsterdam: The HIV & HPV in MSM Study.** *Sex Transm Dis. 2015;42(6):297-304.*

Theses in 2015 that included ACS data

Thijs Booiman – 5 February 2015: **Host factors in HIV-1 replication: the good, the bad and the ugly.** Supervisor: Prof. T.B. Geijtenbeek (AMC); co-supervisor: Dr N.A. Kootstra (AMC).

Xiomara Thomas – 13 March 2015: **Epidemiological, immunological and virological aspects of acute and chronic hepatitis C virus infections.** Supervisor: Prof. M.D. de Jong (AMC); co-supervisors: Dr C.J. Schinkel (AMC) and Dr R. Molenkamp (AMC).

Sofie Mooij – 27 March 2015: **Epidemiology of anal and penile HPV infections.** Supervisor: Prof. R.A. Coutinho (AMC/University Utrecht); co-supervisor: Dr M.F. Schim van der Loeff (GGD Amsterdam/AMC).

Bart Grady – 4 June 2015: **Hepatitis C virus: risk factors and disease progression.** Supervisor: Prof. M. Prins (GGD Amsterdam/AMC); co-supervisor: Dr D. van Baarle (University Utrecht/RIVM).

Rosa Sloot – 10 June 2015: **Epidemiological studies on tuberculosis control and respiratory viruses.** Supervisors: Prof. M.W. Borgdorff (AMC) and Prof. M.D. de Jong (AMC); co-supervisor: Dr M.F. Schim van der Loeff (GGD Amsterdam/AMC).

Amy Matser – 6 November 2015: **Sexually transmitted infections: Unravelling transmission & impact.** Supervisors: Prof. M. Prins (GGD Amsterdam/AMC) and Prof. M.E.E. Kretzschmar (University Utrecht/RIVM); co-supervisors: Dr M.F. Schim van der Loeff (GGD Amsterdam/AMC) and Dr R.B. Geskus (AMC/GGD Amsterdam).

9. Curaçao

Ashley Duits, Gonneke Hermanides, Ard van Sighem

Introduction

For a decade, Stichting HIV Monitoring (SHM) has assisted in collecting demographic and clinical data about HIV-positive 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, which is unique for the region, giving a clear picture of the HIV-positive 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 the treatment of HIV infection in Curaçao.

Patients in clinical care

In total, 573 (57%) of the 1,013 registered patients were still under clinical observation as of May 2016. Of the 440 patients who were no longer in clinical care, 173 (39%) were known to have died, and 10 (2%) to have moved abroad. Patients were considered to be in clinical care if they were known to be alive and not to have moved abroad and if data were available in 2015 or 2016. Thus, 257 patients, or 25% of all registered patients, were considered lost to follow up.

Retention in care

Of the 532 patients who entered HIV care between 2005 and 2014, 147, or 28%, were lost to care before 2015 and were not reported as having died or moved abroad. Retention in care was highest for patients originating from the former Dutch Antilles: 74% were estimated to be still in care after 5 years. Of the patients originating from Haiti or the Dominican Republic, 59% were still in care after 5 years, as were 66% of patients originating from other regions (*Table 9.1*).

< Back to chapter 1

Table 9.1: Characteristics of the 573 HIV-positive patients in clinical care in Curaçao as of May 2016.

	Men (n=353, 62%)		Women (n=220, 38%)		Total (n=573)	
	n	%	n	%	n	%
Transmission						
MSM	146	41	-	-	146	25
Heterosexual	165	47	206	94	371	65
Other/unknown	42	12	14	6	56	10
Current age (years)						
0-12	0	0	0	0	0	0
13-17	0	0	1	0	1	0
18-24	16	5	10	5	26	5
25-34	47	13	33	15	80	14
35-44	69	20	37	17	106	18
45-54	118	33	81	37	199	35
55-64	65	18	36	16	101	18
65-74	30	8	16	7	46	8
75	8	2	6	3	14	2
Country of origin						
Former Netherlands Antilles	294	83	142	65	436	76
Dominican Republic	8	2	40	18	48	8
Haiti	17	5	21	10	38	7
The Netherlands	12	3	0	0	12	2
Other	22	6	17	8	39	7
Years aware of HIV infection						
<1	30	8	12	5	42	7
1-2	48	14	25	11	73	13
3-4	55	16	37	17	92	16
5-10	74	21	53	24	127	22
10-20	106	30	75	34	181	32
>20	36	10	17	8	53	9
Unknown	4	1	1	0	5	1

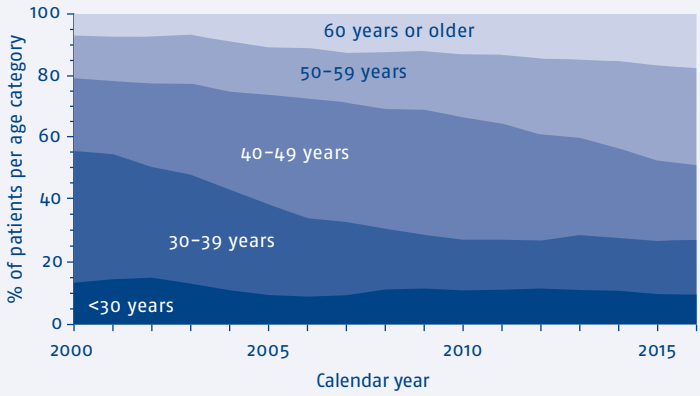
Legend: *MSM=men who have sex with men; IDU=injection drug use.*

Ageing population

The median age of the population currently in clinical care stands at 49 (interquartile range [IQR], 39-56) and has been increasing since 2005 (*Figure 9.1*). This increase in age is mainly a result of the improved life expectancy of HIV-positive patients after the introduction of combination antiretroviral treatment (cART). As a result, almost half of all patients currently in care (49%) are 50 years or

older, including 50% of men and 46% of women; 17% of the patients are 60 years or older.

Figure 9.1: Increasing age of the HIV-positive population in clinical care in Curaçao over calendar time. In 2000, 13% of the patients in care were younger than 30 years of age, whereas 21% were 50 years or older. In 2016, these proportions were 10% and 49%, respectively, while 17% 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.



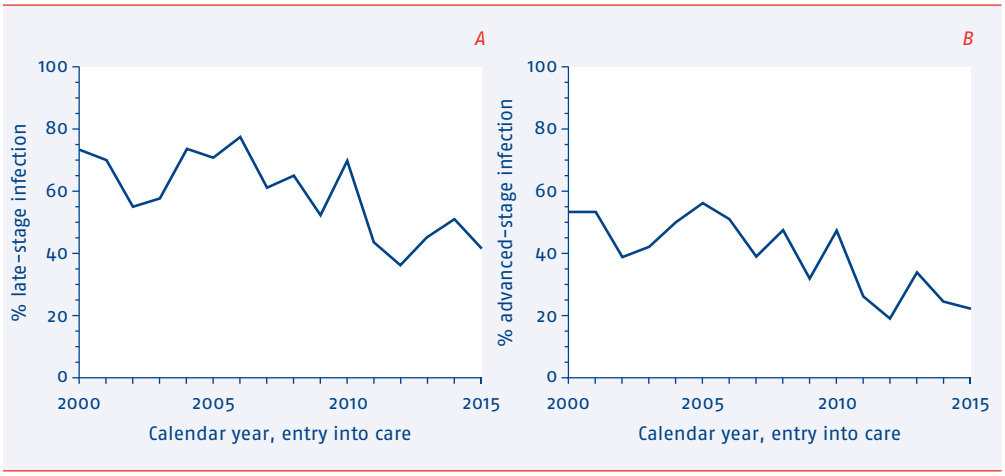
Duration of infection

On average, patients in clinical care as of May 2016 were diagnosed with HIV 9.4 years ago. Thus, a large group (41%) of those in care have been living with HIV for more than 10 years, while 9% had done so for more than 20 years. The average time since diagnosis was 8.5 years for men who have sex with men (MSM), 9.8 years for other men, and 9.6 years for women.

Late presentation and start of treatment

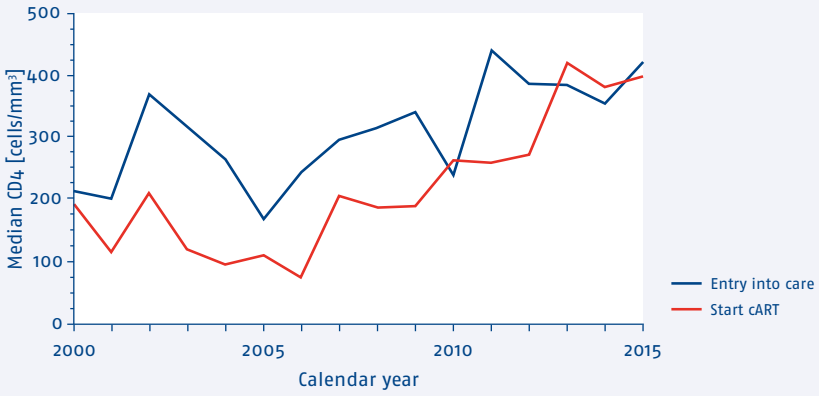
Overall, 58% of the patients who entered care in 2000 or later were late presenters, i.e., individuals either presenting for care with a CD4 count below 350 cells/mm^3 or presenting with an AIDS-defining event regardless of CD4 count[3]. Although the proportion of late presenters has decreased over time, in recent years (2013 or later), 47% of patients entered clinical care late in their infection (*Figure 9.2*). 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 28% in 2013 or later.

Figure 9.2: Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection at the time of entry into care. From 2000 (2013) onwards, 58% (47%) presented with late HIV disease while 39% (28%) were advanced presenters. 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.



In recent years, there has been an increase in CD4 cell counts at the start of cART (*Figure 9.3*). Between 2013 and 2015, 22% of the patients for whom a CD4 count was available at the start of cART had less than 200 CD4 cells/mm³, 20% had CD4 counts between 200 and 349 cells/mm³, 25% had CD4 counts between 350 and 499 cells/mm³, and 32% had CD4 counts of 500 cells/mm³ or higher. During the same period, 98% of the patients entering care with less than 350 cells/mm³, 88% of those with CD4 counts between 350 and 499 cells/mm³, and 67% of patients with 500 CD4 cells/mm³ or more received treatment within six months.

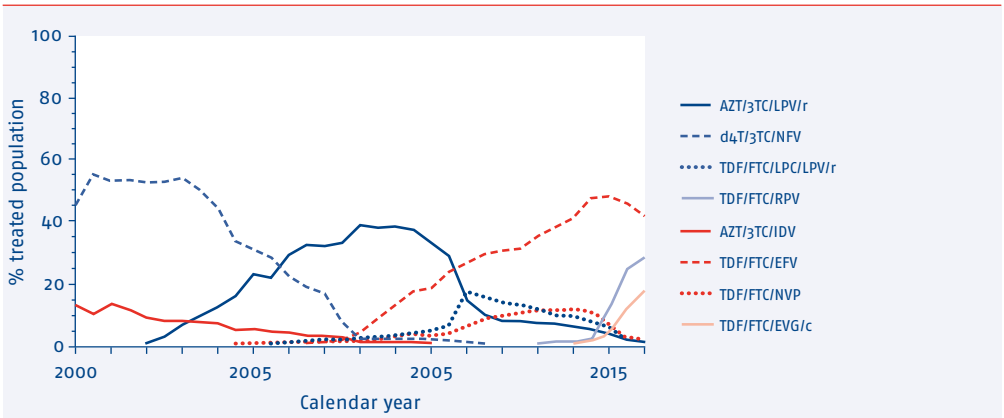
Figure 9.3: Changes over calendar time in median CD4 counts at entry into care and at the start of combination antiretroviral therapy (cART). Between 2000 and 2015, the median CD4 count at the time of entry into care increased from 214 cells/mm³ (interquartile range [IQR], 105–407) to 422 (262–644) cells/mm³. During the same period, CD4 counts at start of cART increased from 195 cells/mm³ (69–336) to 398 (270–58) cells/mm³.



Combination treatment

In total, 848 (83%) of the 1,013 registered patients started cART. Over time, there have been clear shifts in the treatment regimens prescribed in Curaçao (*Figure 9.4*). Around 2008, a combination of tenofovir/emtricitabine and ritonavir-boosted lopinavir was frequently prescribed. At the beginning of 2016, the most commonly prescribed regimens were a combination of tenofovir/emtricitabine with either efavirenz, rilpivirine, or cobicistat-boosted elvitegravir. Of the 557 patients who started cART and were still in care as of May 2016, 37% were treated with tenofovir/emtricitabine/efavirenz, 32% with tenofovir/emtricitabine/rilpivirine, and 20% with tenofovir/emtricitabine/cobicistat-boosted elvitegravir. The majority of the patients, 94%, used a once-daily regimen.

Figure 9.4: Percentage of patients treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. At the beginning of 2016, 41% of the patients were receiving TDF/FTC/EFV, 28% RPV/TDF/FTC, and 18% TDF/FTC/EVG/c.

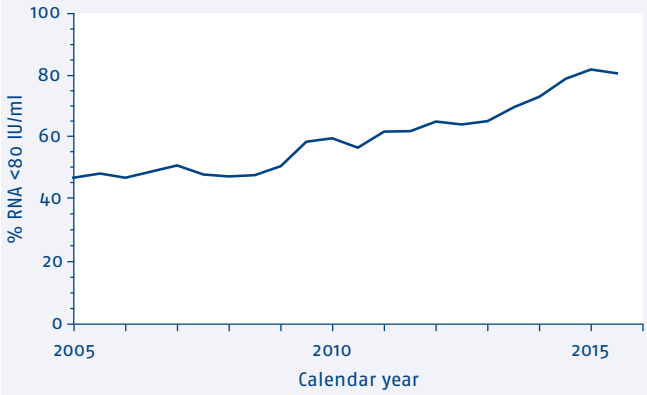


Legend: AZT=zidovudine; 3TC=lamivudine; LPV/r=ritonavir-boosted lopinavir; d4T=stavudine; NFV=nelfinavir; TDF=tenofovir; FTC=emtricitabine; RPV=rilpivirine; IDV=indinavir; EFV=efavirenz; NVP=nevirapine; EVG/c=cobicistat-boosted elvitegravir.

Treatment outcome

In the total population still in care, the median current CD4 count was 526 (IQR 374-726) cells/mm^3. CD4 counts were similar between MSM (578 [422-769] cells/mm^3) and women (572 [411-782] cells/mm^3), but men who acquired their infection via other modes of transmission had lower CD4 counts (451 [295-611] cells/mm^3). Among patients with a viral load measurement, the proportion with HIV RNA levels below 80 IU/ml increased from 47% in 2005 to 81% in 2015 (*Figure 9.5*); for 71% of all patients currently in care, the most recent viral load measurement was below 80 IU/ml. Altogether, 14% of the patients had ever been diagnosed with an AIDS-defining disease; 34% of these patients were diagnosed with AIDS concurrently with their HIV diagnosis.

Figure 9.5: Proportion of patients with HIV RNA <80 IU/ml among those with a viral load measurement.



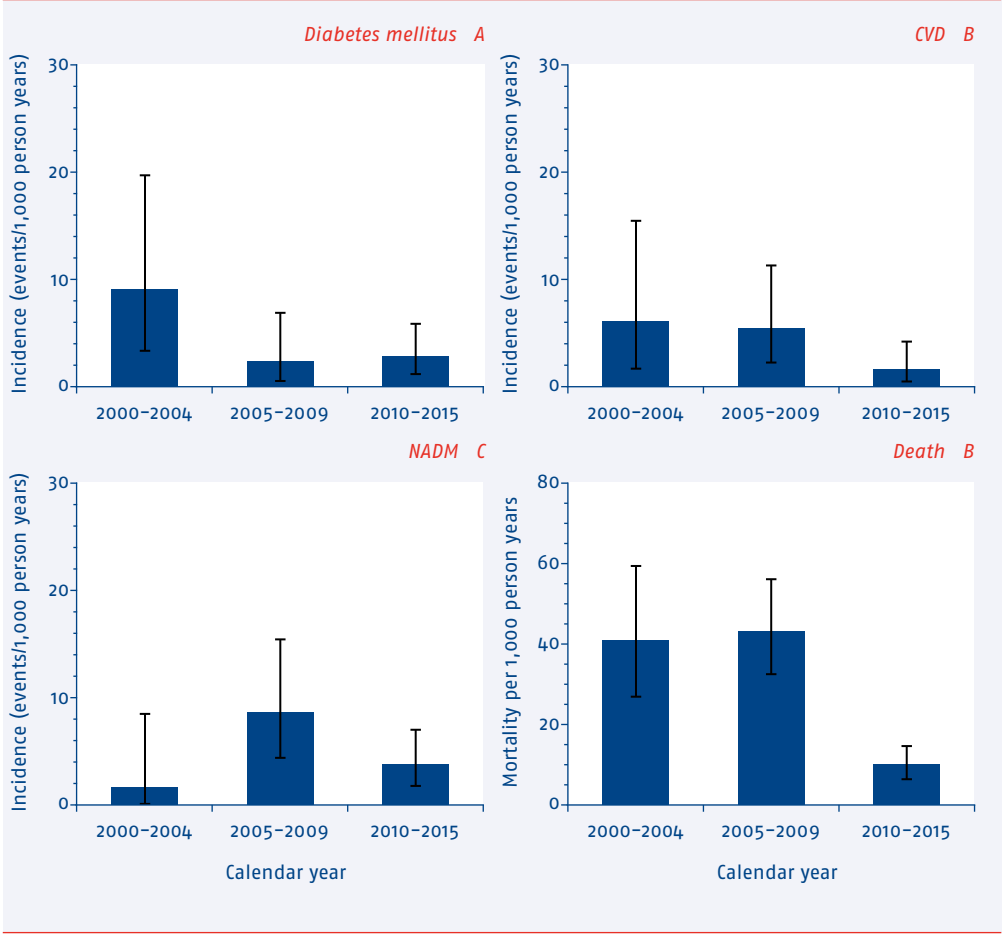
Non-HIV-related morbidity

In the population who started cART and were in follow up from 2000 onwards, we looked at the incidence of diabetes mellitus, major cardiovascular diseases, including myocardial infarction, stroke, and invasive coronary procedures, and non-AIDS-defining malignancies[104, 188]. In total, there were 16 cases of diabetes mellitus, 15 cardiovascular diseases (8 strokes and 7 myocardial infarctions), and 21 non-AIDS defining malignancies, including 4 cases of cervical dysplasia, 2 prostate cancer, and 2 bladder cancer (*Figure 9.6A-C*).

Mortality

Mortality rates after start of cART were 40 (27-59) per 1,000 person years between 2000 and 2004 and 43 (33-56) between 2005 and 2009 (*Figure 9.6D*). After 2010, the mortality rate dropped to 10 (6-15) per 1,000 person years. This may have been partly a consequence of patients being lost to follow up: before 2010, only 23 patients were lost to follow up, but after 2010 this number increased to 146.

Figure 9.6: Incidence rate after start of combination antiretroviral treatment of (A) diabetes mellitus, (B) major cardiovascular diseases, including myocardial infarction, stroke, and invasive coronary procedures, (C) non-AIDS-defining malignancies, and (D) death. Error bars indicate 95% confidence intervals. Non-AIDS-defining malignancies were all malignancies other than AIDS-defining cancers, basal and squamous cell skin cancers, pre-malignant lesions, and recurrent cancers, in accordance with the DAD protocol for collecting non-AIDS-defining malignancies.



Legend: CVD=cardiovascular disease; NADM=non-AIDS-defining malignancies.

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 at 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 treatment offered to HIV-positive patients in Curaçao has improved considerably over the years, although adherence to treatment is still not optimal as illustrated by the relatively low proportion of patients with a suppressed viral load. Furthermore, levels of retention in care are worryingly low, although these may be affected by underreporting of death and/or emigration.

Recommendations

Curaçao is in a unique position in the Caribbean in that data from HIV patients in care are regularly collected and monitored; however, it is important that the quality of these data is maintained. Special attention should be paid to the collection of data from patients who interrupt care and to the collection of comorbidities in the ageing population, as underreporting may be influencing outcome. Currently, no regular data collection is done in HIV-positive children and therefore the quality of these data is not guaranteed and data cannot be used for strategic planning of HIV care for this specific population.

Early start of cART appears to be possible, but long-term continuous follow up should be guaranteed to optimise the effect of cART. A relatively large, albeit decreasing, proportion of patients enter care late in their infection and therefore HIV screening followed by linkage to care should focus on this particular group.

Appendix figures and tables

Appendix figures and tables are listed by chapter

Appendix Table 1.1: *Annual number of HIV-1 diagnoses among children and among adults per transmission risk group, including men who have sex with men (MSM), individuals infected via heterosexual contact, injecting drug use (IDU), contact with contaminated blood, or other or unknown modes of transmission. Note: data collection for 2014 and 2015 had not yet been finalised at the time of writing.*

	MSM	Heterosexual		IDU	
Year of diagnosis	**Men**	**Men**	**Women**	**Men**	**Women**
≤1995	2,222	267	391	285	133
1996	386	89	83	31	8
1997	446	113	127	40	10
1998	332	108	114	22	6
1999	356	108	136	19	7
2000	381	160	193	18	3
2001	449	166	215	15	5
2002	468	166	250	16	3
2003	459	180	275	22	5
2004	584	201	264	9	4
2005	638	197	262	17	2
2006	674	162	196	10	5
2007	772	155	208	11	4
2008	855	178	179	6	1
2009	779	157	181	8	0
2010	777	182	163	6	1
2011	766	146	148	4	1
2012	702	146	143	6	1
2013	722	115	127	2	2
2014	586	105	110	0	0
*2014**	*604*	*108*	*113*	*0*	*0*
2015	503	110	111	1	0
*2015**	*558*	*122*	*123*	*1*	*0*
2016	97	13	17	0	0
Total	**13,955**	**3,224**	**3,893**	**548**	**201**

**Projected numbers*

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

< Back to page 21

Blood or blood products		Other/unknown		Children		Total
Men	Women	Men	Women	Men	Women	
62	21	157	51	50	37	3,676
3	4	35	6	11	3	659
7	3	41	8	9	9	813
6	5	30	8	8	8	647
7	4	19	7	11	13	687
3	4	34	4	14	29	843
7	5	41	8	15	34	960
15	7	59	4	18	21	1,027
9	3	61	14	16	21	1,065
4	3	69	10	14	12	1,174
3	7	61	10	11	11	1,219
4	7	57	4	7	10	1,136
2	6	49	7	7	12	1,233
5	3	53	6	13	16	1,315
2	1	50	9	12	15	1,214
6	3	39	7	18	16	1,218
8	7	56	4	10	8	1,158
4	3	36	10	7	14	1,073
11	1	41	5	6	3	1,035
7	4	41	8	4	6	871
7	*4*	*42*	*8*	*4*	*6*	*896*
2	1	42	5	3	2	780
2	*1*	*47*	*6*	*3*	*2*	*865*
1	0	7	2	0	0	137
178	**102**	**1,078**	**197**	**264**	**300**	**23,940**

Appendix Table 1.2: *Region of origin of the 23,376 adult HIV-1-positive patients with a recorded date of diagnosis stratified according to year of HIV diagnosis.*

	MSM			Other men		
	<2013	**≥2013**	**Total**	**<2013**	**≥2013**	**Total**
The Netherlands	8,512	1,362	9,874	1,976	283	2,259
	70.7%	71.4%	70.8%	43.6%	56.8%	44.9%
Sub-Saharan Africa	179	25	204	1,223	98	1,321
	1.5%	1.3%	1.5%	27.0%	19.7%	26.3%
Western Europe	976	94	1,070	259	14	273
	8.1%	4.9%	7.7%	5.7%	2.8%	5.4%
Central Europe	231	77	308	139	17	156
	1.9%	4.0%	2.2%	3.1%	3.4%	3.1%
Eastern Europe	73	17	90	55	8	63
	0.6%	0.9%	0.6%	1.2%	1.6%	1.3%
South America	816	110	926	375	29	404
	6.8%	5.8%	6.6%	8.3%	5.8%	8.0%
Caribbean	410	87	497	193	18	211
	3.4%	4.6%	3.6%	4.3%	3.6%	4.2%
South and Southeast Asia	356	50	406	115	12	127
	3.0%	2.6%	2.9%	2.5%	2.4%	2.5%
Other/unknown	494	86	580	195	19	214
	4.1%	4.5%	4.2%	4.3%	3.8%	4.3%

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

< Back to page 25

	Women		
	<2013	≥2013	Total
	1,059	158	1,217
	26.5%	40.2%	27.7%
	1,731	132	1,863
	43.3%	33.6%	42.4%
	213	9	222
	5.3%	2.3%	5.1%
	74	8	82
	1.9%	2.0%	1.9%
	42	6	48
	1.1%	1.5%	1.1%
	362	37	399
	9.1%	9.4%	9.1%
	211	11	222
	5.3%	2.8%	5.1%
	234	21	255
	5.9%	5.3%	5.8%
	74	11	85
	1.9%	2.8%	1.9%

Appendix Table 1.3: Characteristics of the 18,866 people living with HIV and in care as of May 2016.

	MSM	Heterosexual	
	Men	Men	Women
	n=11,616	n=2,392	n=3,117
Current age [years]			
0–12	0	0	0
	0.0%	0.0%	0.0%
13–17	1	0	2
	0.0%	0.0%	0.1%
18–24	192	10	38
	1.7%	0.4%	1.2%
25–34	1,359	215	535
	11.7%	9.0%	17.2%
35–44	2,585	515	1,037
	22.3%	21.5%	33.3%
45–54	4,109	882	924
	35.4%	36.9%	29.6%
55–64	2,389	514	407
	20.6%	21.5%	13.1%
65–74	857	215	138
	7.4%	9.0%	4.4%
≥75	124	41	36
	1.1%	1.7%	1.2%
Current age 50 years or older			
No	6,123	1,203	2,144
	52.7%	50.3%	68.8%
Yes	5,493	1,189	973
	47.3%	49.7%	31.2%
Current age 60 years or older			
No	9,725	1,949	2,813
	83.7%	81.5%	90.2%
Yes	1,891	443	304
	16.3%	18.5%	9.8%

< Back to page 40

IDU		Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women	Men	Women
n=231	n=92	n=144	n=95	n=892	n=287	n=15,275	n=3,591
0	0	0	0	56	77	56	77
0.0%	0.0%	0.0%	0.0%	6.3%	26.8%	0.4%	2.1%
0	0	1	2	45	25	47	29
0.0%	0.0%	0.7%	2.1%	5.0%	8.7%	0.3%	0.8%
0	0	1	1	58	46	261	85
0.0%	0.0%	0.7%	1.1%	6.5%	16.0%	1.7%	2.4%
9	3	16	12	107	33	1,706	583
3.9%	3.3%	11.1%	12.6%	12.0%	11.5%	11.2%	16.2%
33	13	26	25	158	38	3,317	1,113
14.3%	14.1%	18.1%	26.3%	17.7%	13.2%	21.7%	31.0%
98	41	49	30	226	40	5,364	1,035
42.4%	44.6%	34.0%	31.6%	25.3%	13.9%	35.1%	28.8%
79	30	26	17	153	22	3,161	476
34.2%	32.6%	18.1%	17.9%	17.2%	7.7%	20.7%	13.3%
12	5	22	7	73	5	1,179	155
5.2%	5.4%	15.3%	7.4%	8.2%	1.7%	7.7%	4.3%
0	0	3	1	16	1	184	38
0.0%	0.0%	2.1%	1.1%	1.8%	0.3%	1.2%	1.1%
79	22	63	59	536	239	8,004	2,464
34.2%	23.9%	43.8%	62.1%	60.1%	83.3%	52.4%	68.6%
152	70	81	36	356	48	7,271	1,127
65.8%	76.1%	56.3%	37.9%	39.9%	16.7%	47.6%	31.4%
190	80	112	81	746	273	12,722	3,247
82.3%	87.0%	77.8%	85.3%	83.6%	95.1%	83.3%	90.4%
41	12	32	14	146	14	2,553	344
17.7%	13.0%	22.2%	14.7%	16.4%	4.9%	16.7%	9.6%

Appendix Table 1.3: Continued.

	MSM	Heterosexual	
	Men	Men	Women
	n=11,616	n=2,392	n=3,117
Region of origin			
Netherlands	8,502	1,122	906
	73.2%	46.9%	29.1%
Sub-Saharan Africa	153	658	1,336
	1.3%	27.5%	42.9%
Western Europe	723	81	75
	6.2%	3.4%	2.4%
South America	718	210	300
	6.2%	8.8%	9.6%
Caribbean	433	126	164
	3.7%	5.3%	5.3%
Other	1,043	190	329
	9.0%	7.9%	10.6%
Unknown	44	5	7
	0.4%	0.2%	0.2%
Years aware of HIV infection			
<1	414	84	96
	3.6%	3.5%	3.1%
1-2	1,211	207	207
	10.4%	8.7%	6.6%
3-4	1,355	264	251
	11.7%	11.0%	8.1%
5-10	3,441	639	768
	29.6%	26.7%	24.6%
10-20	3,695	1,035	1,481
	31.8%	43.3%	47.5%
>20	1,494	159	295
	12.9%	6.6%	9.5%
Unknown	6	4	19
	0.1%	0.2%	0.6%
Current CD4 count [cells/mm^3], median / IQR	654	575	640
	494-830	410-780	470-850
Current CD8 count [cells/mm^3], median / IQR	870	860	780
	650-1,180	614-1,190	570-1,060
Current HIV RNA <500 copies/ml	10,685	2,145	2,776
	92.0%	89.7%	89.1%

IDU		Blood or blood products		Other / unknown		Total	
Men	Women	Men	Women	Men	Women	Men	Women
n=231	n=92	n=144	n=95	n=892	n=287	n=15,275	n=3,591
136	47	94	19	417	112	10,271	1,084
58.9%	51.1%	65.3%	20.0%	46.7%	39.0%	67.2%	30.2%
4	0	28	42	245	101	1,088	1,479
1.7%	0.0%	19.4%	44.2%	27.5%	35.2%	7.1%	41.2%
22	28	3	3	39	26	868	132
9.5%	30.4%	2.1%	3.2%	4.4%	9.1%	5.7%	3.7%
10	1	2	9	41	11	981	321
4.3%	1.1%	1.4%	9.5%	4.6%	3.8%	6.4%	8.9%
5	1	3	4	34	2	601	171
2.2%	1.1%	2.1%	4.2%	3.8%	0.7%	3.9%	4.8%
54	15	14	16	107	32	1,408	394
23.3%	16.3%	9.7%	17.6%	12.0%	11.1%	9.2%	11.0%
0	0	0	0	9	3	58	10
0.0%	0.0%	0.0%	0.0%	1.0%	1.0%	0.4%	0.3%
1	0	1	1	31	7	531	104
0.4%	0.0%	0.7%	1.1%	3.45%	2.4%	3.5%	2.9%
1	2	11	5	84	16	1,514	230
0.4%	2.2%	7.6%	5.3%	9.4%	5.6%	9.9%	6.4%
3	2	17	7	77	31	1,716	291
1.3%	2.2%	11.8%	7.4%	8.6%	10.8%	11.2%	8.1%
21	6	15	19	187	74	4,303	867
9.1%	6.5%	10.4%	20.0%	21.0%	25.8%	28.2%	24.1%
97	20	48	42	325	106	5,200	1,649
42.0%	21.7%	33.3%	44.2%	36.4%	36.9%	34.0%	45.9%
108	62	50	21	82	42	1,893	420
46.8%	67.4%	34.7%	22.1%	9.2%	14.6%	12.4%	11.7%
0	0	2	0	106	11	118	30
0.0%	0.0%	1.4%	0.0%	11.9%	3.8%	0.8%	0.8%
550	642	540	752	560	800	633	650
340–801	413–868	370–760	555–950	370–790	490–1,110	470–826	470–860
895	881	810	860	860	760	870	786
604–1,225	690–1,189	538–1,080	595–1,215	620–1,180	560–1,125	640–1,180	570–1,070
213	79	132	85	732	249	13,907	3,189
92.2%	85.9%	91.7%	89.5%	82.1%	86.8%	91.0%	88.8%

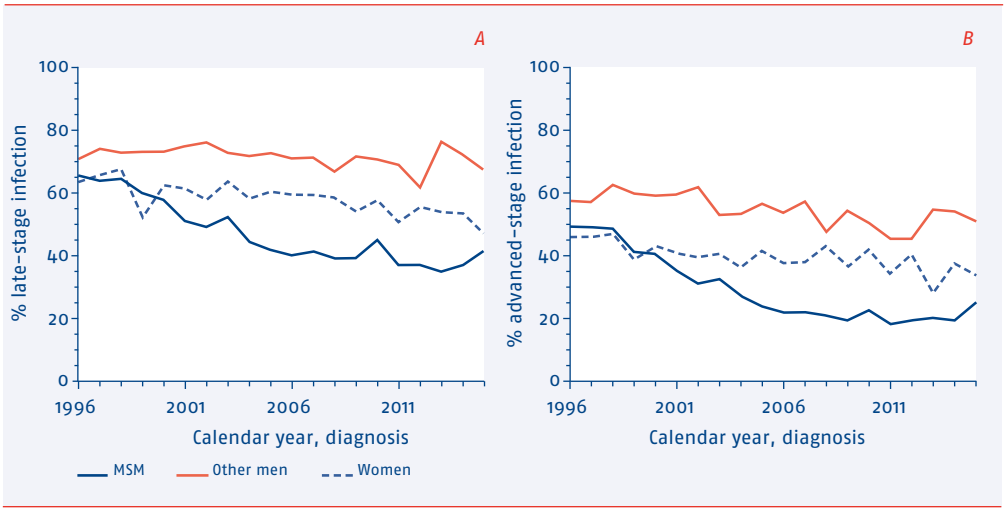
Appendix Table 1.3: Continued.

	MSM	Heterosexual	
	Men	Men	Women
	n=11,616	n=2,392	n=3,117
Current HIV RNA <100 copies/ml	89.7%	2,776	2,693
	89.1%	87.8%	86.4%
Ever AIDS	2,074	727	672
	17.9%	30.4%	21.6%
AIDS at diagnosis	1,090	507	393
	9.4%	21.2%	12.6%
Current treatment			
cART	11,093	2,279	2,948
	95.5%	95.3%	94.6%
Non-cART	20	4	6
	0.2%	0.2%	0.2%
Not started	503	109	163
	4.3%	4.6%	5.2%

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

	IDU		Blood or blood products		Other / unknown		Total	
	Men	Women	Men	Women	Men	Women	Men	Women
	n=231	n=92	n=144	n=95	n=892	n=287	n=15,275	n=3,591
	209	77	130	80	707	240	13,649	3,090
	90.5%	83.7%	90.3%	84.2%	79.3%	83.6%	89.4%	86.0%
	84	37	45	26	270	81	3,200	816
	36.4%	40.2%	31.3%	27.4%	30.3%	28.2%	20.9%	22.7%
	18	8	27	12	198	47	1,840	460
	7.8%	8.7%	18.8%	12.6%	22.2%	16.4%	12.0%	12.8%
	226	90	140	93	770	270	14,508	3,401
	97.8%	97.8%	97.2%	97.9%	86.3%	94.1%	95.0%	94.7%
	1	0	0	1	2	1	27	8
	0.4%	0.0%	0.0%	1.1%	0.2%	0.3%	0.2%	0.2%
	4	2	4	1	120	16	740	182
	1.7%	2.2%	2.8%	1.1%	13.5%	5.6%	4.8%	5.1%

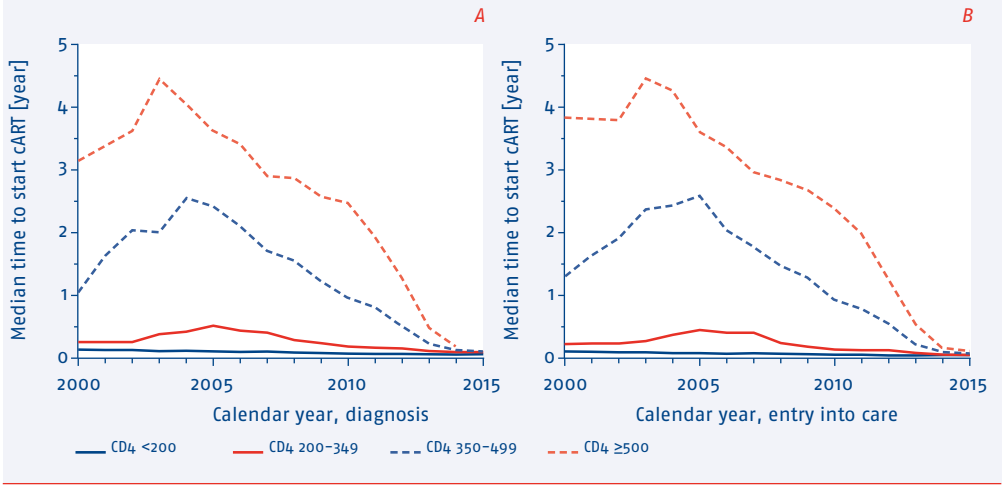
Appendix Figure 1.1: *Proportion of patients classified as presenting with (A) late or (B) advanced HIV infection at the time of HIV diagnosis. From 1996 (2013) onwards, 53% (46%) were diagnosed with late-stage HIV: men who have sex with men (MSM) 44% (37%), other men 72% (72%), and women 58% (52%). Overall, 35% (29%) were advanced presenters: MSM 26% (21%), other men 54% (53%), and women 39% (33%). 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.*

< Back to page 30

Appendix Figure 1.2: *Estimated median time to start of combination antiretroviral treatment (cART) by (A) year of diagnosis and stratified by CD4 count at the time of diagnosis and (B) year of entry into care and stratified by CD4 count at the time of entry into care.*



< Back to page 35

Appendix Table 2.1: *Number of individuals with evidence of various levels of resistance to specific antiretroviral drugs. Altogether, out of 18,866 individuals still in follow up as of May 2016, 2,137 (11%) with at least one major resistance-associated mutation from the July 2015 International Antiviral Society-USA (IAS-USA) list were included[31]. Predicted drug susceptibility was assessed using the Stanford algorithm[32].*

	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	n	%	n	%	n	%	n	%	n	%
Protease inhibitors (PIs)[a]										
Fosamprenavir	1,561	74	126	6	96	5	117	6	218	10
Indinavir	1,564	74	111	5	32	2	130	6	281	13
Nelfinavir	1,311	62	172	8	128	6	37	2	470	22
Saquinavir	1,677	79	10	0	45	2	124	6	262	12
Lopinavir	1,593	75	97	5	107	5	99	5	222	10
Atazanavir	1,570	74	105	5	85	4	76	4	282	13
Tipranavir	1,701	80	92	4	122	6	135	6	68	3
Darunavir	1,937	91	14	1	122	6	38	2	7	0
Any PI	1,284	61	174	8	145	7	35	2	480	23
Nucleoside reverse transcriptase inhibitors (NRTIs)										
Abacavir	574	27	141	7	540	25	314	15	568	27
Zidovudine	1,130	53	41	2	198	9	190	9	578	27
Stavudine	1,002	47	48	2	202	9	306	14	579	27
Didanosine	545	26	522	24	214	10	273	13	583	27
Tenofovir	1,105	52	143	7	239	11	246	12	404	19
Any NRTI	517	24	37	2	582	27	203	9	798	37
Lamivudine/ emtricitabine	812	38	57	3	65	3	71	3	1,132	53
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)										
Efavirenz	985	46	133	6	37	2	208	10	774	36
Nevirapine	985	46	63	3	49	2	62	3	978	46
Etravirine	1,159	54	338	16	164	8	393	18	83	4
Rilpivirine	1,159	54	60	3	361	17	350	16	207	10
Any NNRTI	800	37	34	2	249	12	74	3	980	46
Integrase inhibitors (INSTIs)[b]										
Raltegravir	21	64	0	0	1	3	2	6	9	27
Elvitegravir	21	64	1	3	1	3	1	3	9	27
Dolutegravir	25	76	6	18	1	3	1	3	0	0
Any INSTI	21	64	0	0	1	3	1	3	10	30

[a] *Available for 2,118 individuals;*

[b] *Available for 33 individuals.*

< Back to page 81

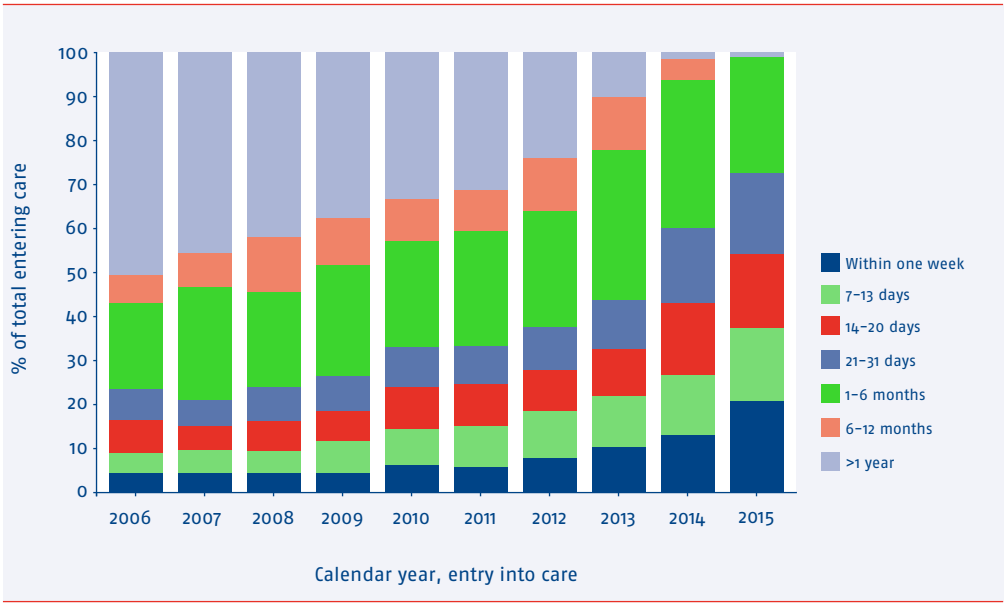
Appendix Table 2.2: *Individuals with evidence of various levels of resistance to specific antiretroviral drugs. Altogether, out of 18,866 individuals still in follow up as of May 2016, 7,815 (41%) with at least one genotypic sequence were included. Predicted drug susceptibility was assessed using the Stanford algorithm [32]. Note that due to small differences in resistance-associated mutations between the Stanford algorithm and the International Antiviral Society-USA (IAS-USA) list [31], the number of individuals with resistance may be different from those reported in Appendix Table 2.1.*

	Susceptible		Potential low-level		Low-level		Intermediate		High-level	
	n	%	n	%	n	%	n	%	n	%
Protease inhibitors (PIs)[a]										
Fosamprenavir	7,018	92	168	2	96	1	117	2	218	3
Indinavir	7,040	92	132	2	34	0	130	2	281	4
Nelfinavir	6,240	82	661	9	205	3	41	1	470	6
Saquinavir	7,172	94	10	0	49	1	124	2	262	3
Lopinavir	7,090	93	98	1	108	1	99	1	222	3
Atazanavir	7,061	93	109	1	89	1	76	1	282	4
Tipranavir	7,176	94	112	1	126	2	135	2	68	1
Darunavir	7,436	98	14	0	122	2	38	0	7	0
Any PI	6,195	81	681	9	222	3	39	1	480	6
Nucleoside reverse transcriptase inhibitors (NRTIs)[b]										
Abacavir	6,090	78	290	4	540	7	315	4	568	7
Zidovudine	6,644	85	47	1	343	4	191	2	578	7
Stavudine	6,500	83	69	1	348	5	307	4	579	7
Didanosine	6,000	77	727	9	215	3	278	4	583	7
Tenofovir	6,766	87	148	2	239	3	246	3	404	5
Any NRTI	5,967	76	102	1	728	9	208	3	798	10
Lamivudine/ emtricitabine	6,473	83	62	1	65	1	71	1	1132	15
Non-nucleoside reverse transcriptase inhibitors (NNRTIs)[b]										
Efavirenz	6,520	84	256	3	40	1	212	3	775	10
Nevirapine	6,520	84	170	2	50	1	82	1	981	13
Etravirine	6,702	86	460	6	164	2	394	5	83	1
Rilpivirine	6,702	86	167	2	376	5	351	4	207	3
Any NNRTI	6,335	81	141	2	250	3	94	1	983	13
Integrase inhibitors (INSTIs)[c]										
Raltegravir	41	76	0	0	2	4	2	4	9	17
Elvitegravir	41	76	1	2	2	4	1	2	9	17
Dolutegravir	46	85	6	11	1	2	1	2	0	0
Any INSTI	41	76	0	0	2	4	1	2	10	19

[a] *Available for 7,617 individuals;* [b] *Available for 7,803 individuals;* [c] *Available for 54 individuals.*

< Back to page 81

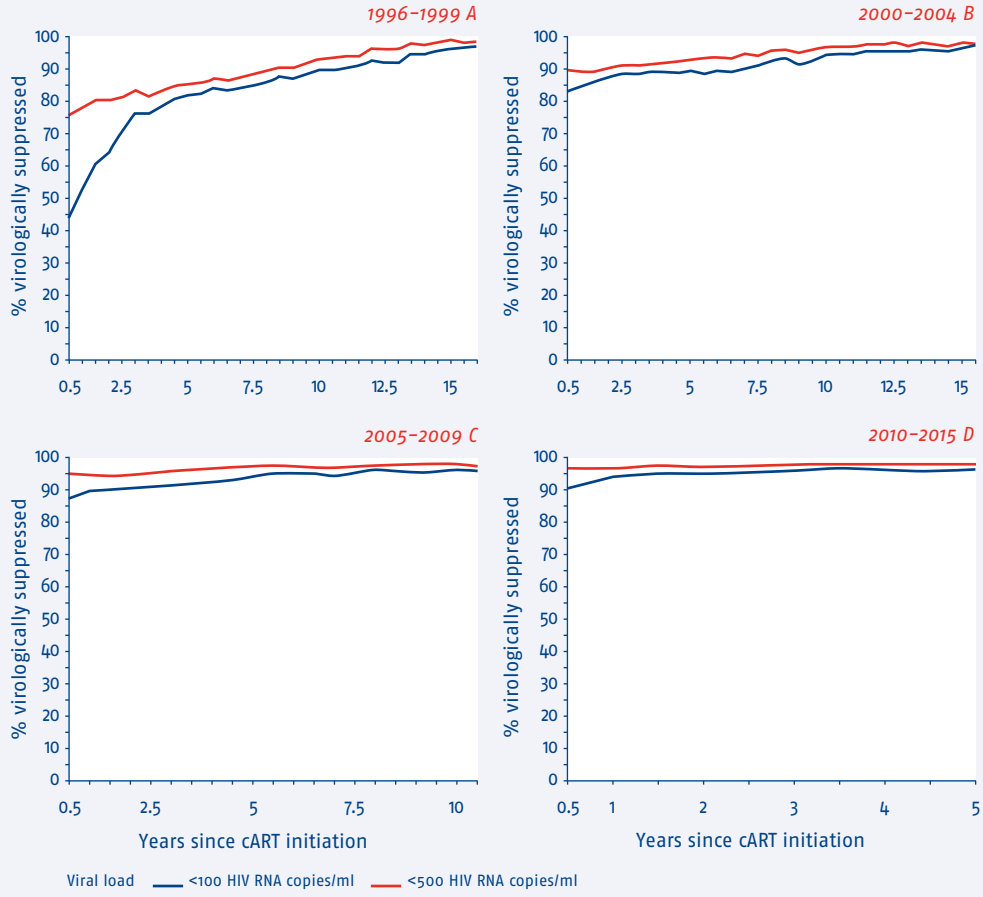
Appendix Figure 2.1: *Time between entry into HIV care and initiation of combination antiretroviral therapy (cART).*



Legend: *cART=combination antiretroviral therapy.*

< Back to page 56

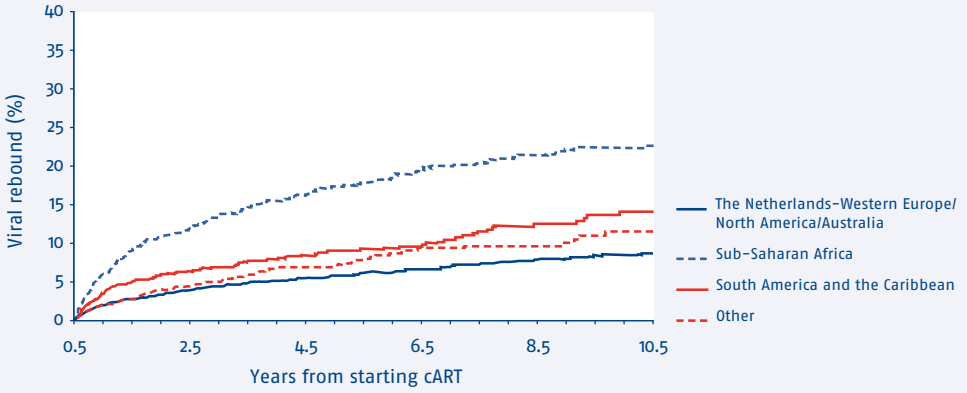
Appendix Figure 2.2: *Viral suppression since combination antiretroviral therapy (cART) initiation, by calendar period of therapy initiation: A) 1996–1999; B) 2000–2004; C) 2005–2009; D) 2010–2015.*



Legend: *cART=combination antiretroviral therapy.*

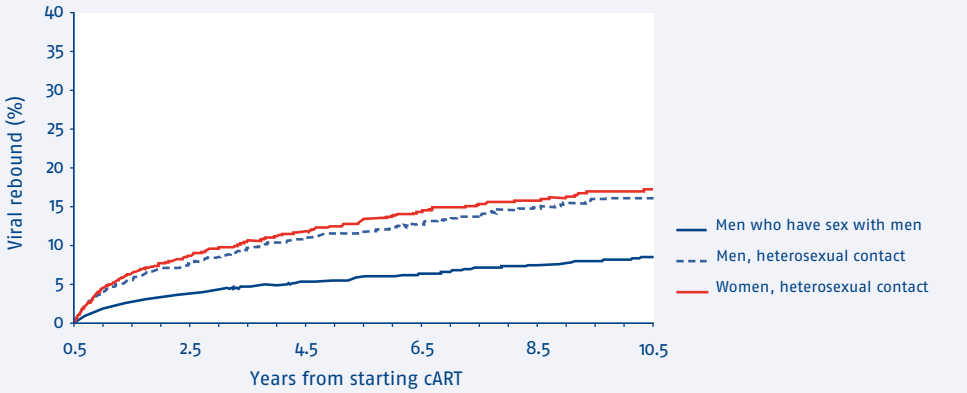
< Back to page 73

Appendix Figure 2.3: *Kaplan-Meier estimates of viral rebound according to region of origin.*



Legend: *cART=combination antiretroviral therapy.*

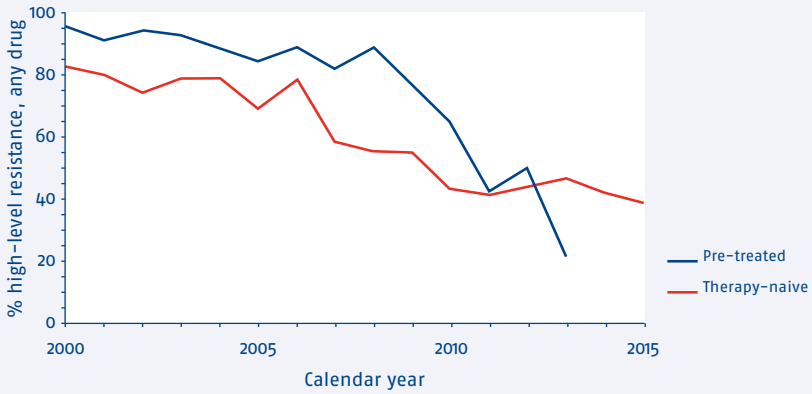
Appendix Figure 2.4: *Kaplan-Meier estimates of viral rebound according to risk group.*



Legend: *cART=combination antiretroviral therapy.*

< Back to page 74

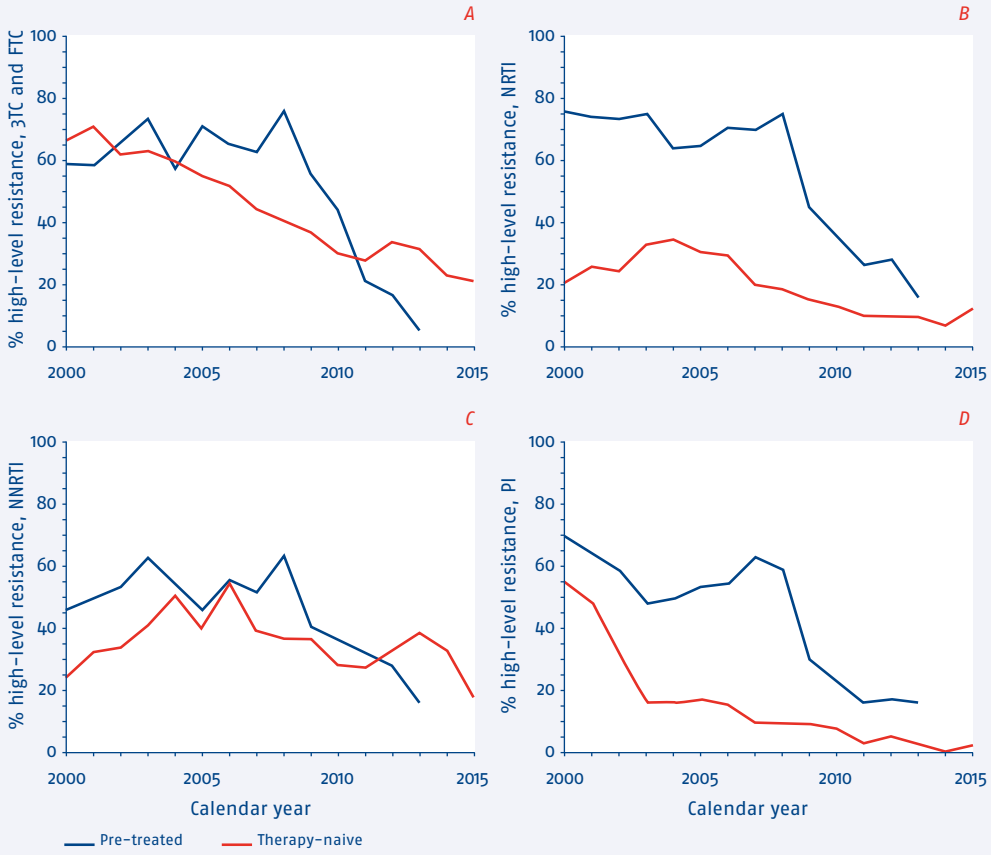
Appendix Figure 2.5: *Annual proportion of sequences obtained at the time of virological failure with evidence of high-level resistance to any antiretroviral drug, according to pre-treatment exposure to monotherapy or dual therapy before commencing combination antiretroviral therapy (cART). Resistance was assessed using the Stanford algorithm[32].*



Note: *The number of sequences in 2014–2015 in pre-treated patients was too low to give meaningful proportions.*

< Back to page 79

Appendix Figure 2.6: *Annual proportion of sequences obtained at the time of virological failure with evidence of high-level resistance by antiretroviral drug, according to pre-treatment exposure to monotherapy or dual therapy before commencing combination antiretroviral therapy. Resistance was assessed using the Stanford algorithm [32]. A) High-level resistance against emtricitabine and lamivudine; B) High-level resistance against nucleoside reverse transcriptase inhibitors; C) High-level resistance against non-nucleoside reverse transcriptase inhibitors; D) High-level resistance against protease inhibitors.*

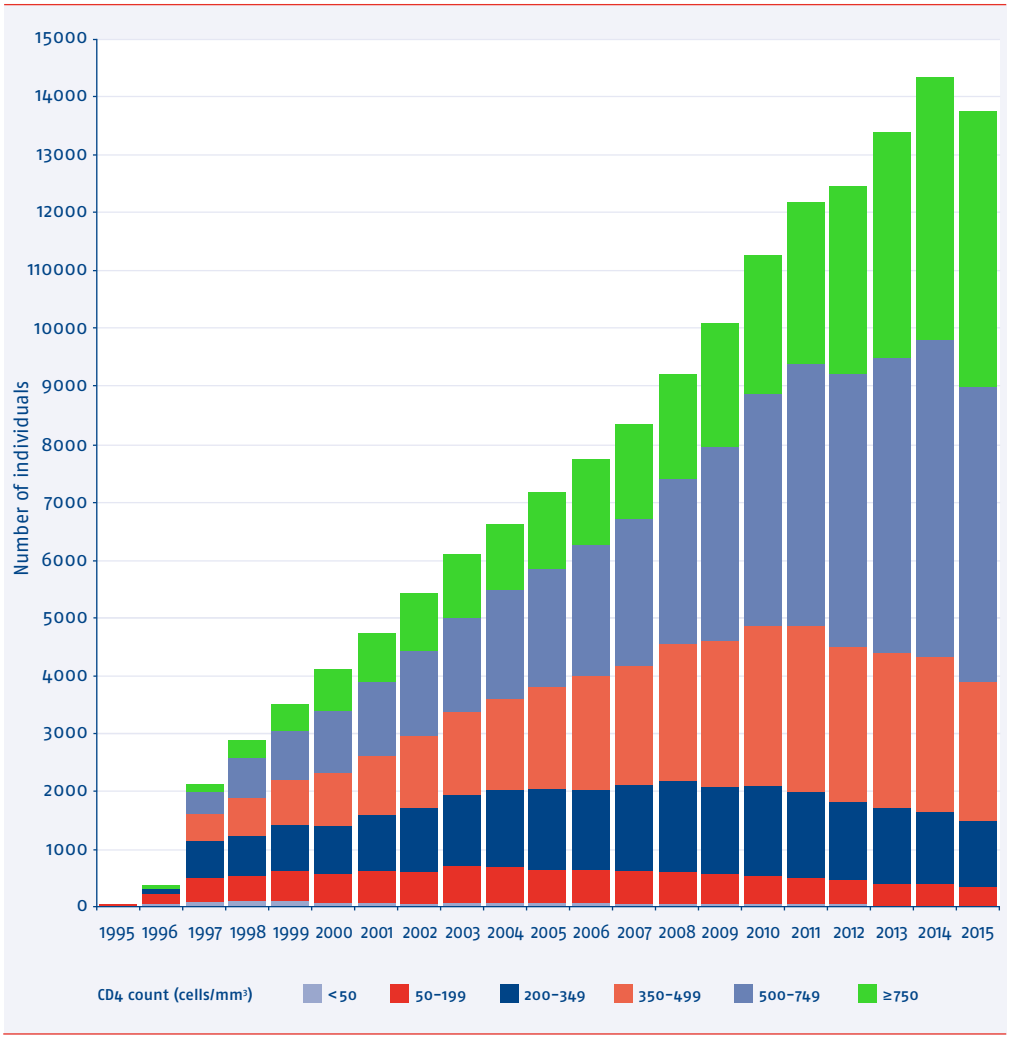


Note: *The number of sequences in 2014-2015 in pre-treated patients was too low to give meaningful proportions.*

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

< Back to page 79

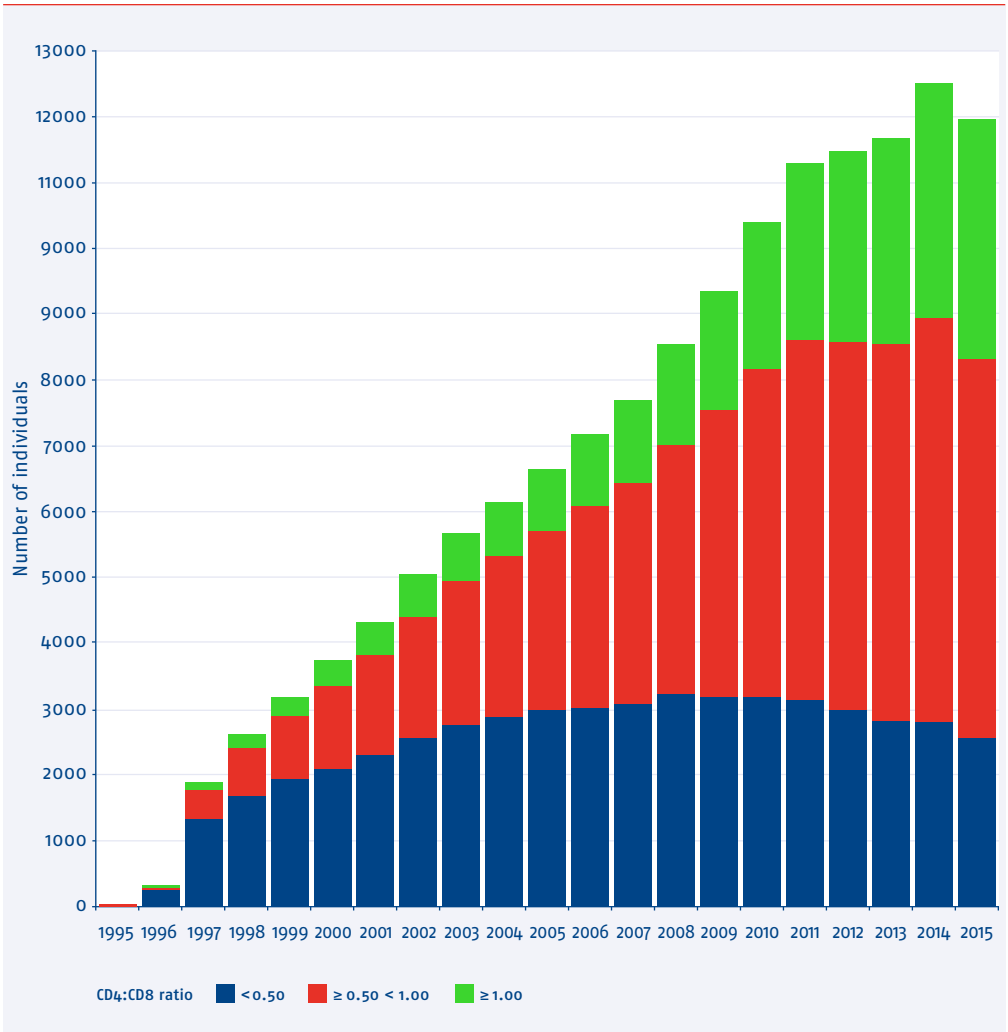
Appendix Figure 2.7: *Last available CD4 cell count (cells/mm³) in each calendar year after the start of combination antiretroviral therapy (cART).*



Note: *Numbers for 2015 may increase slightly because data collection is not yet complete.*

< Back to page 84

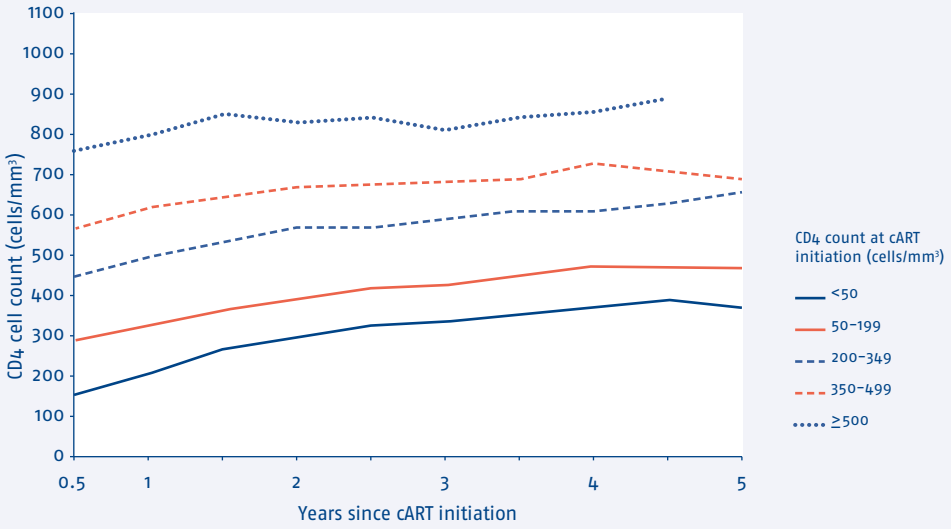
Appendix Figure 2.8: *Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy.*



Note: *Numbers for 2015 may increase slightly because data collection is not yet complete.*

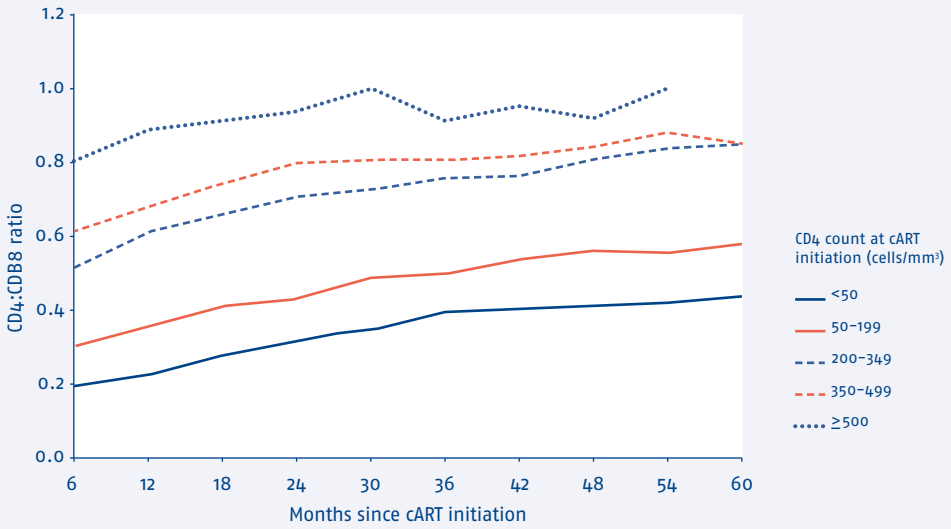
< Back to page 84

Appendix Figure 2.9: CD4 cell count over time after starting combination antiretroviral therapy (cART) since 2010.



Legend: cART=combination antiretroviral therapy.

Appendix Figure 2.10: CD4:CD8 ratio over time after starting combination antiretroviral therapy (cART) since 2010.



Legend: cART=combination antiretroviral therapy.

< Back to page 87

Appendix Table 3.1: Annual number of cases of death and first AIDS events among 23,812 HIV-1-infected patients in the Netherlands recorded up to May 2016.

Annual number of cases of death and first AIDS events	AIDS	AIDS ≥6 weeks after diagnosis	AIDS 4 weeks after start of cART	Death	Death after start of cART
1996	364	227	33	48	30
1997	301	146	58	88	70
1998	242	97	44	85	74
1999	231	114	60	91	90
2000	247	97	63	85	81
2001	250	122	67	83	79
2002	296	117	81	124	87
2003	291	126	81	147	124
2004	286	134	73	145	132
2005	354	163	95	143	126
2006	280	139	83	123	106
2007	295	145	95	154	133
2008	277	142	92	154	139
2009	269	121	74	163	149
2010	283	116	79	131	124
2011	235	112	74	154	144
2012	263	125	86	157	148
2013	217	96	74	149	145
2014	187	79	55	163	155
2015	156	52	71	136	132

Legend: cART=combination antiretroviral therapy.

< Back to page 96

Appendix Table 3.2: *Absolute number of causes of death among HIV-1-infected patients during the periods 1996-2001, 2002-2006, and 2007-2015.*

Causes of death		1996-2001	2002-2006	2007-2015
1. All AIDS-defining causes	Subtotal	245	248	322
	1.1 Infection	82	139	223
	1.2 Malignancy	73	67	81
	1.3 Not specified	90	42	18
2. Non-AIDS-defining malignancies		37	103	266
3. All cardiovascular disease	Subtotal	16	30	38
	3.1 Myocardial infarction	12	17	14
	3.2 Stroke	4	12	13
	3.3 Other ischaemic heart disease	.	1	9
	3.4 Other cardiovascular disease	.	.	2
4. Non-AIDS-defining infection		10	29	32
5. Liver-related death		13	26	81
6. Lung-related		4	9	36
7. Non-natural death	Subtotal	27	43	34
	7.1 Accident or violent death	8	14	24
	7.2 Suicide	11	25	10
	7.3 Euthanasia	8	4	.
8. Substance abuse		12	14	41
9. Other causes		31	51	168
10. Unknown		82	129	207
Total		**477**	**682**	**1,225**

< Back to page 97

Appendix Table 3.3: Adjusted risk factors for death and AIDS among HIV-1-infected patients.

Risk factors	Death			AIDS		
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
Male gender	1.43 (1.24-1.66)	0.00		1.07 (0.96-1.20)	0.23	
Region of birth						
Netherlands	1.00		0.00	1.00		0.01
Other	0.80 (0.72-0.89)	0.00		0.88 (0.81-0.96)	0.00	
Missing information	1.31 (0.58-2.92)	0.52		1.47 (0.85-2.55)	0.17	
HIV-1 transmission route						
Other	2.24 (1.71-2.94)	0.00	0.00	0.48 (0.36-0.64)	0.00	0.00
MSM	1.00			1.00		
Heterosexual	1.06 (0.93-1.20)	0.38		1.07 (0.96-1.19)	0.21	
IDU	1.73 (1.42-2.10)	0.00		0.52 (0.42-0.64)	0.00	
Blood contact	0.77 (0.55-1.09)	0.14		0.77 (0.56-1.06)	0.11	
Children	0.31 (0.04-2.23)	0.24				
Unknown	1.19 (0.96-1.47)	0.11		1.66 (1.43-1.94)	0.00	
Age*						
18-29	0.98 (0.73-1.32)	0.89	0.00	1.02 (0.89-1.17)	0.75	0.00
30-39	1.00			1.00		
40-49	1.50 (1.29-1.73)	0.00		1.23 (1.12-1.35)	0.00	
50-59	2.51 (2.17-2.91)	0.00		1.57 (1.41-1.75)	0.00	
60-69	4.34 (3.68-5.12)	0.00		1.88 (1.61-2.20)	0.00	
70+	8.98 (7.27-11.09)	0.00		2.94 (2.16-4.00)	0.00	
CD4 cell count**						
<50	17.61 (14.77-20.98)	0.00	0.00	31.22 (27.13-35.92)	0.00	0.00
50-199	5.61 (4.84-6.49)	0.00		8.27 (7.23-9.47)	0.00	
200-349	2.33 (2.01-2.70)	0.00		2.64 (2.29-3.04)	0.00	
350-499	1.39 (1.19-1.63)	0.00		1.52 (1.31-1.76)	0.00	
500-749	1.00			1.00		
750+	0.93 (0.77-1.11)	0.41		1.00 (0.82-1.22)	0.99	
Per year longer with HIV RNA>1000 copies/ml	1.06 (1.05-1.08)	0.00	0.00	0.89 (0.88-0.91)	0.00	0.00
Treatment status						
Not (yet) started cART	0.18 (0.13-0.26)	0.00	0.00	3.18 (2.93-3.45)	0.00	0.00
Treatment-experienced at start cART	1.14 (1.03-1.25)	0.01		0.61 (0.54-0.70)	0.00	
Treatment-naive at start	1.00			1.00		
Prior AIDS event	1.86 (1.69-2.04)	0.00				
HBV positive	1.32 (1.15-1.52)	0.00		0.82 (0.71-0.95)	0.01	

< Back to page 98

Risk factors	Death			AIDS		
	RR (95% CI)	p-value	Overall p-value	RR (95% CI)	p-value	Overall p-value
HCV positive	1.35 (1.15-1.59)	0.00		1.14 (0.97-1.33)	0.11	
Body mass index*						
<18	2.52 (2.20-2.88)	0.00	0.00			
18-25	1.00					
25-30	0.71 (0.63-0.80)	0.00				
≥30	0.76 (0.62-0.93)	0.01				
Smoking status						
Missing information	3.33 (2.89-3.83)	0.00	0.00	1.05 (0.95-1.16)	0.36	0.00
Current smoker	1.32 (1.14-1.51)	0.00		0.73 (0.66-0.80)	0.00	
Never smoker	1.00			1.00		
Past smoker	1.79 (1.53-2.08)	0.00		1.11 (0.99-1.26)	0.08	

** Time-updated.*

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

***Legend:** RR=risk ratio; cART=combination antiretroviral therapy; IDU=injecting drug use; HBV=hepatitis B virus; HCV=hepatitis C virus.*

Appendix Table 3.4: Lost to follow up (no follow up after 31 December 2015) by region of origin and time-updated CD4 cell count.

Lost to follow up	Total			Caribbean			Western Europe / North America		
	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)
Last CD4									
<50	56	1,781	31.5 (23.8-40.8)	1	130	7.7 (0.2-43.0)	11	163	67.3 (33.6-120.4)
50-199	201	6,603	30.4 (26.4-35.0)	10	341	29.4 (14.1-54.0)	41	754	54.4 (39.0-73.8)
200-349	368	1,5517	23.7 (21.4-26.3)	14	625	22.4 (12.3-37.6)	70	1,240	56.5 (44.0-71.3)
350-499	485	29,697	16.3 (14.9-17.9)	25	1,328	18.8 (12.2-27.8)	104	2,532	41.1 (33.6-49.8)
500-749	585	61,778	9.5 (8.7-10.3)	31	2,519	12.3 (8.4-17.5)	142	4,855	29.2 (24.6-34.5)
750+	322	56,396	5.7 (5.1-6.4)	19	2,372	8.0 (4.8-12.5)	100	4,687	21.3 (17.4-25.9)

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

< Back to page 98

	Netherlands			sub-Saharan Africa			South and Southeast Asia		
	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)
	7	1,192	5.9 (2.4-12.1)	30	225	133.5 (90.1-190.6)	7	71	98.7 (39.7-203.3)
	28	3,984	7.0 (4.7-10.2)	114	1,301	87.6 (72.3-105.3)	8	223	35.8 (15.5-70.6)
	73	9,902	7.4 (5.8-9.3)	195	3,198	61.0 (52.7-70.2)	16	551	29.0 (16.6-47.1)
	102	19,164	5.3 (4.3-6.5)	234	5,398	43.3 (38.0-49.3)	20	1,275	15.7 (9.6-24.2)
	174	42,088	4.1 (3.5-4.8)	224	9,864	22.7 (19.8-25.9)	14	2,452	5.7 (3.1-9.6)
	101	40,428	2.5 (2.0-3.0)	95	7,218	13.2 (10.6-16.1)	7	1,691	4.1 (1.7-8.5)

Appendix Table 3.5: *Absolute number of AIDS events among HIV-1-infected patients during the periods 1996-2001, 2002-2006, and 2007-2015.*

CDC event	1996-2001	2002-2006	2007-2015	Total	
	n	n	n	n	%
AIDS dementia complex / HIV encephalopathy	55	52	86	193	3.38
CMV disease (other than lymph node, liver or spleen)	34	34	56	124	2.17
CMV retinitis	31	18	21	70	1.23
Candidiasis oesophageal	298	228	411	937	16.42
Candidiasis trachea, bronchi, lungs	8	15	11	34	0.60
Cervical cancer, invasive	6	4	9	19	0.33
Coccidioidomycosis, disseminated or extrapulmonary	.	.	1	1	0.02
Cryptococcosis extrapulmonary	27	33	37	97	1.70
Cryptosporidiosis, chronic intestinal (>1 month)	23	16	14	53	0.93
Herpes simplex virus: chronic ulcer (>1 month)	36	49	80	165	2.89
Histoplasmosis, disseminated or extrapulmonary	10	16	13	39	0.68
Isosporiasis, chronic intestinal (>1 month)	6	7	4	17	0.30
Kaposi's sarcoma	179	176	279	634	11.11
Leishmaniasis, visceral	.	2	4	6	0.11
Lymphoma, Burkitt's or immunoblastic	71	94	159	324	5.68
Lymphoma, primary, of brain	7	3	8	18	0.32
MAI / M. kansasii, disseminated or extrapulmonary	32	15	34	81	1.42
Microsporidiosis, chronic intestinal (>1 month)	11	1	3	15	0.26
Mycobacterium, other species (disseminated / extrapulmonary)	24	9	15	48	0.84
Other CDC C-event, specify	3	4	.	7	0.12
Penicilliosis	.	.	2	2	0.04
Pneumocystis carinii pneumonia	384	304	512	1,200	21.03
Pneumocystis, extrapulmonary	1	1	3	5	0.09
Pneumonia, recurrent (more than one episode in a 1-year period)	58	63	119	240	4.21
Progressive multifocal leucoencephalopathy	23	22	53	98	1.72
Salmonella septicaemia, recurrent	4	.	.	4	0.07
Toxoplasmosis of the brain	80	109	79	268	4.70
Tuberculosis, extrapulmonary	96	115	102	313	5.48
Tuberculosis, pulmonary	139	158	147	444	7.78
Wasting syndrome due to HIV	56	58	137	251	4.40
Total	**1,702**	**1,606**	**2,399**	**5,707**	**100**

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

< Back to page 99

Appendix Table 3.6.A: Incidence of diabetes mellitus from 2000 onwards according to gender and age.

Incidence	Male			Female		
per 1000 PY	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)
Age						
18-29	6	9,024	0.7 (0.2-1.4)	24	5,842	4.1 (2.6-6.1)
30-39	78	33,686	2.3 (1.8-2.9)	63	13,435	4.7 (3.6-6.0)
40-49	240	55,092	4.4 (3.8-4.9)	85	11,801	7.2 (5.8-8.9)
50-59	256	34,721	7.4 (6.5-8.3)	46	4,732	9.7 (7.1-13.0)
60-69	161	12,294	13.1 (11.2-15.3)	15	1,536	9.8 (5.5-16.1)
70+	29	2,450	11.8 (7.9-17.0)	6	395	15.2 (5.6-33.0)

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

Appendix Table 3.6.B: Incidence of cardiovascular disease (myocardial infarction, stroke, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy) from 2000 onwards according to gender and age.

Incidence	Male			Female		
per 1000 PY	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)
Age						
18-29	6	9,009	0.7 (0.2-1.4)	5	5,827	0.9 (0.3-2.0)
30-39	68	33,601	2.0 (1.6-2.6)	23	13,373	1.7 (1.1-2.6)
40-49	364	54,507	6.7 (6.0-7.4)	71	11,677	6.1 (4.7-7.7)
50-59	555	33,687	16.5 (15.1-17.9)	33	4,670	7.1 (4.9-9.9)
60-69	371	11,446	32.4 (29.2-35.9)	34	1,483	22.9 (15.9-32.0)
70+	104	2,163	48.1 (39.3-58.2)	6	361	16.6 (6.1-36.2)

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

< Back to page 99

Appendix Table 3.6.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 2007 onwards, according to gender and age.*

Incidence	Male			Female		
per 1000 PY	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)
Age						
18-29	45	5,856	7.7 (5.6-10.3)	11	2,853	3.9 (1.9-6.9)
30-39	100	18,041	5.5 (4.5-6.7)	32	7,359	4.3 (3.0-6.1)
40-49	172	34,347	5.0 (4.3-5.8)	60	7,990	7.5 (5.7-9.7)
50-59	218	24,892	8.8 (7.6-10.0)	87	3,560	24.4 (19.6-30.1)
60-69	284	9,285	30.6 (27.1-34.4)	60	924	64.9 (49.6-83.6)
70+	170	1,384	122.8 (105.1-142.8)	34	147	232.1 (160.7-324.3)

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

Appendix Table 3.6.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 2000 onwards, according to gender and age.*

Incidence	Male			Female		
per 1000 PY	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)
Age						
18-29	5	9,023	0.6 (0.2-1.3)	3	5,910	0.5 (0.1-1.5)
30-39	55	33,761	1.6 (1.2-2.1)	20	13,641	1.5 (0.9-2.3)
40-49	184	55,635	3.3 (2.8-3.8)	44	12,142	3.6 (2.6-4.9)
50-59	263	35,507	7.4 (6.5-8.4)	35	4,955	7.1 (4.9-9.8)
60-69	187	12,702	14.7 (12.7-17.0)	10	1,568	6.4 (3.1-11.7)
70+	56	2,415	23.2 (17.5-30.1)	8	427	18.7 (8.1-36.9)

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

Appendix Table 3.6.E: Incidence of non-AIDS disease (first occurrence of cardiovascular disease, diabetes mellitus, or non-AIDS malignancy) from 2000 onwards, according to gender and age.

Incidence	Male			Female		
per 1000 PY	n	PY	Inc (95% CI)	n	PY	Inc (95% CI)
Age						
18-29	16	8,998	1.8 (1.0-2.9)	30	5,820	5.2 (3.5-7.4)
30-39	196	33,472	5.9 (5.1-6.7)	101	13,345	7.6 (6.2-9.2)
40-49	755	54,026	14.0 (13.0-15.0)	189	11,545	16.4 (14.1-18.9)
50-59	1,002	33,114	30.3 (28.4-32.2)	108	4,566	23.7 (19.4-28.6)
60-69	623	10,991	56.7 (52.3-61.3)	57	1,446	39.4 (29.9-51.1)
70+	161	1,942	82.9 (70.6-96.7)	16	338	47.4 (27.1-76.9)

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

Appendix Table 3.7: Adjusted risk factors for non-AIDS morbidity.

Adjusted risk factors for non-AIDS morbidity	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p-value	overall p-value	IRR (95% CI)	p-value	overall p-value
Male gender	1.14 (1.00-1.31)	0.056		1.79 (1.38-2.32)	0.000	
Region of birth						
Netherlands	1.00		0.787	1.00		0.005
Other	1.03 (0.94-1.14)	0.533		0.77 (0.65-0.90)	0.002	
Missing information	0.85 (0.27-2.64)	0.779		1.40 (0.35-5.62)	0.636	
HIV-1 transmission route						
Other	1.16 (0.78-1.71)	0.467	0.000	1.17 (0.61-2.25)	0.631	0.011
MSM	1.00			1.00		
Heterosexual	1.25 (1.11-1.41)	0.000		1.37 (1.14-1.65)	0.001	
IDU	1.23 (0.96-1.57)	0.099		1.16 (0.77-1.74)	0.490	
Blood contact	1.39 (1.04-1.86)	0.026		1.09 (0.64-1.84)	0.755	
Children	0.00 (0.00-99.9)	0.998		0.00 (0.00-99.9)	0.999	
Unknown	1.44 (1.17-1.77)	0.001		1.63 (1.19-2.24)	0.003	
Age*						
18-29	0.61 (0.43-0.87)	0.006	0.000	0.67 (0.32-1.41)	0.292	0.000
30-39	1.00			1.00		
40-49	1.94 (1.66-2.26)	0.000		2.65 (1.95-3.60)	0.000	
50-59	3.68 (3.14-4.30)	0.000		5.65 (4.17-7.65)	0.000	
60-69	6.47 (5.45-7.69)	0.000		10.21 (7.41-14.07)	0.000	
70+	9.61 (7.57-12.19)	0.000		14.88 (10.05-22.03)	0.000	
CD4 cell count**						
<50	3.03 (2.22-4.14)	0.000	0.000	2.11 (1.15-3.88)	0.016	0.024
50-199	1.61 (1.34-1.94)	0.000		1.57 (1.16-2.12)	0.003	
200-349	1.17 (1.03-1.34)	0.019		1.21 (0.97-1.50)	0.086	
350-499	1.01 (0.90-1.14)	0.883		1.03 (0.85-1.25)	0.750	
500-749	1.00			1.00		
750+	1.08 (0.96-1.22)	0.202		1.14 (0.94-1.38)	0.176	
Per year longer with CD4<200 cells/mm^3	1.01 (0.98-1.04)	0.558		1.01 (0.96-1.05)	0.804	
Per year longer with HIV RNA>1000 copies/ml	1.01 (0.99-1.03)	0.365		1.02 (0.99-1.05)	0.277	
Treatment status						
Not yet started cART	1.00 (0.84-1.20)	0.975	0.000	0.94 (0.68-1.29)	0.690	0.021
ART-experienced at start cART	1.31 (1.18-1.46)	0.000		1.26 (1.07-1.49)	0.007	
ART-naive at start cART	1.00			1.00		

< Back to page 102

	Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
	IRR (95% CI)	p-value	overall p-value	IRR (95% CI)	p-value	overall p-value	IRR (95% CI)	p-value	overall p-value
	0.95 (0.74–1.20)	0.649		1.15 (0.94–1.41)	0.167		0.43 (0.35–0.53)	0.000	
	1.00		0.311	1.00		0.000	1.00		0.000
	0.88 (0.75–1.04)	0.134		1.42 (1.22–1.65)	0.000		1.48 (1.27–1.72)	0.000	
	0.77 (0.11–5.51)	0.798		0.00 (0.00–99.9)	0.999		2.44 (0.61–9.79)	0.210	
	1.24 (0.67–2.27)	0.490	0.379	1.25 (0.65–2.42)	0.501	0.003	1.16 (0.65–2.04)	0.619	0.087
	1.00			1.00			1.00		
	1.03 (0.84–1.26)	0.801		1.41 (1.17–1.70)	0.000		1.13 (0.93–1.37)	0.232	
	1.25 (0.85–1.84)	0.249		1.40 (0.94–2.09)	0.099		1.77 (1.25–2.52)	0.001	
	1.69 (1.10–2.61)	0.018		1.56 (1.01–2.41)	0.043		1.10 (0.69–1.75)	0.680	
	0.00 (0.00–99.9)	0.999		0.00 (0.00–99.9)	0.999		0.00 (0.00–99.9)	0.999	
	1.05 (0.71–1.55)	0.800		1.61 (1.17–2.23)	0.004		0.98 (0.68–1.42)	0.930	
	0.55 (0.27–1.10)	0.090	0.000	0.73 (0.47–1.14)	0.169	0.000	0.24 (0.08–0.79)	0.019	0.000
	1.00			1.00			1.00		
	2.16 (1.62–2.87)	0.000		1.48 (1.19–1.84)	0.000		2.36 (1.65–3.38)	0.000	
	4.45 (3.35–5.93)	0.000		2.41 (1.91–3.03)	0.000		6.75 (4.77–9.55)	0.000	
	8.50 (6.26–11.54)	0.000		4.45 (3.44–5.75)	0.000		25.72 (18.13–36.49)	0.000	
	16.89 (11.71–24.37)	0.000		4.23 (2.78–6.45)	0.000		106.0 (73.15–153.7)	0.000	
	2.16 (1.14–4.06)	0.017	0.004	4.51 (2.99–6.81)	0.000	0.000	4.76 (3.01–7.53)	0.000	0.000
	1.71 (1.26–2.33)	0.001		1.44 (1.07–1.93)	0.016		2.11 (1.57–2.83)	0.000	
	1.34 (1.08–1.67)	0.008		0.95 (0.76–1.18)	0.639		1.27 (1.02–1.58)	0.030	
	1.11 (0.91–1.35)	0.309		0.85 (0.70–1.03)	0.098		1.02 (0.84–1.23)	0.837	
	1.00			1.00			1.00		
	0.96 (0.78–1.19)	0.724		1.10 (0.91–1.33)	0.319		0.92 (0.76–1.11)	0.374	
	1.00 (0.96–1.04)	0.904		1.02 (0.98–1.06)	0.400		0.97 (0.94–1.01)	0.119	
	1.01 (0.98–1.04)	0.534		1.00 (0.97–1.03)	0.892		0.97 (0.95–1.00)	0.061	
	1.08 (0.79–1.46)	0.636	0.133	1.17 (0.88–1.56)	0.291	0.001	0.68 (0.43–1.07)	0.093	0.103
	1.20 (1.00–1.44)	0.046		1.38 (1.16–1.64)	0.000		1.10 (0.93–1.31)	0.260	
	1.00			1.00			1.00		

Appendix Table 3.7: Continued.

Adjusted risk factors for non-AIDS morbidity	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p-value	overall p-value	IRR (95% CI)	p-value	overall p-value
Per year on cART	1.00 (0.99-1.01)	0.925		1.00 (0.99-1.02)	0.473	
Body mass index*						
<18	1.48 (1.18-1.84)	0.001	0.000	1.22 (0.84-1.77)	0.287	0.216
18-25	1.00			1.00		
25-30	1.14 (1.03-1.26)	0.009		0.94 (0.80-1.10)	0.420	
>=30	1.66 (1.44-1.91)	0.000		1.20 (0.94-1.54)	0.151	
Prior AIDS event	1.27 (1.16-1.39)	0.000		1.12 (0.96-1.29)	0.152	
HBV positive	1.22 (1.05-1.42)	0.010		0.90 (0.68-1.18)	0.442	
HCV positive	1.12 (0.95-1.32)	0.173		0.99 (0.75-1.31)	0.943	
Hypertension	1.24 (1.13-1.36)	0.000		1.36 (1.18-1.57)	0.000	
Smoking status						
Missing information	1.15 (0.99-1.32)	0.064	0.000	1.54 (1.21-1.97)	0.000	0.000
Current smoker	1.38 (1.23-1.54)	0.000		1.90 (1.58-2.30)	0.000	
Never smoker	1.00			1.00		
Past smoker	1.24 (1.09-1.41)	0.001		1.64 (1.33-2.04)	0.000	
Calendar year period						
2000-2005	1.14 (1.01-1.30)	0.037	0.026	1.38 (1.13-1.68)	0.002	0.006
2006-2010	1.14 (1.03-1.25)	0.013		1.07 (0.91-1.26)	0.407	
2011-2015	1.00			1.00		
Early cART[&]	0.84 (0.63-1.10)	0.208	0.195	1.10 (0.74-1.64)	0.633	
Per year on LOP/r				1.01 (0.99-1.03)	0.503	
Per year on IDV				1.01 (0.99-1.03)	0.188	
Recent use of ABC[#]				1.74 (1.49-2.02)	0.000	.
Per year on ZDV						
Per year on d4T						
Per year on ddI						
Per year on TDF						
Prior CVD						
Prior diabetes						

**Time-updated.*

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

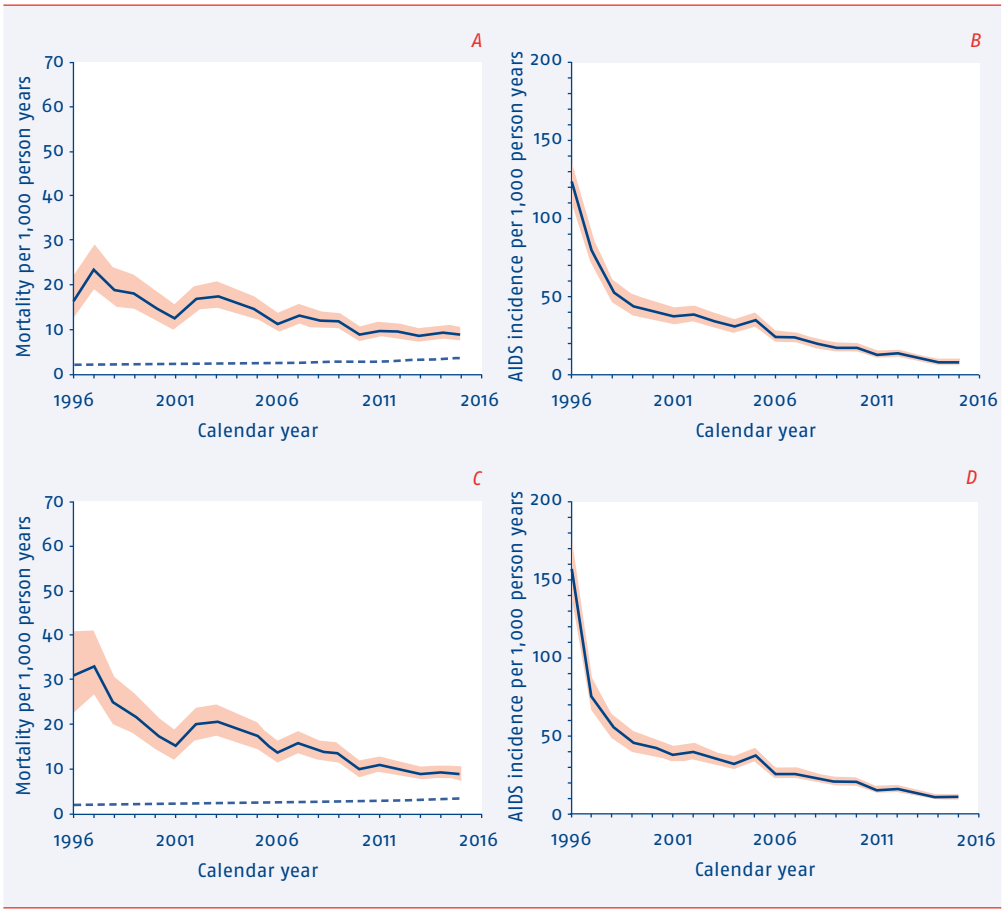
[#]Current use or recently used in the past 6 months.

[&]cART started within 12 months after last HIV-negative test or within 6 months of diagnosed acute HIV infection.

***Legend:** HBV=hepatitis B virus; HCV=hepatitis C virus; CKD=chronic kidney disease; IDU=injecting drug use; cART=combination antiretroviral therapy; LOP/r=lopinavir/ritonavir; IDV=indinavir; ABC=abacavir; ZDV=zidovudine; ddI=didanosine, d4T=stavudine, ZDV=zidovudine, TDF=tenofovir disoproxil fumarate; CVD=cardiovascular event; d4T=stavudine; ddI=didanosine; BMI: <18 kg/m²=underweight; 18-25 kg/m²=normal; 25-30 kg/m²=overweight; >30 kg/m²=severely overweight.*

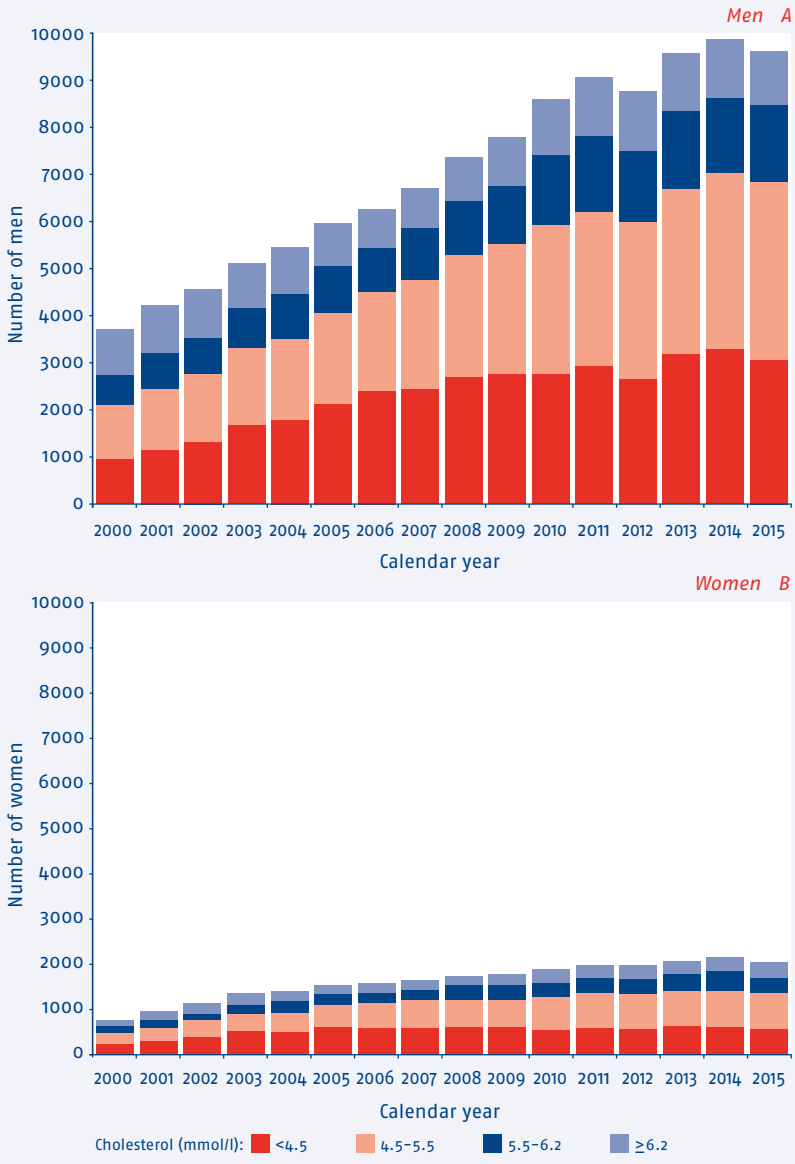
	Non-AIDS-defining malignancy			Diabetes mellitus			CKD		
	IRR (95% CI)	p-value	overall p-value	IRR (95% CI)	p-value	overall p-value	IRR (95% CI)	p-value	overall p-value
	1.00 (0.98–1.01)	0.786		1.00 (0.99–1.01)	0.697		1.01 (1.00–1.02)	0.235	
	1.73 (1.27–2.35)	0.001	0.000	1.48 (1.00–2.20)	0.051	0.000	5.03 (4.05–6.24)	0.000	0.000
	1.00			1.00			1.00		
	0.82 (0.70–0.97)	0.023		1.91 (1.63–2.24)	0.000		0.37 (0.31–0.44)	0.000	
	0.65 (0.47–0.89)	0.007		3.98 (3.28–4.83)	0.000		0.17 (0.11–0.25)	0.000	
	1.26 (1.08–1.47)	0.003		1.43 (1.24–1.66)	0.000		1.17 (1.02–1.36)	0.029	
	1.59 (1.27–2.00)	0.000		1.23 (0.97–1.56)	0.094		1.22 (0.94–1.57)	0.130	
	1.12 (0.86–1.47)	0.401		1.24 (0.95–1.62)	0.116		1.34 (1.06–1.71)	0.016	
	1.12 (0.96–1.31)	0.147		1.19 (1.02–1.38)	0.025		1.14 (0.98–1.31)	0.082	
	1.21 (0.94–1.56)	0.139	0.000	0.95 (0.76–1.18)	0.635	0.524	1.05 (0.84–1.31)	0.677	0.936
	1.62 (1.34–1.95)	0.000		0.93 (0.78–1.11)	0.408		1.04 (0.87–1.24)	0.650	
	1.00			1.00			1.00		
	1.21 (0.97–1.52)	0.091		1.07 (0.88–1.31)	0.481		0.99 (0.82–1.21)	0.949	
	0.87 (0.70–1.09)	0.224	0.099	1.18 (0.96–1.44)	0.118	0.183			
	1.09 (0.93–1.28)	0.299		1.14 (0.97–1.34)	0.111		0.89 (0.76–1.04)	0.133	
	1.00			1.00			1.00		
	0.94 (0.60–1.45)	0.775		0.65 (0.38–1.11)	0.116		0.69 (0.44–1.08)	0.107	
				1.01 (1.00–1.02)	0.078				
				1.01 (1.00–1.03)	0.106				
				1.01 (1.00–1.03)	0.040				
							1.00 (0.99–1.02)	0.571	
							1.71 (1.37–2.13)	0.000	
							1.59 (1.26–2.01)	0.000	

Appendix Figure 3.1: *(A,C) Annual mortality and (B,D) incidence of AIDS in 23,812 HIV-1-infected patients in the Netherlands (A, B) after entry into care following HIV diagnosis and (C, D) in a subpopulation of 23,675 treated patients who started combination antiretroviral therapy (cART) from 1996 onwards. Solid lines represent the incidence, while the shaded areas are the 95% confidence intervals. The dashed line is the mortality rate for age- and gender-matched individuals from the general population in the Netherlands.*



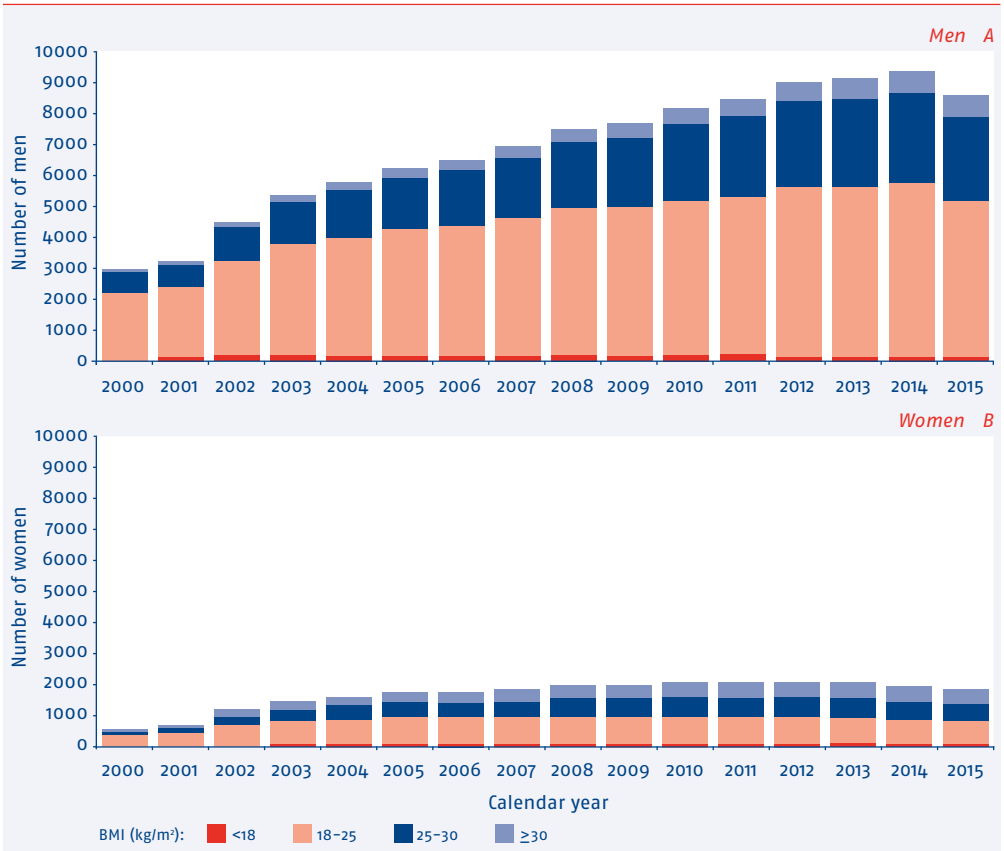
< Back to page 96

Appendix Figure 3.2: *Absolute number of (A) men and (B) women within cholesterol categories at the end of each calendar year. For each individual, the last available measurement in each year was selected.*



< Back to page 104

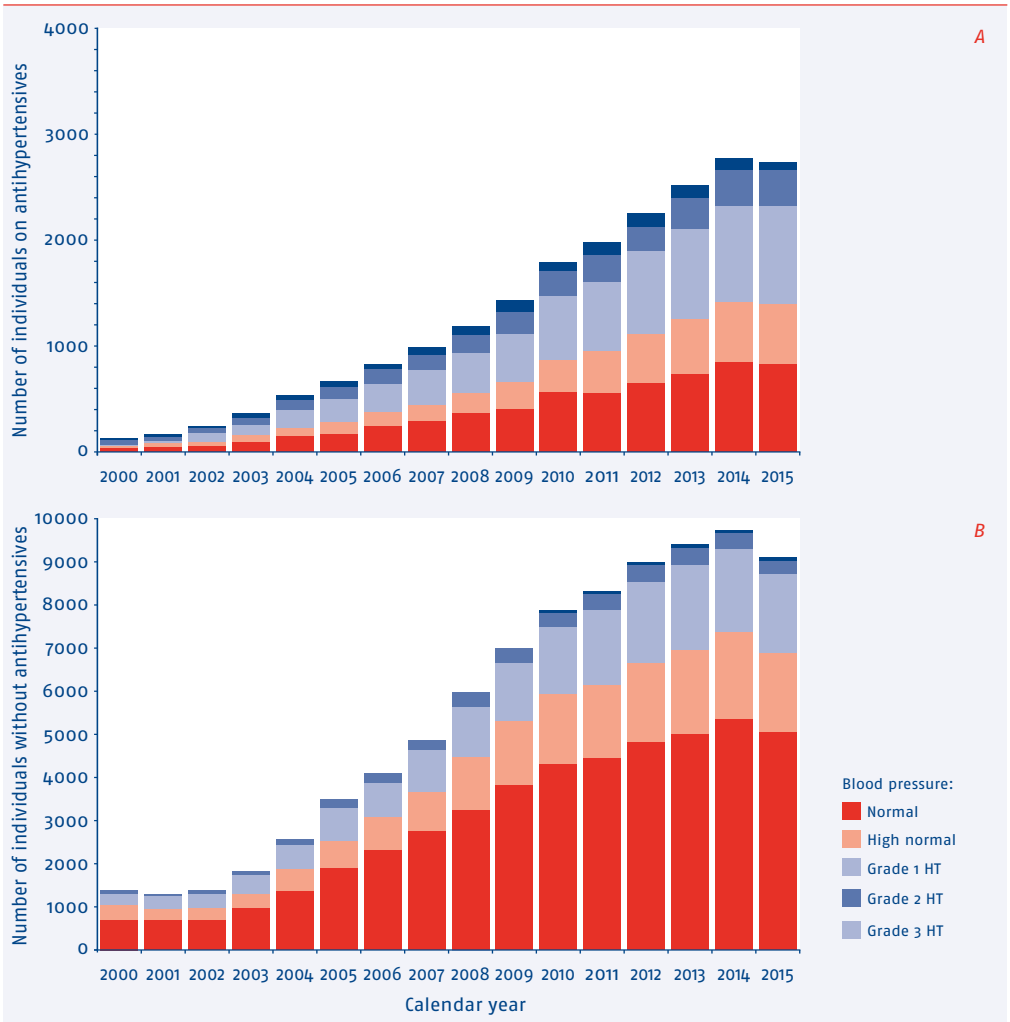
Appendix Figure 3.3: *Absolute number of (A) men and (B) women within body mass index (BMI) categories at the end of each calendar year. For each patient, the last available weight measurement in each year was selected.*



Legend: *BMI=body mass index.*

< Back to page 104

Appendix Figure 3.4: *Absolute number of individuals with graded blood pressure at the end of each calendar year in (A) individuals known to be receiving antihypertensive treatment and (B) those not recorded as being treated for hypertension. 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 [75].*



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.

< Back to page 104

Appendix Table 5.1: *Characteristics of 564 HIV-1 infected children in the Netherlands on combination antiretroviral therapy (cART).*

Characteristic	Vertically infected children			Non-vertically infected children
Age at cART initiation	0-2 years	2-5 years	5-18 years	5-18 years
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)*	1,280 (601-2,150)	623 (388-1,060)	319 (175-445)	290 (177-410)
CD4 z-score at cART initiation*	-0.97 (-1.5 to -0.4)	-1.00 (-1.3 to -0.4)	-0.92 (-1.2 to -0.6)	-0.94 (-1.2 to -0.6)
HIV-1 RNA level at cART initiation (log copies/ml)*	5.8 (5.3-6.2)	5.1 (4.5-5.7)	4.7 (4.3-5.3)	4.7 (3.9-5.3)

**Median (IQR)*

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

< Back to page 163

Acknowledgements

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* denotes site coordinating physician

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HIV nurse consultants: S. Baas, L. Hage de Looff.
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Publications & presentations

The publications and presentations listed below are those available since the publication of the Monitoring Report 2015.

Publications

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, Op de Coul E, Egger M, de Wolf F, Fraser C, Phillips A.
Epidemiology 2015 Sep;26(5):653-60

Health-related quality of life in perinatally HIV-infected children in the Netherlands
Cohen S, Ter Stege JA, Weijsenfeld AM, van der Plas A, Kuijpers TW, Reiss P, Scherpbier HJ, Haverman L, Pajkrt D.
AIDS Care. 2015 Oct;27(10):1279-88

Acute hepatitis C in the Netherlands; characteristics of the epidemic in 2014
Hullegie SJ, van den Berk GE, Leyten EM, Arends JE, Lauw FN, van der Meer JT, Posthouwer D, van Eeden A, Koopmans PP, Richter C, van Kasteren ME, Kroon FP, Bierman WF, Groeneveld PH, Lettinga KD, Soetekouw R, Peters EJ, Verhagen DW, van Sighem AI, Claassen MA, Rijnders BJ.
Clin Microbiol Infect. 2015 Oct 16. pii: S1198-743X(15)00911-8

Bone mineral density and inflammatory and bone biomarkers after darunavir-ritonavir combined with either raltegravir or tenofovir-emtricitabine in antiretroviral-naive adults with HIV-1: a substudy of the NEAT001/ANRS143 randomised trial
Bernardino JI, Mocroft A, Mallon PW, Wallet C, Gerstoft J, Russell C, Reiss P, Katlama C, De Wit S, Richert L, Babiker A, Buño A, Castagna A, Girard PM, Chêne G, Raffi F, Arribas JR; NEAT001/ANRS143 Study Group.
Lancet HIV 2015 Nov;2(11):e464-73

Dispersion of the HIV-1 epidemic in men who have sex with men in the Netherlands: A combined mathematical model and phylogenetic analysis
Bezemer D, Cori A, Ratmann O, van Sighem A, Hermanides HS, Dutilh BE, Gras L, Faria NR, van den Hengel R, Duits AJ, Reiss P, de Wolf F, Fraser A, ATHENA observational cohort.
PLoS Med 2015 12(11):e1001898

Effect of abacavir on sustained virologic response to HCV treatment in HIV/HCV co-infected patients, Cohere in EuroCoord
Hepatitis C working group for COHERE in EuroCoord, Smit C, Arends J, Peters L, Montforte A, Dabis F, Zangerle R, Daikos G, Mussini C, Mallolas J, de Wit S, Zinkernagel A, Cosin J, Chêne G, Raben D, Rockstroh J.
BMC Infect Dis. 2015 Nov 4;15:498

Does rapid HIV disease progression prior to cART hinder optimal CD4+ T-cell recovery once HIV-1 suppression is achieved?
Jarrin I, Pantazis N, Dalmau J, Phillips AN, Olson A, Mussini C, Boufassa F, Costagliola D, Porter K, Blanco J, Del Amo J, Martinez-Picado J for CASCADE Collaboration in EuroCoord.
AIDS 2015 Nov;29(17):2323-33

CD4 cell dynamics in untreated HIV-1 infection: overall rates, and effects of age, viral load, gender and calendar time
Cori A, Pickles M, van Sighem A, Gras L, Bezemer D, Reiss P, Fraser C.
AIDS 2015 Nov;29(18):2435-46

Late presentation for HIV care across Europe: update from the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) from 2010 to 2013
The late presenters working group in COHERE in EuroCoord.
Eurosurveillance 2015 Nov 26;20(47)

Mortality in migrants living with HIV in western Europe (1997–2013): a collaborative cohort study
The Migrants Working Group on behalf of COHERE in EuroCoord.
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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 cell
CD4+ T-lymphocyte, 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 (Centrum Infectieziektebestrijding; www.rivm.nl/cib).

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 public health service *(Geneeskundige en Gezondheidsdienst)*.

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 association for people living with HIV.

HKZ
Foundation for Harmonisation of Healthcare Quality Review *(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 do not 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 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
Person years combines the number of persons and their time contribution (e.g., in years) in a study. In the ATHENA cohort, the person years generally refer to the cumulative number of years that individuals were followed by SHM.

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 *(Rijksinstituut voor Volksgezondheid en Milieu)*.

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.

Sustained virological response (SVR12 or SVR24)
Undetectable hepatitis C virus in blood 12 or 24 weeks after completion of antiviral therapy for chronic hepatitis C virus (HCV) infection.

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.

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

VWS
Dutch Ministry of Health, Welfare and Sport *(Ministerie van Volksgezondheid, Welzijn en Sport)*.

Some of the above definitions were taken from www.aidsinfo.hiv.gov

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