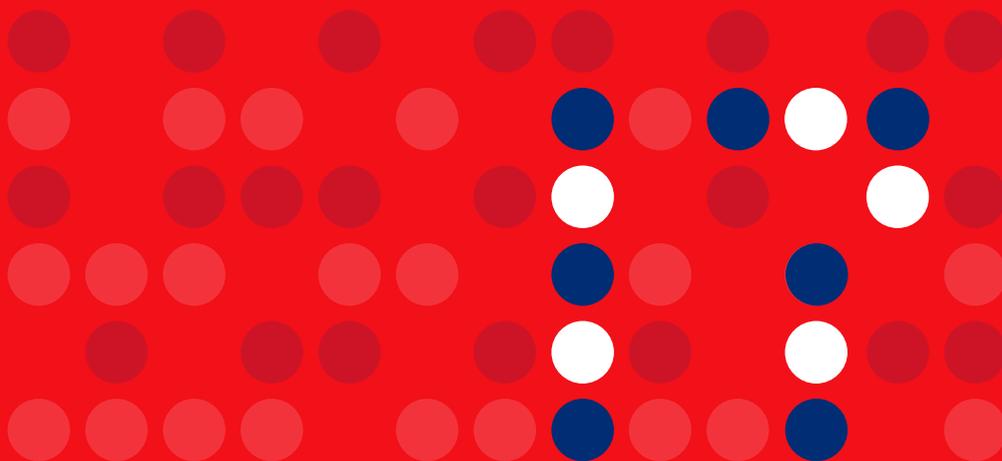


Human immunodeficiency virus (HIV)  
infection in the Netherlands



# HIV Monitoring Report

# 2017







## 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 individuals 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](http://www.hiv-monitoring.nl)

## Acknowledgements

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# Monitoring Report 2017

Human Immunodeficiency Virus (HIV)  
Infection in the Netherlands

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## Interactive PDF user guide

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### Reference numbers

Click on the reference numbers in the text to see the reference details on a web page (which opens in a new window).

### 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 acknowledged 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 2017, 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	DC Klinieken Lairese - HIV Focus Centrum	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	HMC (Haaglanden Medisch Centrum)	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	ETZ (Elisabeth-TweeSteden Ziekenhuis)	Tilburg
25	UMC Utrecht (Universitair Medisch Centrum Utrecht)	Utrecht
26	Isala	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 Kinderziekenhuis	Rotterdam
D	Wilhelmina Kinderziekenhuis (WKZ), UMC Utrecht	Utrecht





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# Introduction

The Monitoring Report 2017 on Human Immunodeficiency Virus (HIV) Infection in the Netherlands is the 16<sup>th</sup> in the series to have been 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 people living with HIV in care in the 26 officially acknowledged HIV treatment centres throughout the country, our work contributes significantly to knowledge of HIV in the Netherlands. 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 also be used by individual treatment centres to support certification as an HIV treatment centre, while at the same time the data provide a nationwide benchmark. Moreover, once research proposals have been approved through appropriate procedures, researchers can access aggregated data from all centres for scientific research purposes. Such 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 population at the time of diagnosis, the effects of combination antiretroviral therapy (cART), trends in cART prescription, the development of resistance to antiretroviral drugs, and morbidity and mortality in the HIV-positive population. In addition, this section contains information on specific populations, including HIV-1-positive 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 direct-acting antivirals (DAAs). The last chapter in this section describes the quality of care in HIV treatment centres in the Netherlands, and centre-specific outcomes will be made available to all treatment centres in the first quarter of 2018. Finally, as in previous years, the Special Reports section includes a chapter on the results from the Amsterdam Cohort Studies and one on HIV in Curaçao.

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.

A handwritten signature in blue ink, appearing to read 'P. Reiss', with a horizontal line underneath.

**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 December 2016

As of December 2016, a total of 19,035 people living with HIV in the Netherlands (18,824 adults and 211 children and adolescents) were known to be in care in one of the 26 adult or 4 paediatric HIV treatment centres. Of these 19,035 adults and children, 97% (18,552) had ever started combination antiretroviral therapy (cART), and 91% (17,280) had suppressed viraemia to below 200 copies/ml at the time of their last available HIV RNA measurement. These results are impressive when compared to figures from some other parts of the world.

### New diagnoses in 2016

In 2016, the majority (67%) of newly-diagnosed infections were in men who have sex with men (MSM), 25% were acquired through heterosexual contact and around 8% through other or unknown modes of transmission. More than a quarter of all newly-diagnosed individuals in 2016 were 50 years or older. Since 2008 there has been a decreasing trend in the annual number of new HIV diagnoses to below 900 new diagnoses in recent years. This decreasing trend continued in 2016, with the caveat that the projected number of diagnoses for that year (816) may have been underestimated as registration of HIV diagnoses for this year has not yet been finalised. Finally, over 95% of persons newly diagnosed with HIV entered 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. Firstly, the proportion of individuals with a previously negative HIV test has increased (71% of MSM, 32% of other men and 40% of women diagnosed in 2016 had a known previous negative test). Moreover, 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 380 and 410 cells/mm<sup>3</sup>, respectively, in 2016.

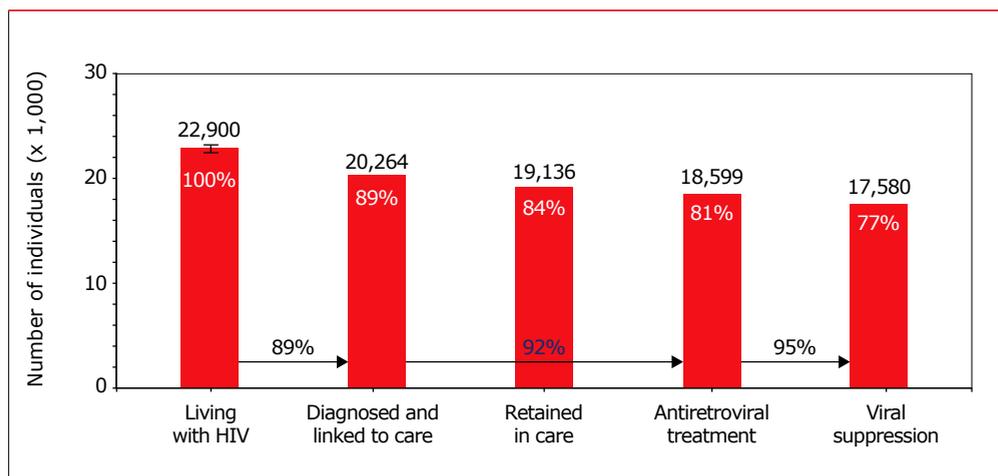
People are increasingly likely to start cART at higher CD4 counts. While in 2015, 87% of individuals with a CD4 count of 500 cells/mm<sup>3</sup> or above had begun cART within 6 months of diagnosis, this proportion rose to 94% in 2016. Nonetheless, far too many individuals continue to present late for care. In 2016, 43% of newly-diagnosed individuals were late presenters, i.e., presenting for care with AIDS or a CD4 count less than 350 cells/mm<sup>3</sup>, and 26% presented with advanced HIV disease, i.e., with a CD4 count less than 200 cells/mm<sup>3</sup> 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 South-East Asia and sub-Saharan Africa, and individuals aged 45 years or older. It is interesting to note that MSM in Amsterdam are now generally being diagnosed earlier in infection than elsewhere in the Netherlands and this may be an early indicator of the effectiveness of Amsterdam's H-TEAM collaboration.

### Continuum of HIV care in 2016

By the end of 2016, 22,900 individuals were estimated to be living with HIV in the Netherlands, of whom 2,600 were still undiagnosed (*Figure 1*). In total, 20,264 individuals, or 89% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM, while 19,136 individuals were considered to still be in care. The majority of these individuals, 18,599 in total, had started cART, and 17,580 had a most recent HIV RNA measurement below 200 copies/ml, irrespective of treatment. Overall, 77% of the total estimated population living with HIV and 87% 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 2016.*



A re-assessment of the continuum of HIV care for 2015, based on the most recent data available in May 2017, showed that there was a significant increase in the number of people on cART by the end of 2015 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 the 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 more rapidly 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. These strategies, for which the H-TEAM collaboration in Amsterdam may serve as an example, should aim to simultaneously reduce the likelihood of HIV infection in key populations at risk, identify HIV-positive individuals early, rapidly link all these people to care, and immediately offer them the possibility of starting combination antiretroviral therapy.*

## Combination antiretroviral therapy in adults

### Starting cART & the initial regimen in 2011–2016

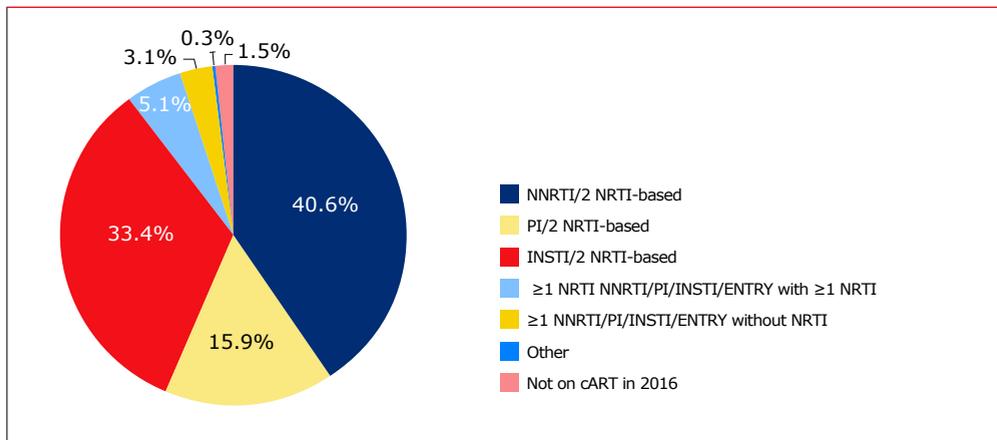
The rapid initiation of cART following a diagnosis of HIV infection, irrespective of CD4 cell count, continued to increase over time. In 2016, the majority of individuals initiating cART did so within a month after diagnosis and at a median CD4 cell count of 410 cells/mm<sup>3</sup>. Three-quarters of people started on an integrase inhibitor-containing regimen in 2016, with abacavir/lamivudine/dolutegravir and tenofovir alafenamide/emtricitabine/cobicistat-boosted elvitegravir being the most frequently prescribed initial regimens in 2016.

As in previous years, intolerance continued to be the main reason for discontinuation and regimen switches of the initial regimen during the first year of treatment. Toxicity-related discontinuations were often central nervous system-related, gastrointestinal, hepatic, or a medication-associated skin rash. Other more recent important reasons for discontinuation or regimen switch during the first year of treatment include simplification or the availability of new drugs. Nonetheless, the time spent on the initial cART regimen has continued to increase over the years.

### HIV-positive people in care and receiving cART in 2016

Among all treated HIV-positive individuals in care in 2016, the majority received a cART regimen based on two nucleoside reverse transcriptase inhibitors (NRTIs), combined with a non-NRTI (NNRTI, 41%), an integrase inhibitor (33%) or a protease inhibitor (16%) (Figure 2). The most common regimens prescribed in 2016 were abacavir/lamivudine/dolutegravir (15%) and tenofovir disoproxil fumarate/emtricitabine combined with efavirenz (15%) or nevirapine (11%).

Figure 2: Combination antiretroviral therapy (cART) use in 2016 among HIV-positive individuals who ever started cART.



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

Since its introduction in recent years, integrase inhibitor-based cART has been implemented on a large scale in the Netherlands: in 2016, 39% of all adults in care and on cART received an integrase inhibitor, compared to 27% in 2015. While two-thirds of the population on cART in 2016 received a backbone consisting of tenofovir disoproxil fumarate/emtricitabine, the availability of new fixed-dose combinations has led to an increase in the use of abacavir/lamivudine and tenofovir alafenamide/emtricitabine.

### Virological response & HIV drug resistance

Both short-term and long-term viral suppression rates remain high and continue to improve. Of all HIV-positive people on cART in 2016, 97% had an undetectable viral load (<200 copies/ml). Those who had been diagnosed with HIV before 1990 and remained in care and on cART in 2016 (i.e., long-term survivors) had equally high levels of viral suppression.

The proportion of people with acquired drug resistance among those who experience virological failure remains low and continues to decline over time. The occurrence of transmitted HIV drug resistance was rare, and the overall prevalence remains low and stable over time. Acquired integrase inhibitor resistance currently remains rare and limited to individuals with extensive prior treatment. To date, transmitted integrase inhibitor resistance has not been observed.

*Following revised HIV treatment guidelines, prompt cART initiation after entry into care has continued to become more common in 2016. In recent years, the introduction of new integrase inhibitor-based once-daily fixed-dose combinations has changed the landscape of cART use in the Netherlands. All currently-recommended regimens are more durable and effective.*

## Quality of care

As to be expected, there was some degree of variation in a number of different quality of care indicators across the 26 adult HIV treatment centres. Overall, retention in care was high, although it was lower for patients from non-Dutch origin. Across most 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 everyone with newly-diagnosed HIV regardless of CD4 count. However, it is important to note that there are some centres in which this policy could be improved further for those individuals who enter care with CD4 cell counts above 350 cells/mm<sup>3</sup>. Finally, viral suppression rates in the first 6 months on cART, as well as during longer term use of cART, were high across all HIV treatment centres in the Netherlands, regardless of centre size.

## Variation in HCV screening

More substantial variation was observed in repeat HCV screening in MSM. To some extent, this may be explained by centres applying a policy of targeted screening, guided by the presence of incident transaminase elevations. This notion is supported by the observation that 90% of MSM not screened for HCV did not have elevated transaminase levels. Furthermore, differences in the MSM population with respect to known risk-taking behaviour for HCV acquisition might also contribute to the inter-centre variation in HCV screening. 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 is certainly 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, the number and proportion of individuals dying of AIDS (15% of the total number of deaths in the period 2014-2016) continues to decrease. Deaths from AIDS are largely driven by late presentation and late entry into care, which once again stresses the importance of identifying and linking individuals to care earlier in the course of the infection.

### **Older age and comorbidities**

As expected, 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 2016, 27% were 50 years or older. At the same time, the overall patient population with HIV in care in the Netherlands continues to age, with 46% currently older than 50 years (45% in 2015, 42% in 2014, and 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<sub>HIV</sub> 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 2000-2016. 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 antiplatelet 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 number of deaths due to these malignancies have 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, as well as expanded screening and treatment for early (pre-malignant) stages of anal cancer, together with a higher proportion of individuals living with higher CD4 cell counts in more recent years. The most common non-AIDS malignancies are lung, anal, gastrointestinal, head and neck cancers, Hodgkin's lymphoma, and prostate cancer.

*Awareness of the role of modifiable, often lifestyle-related risk factors, like 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 a priori risk of comorbidity, 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 C (HCV) and hepatitis B (HBV) co-infection has become part of the standard of HIV care in the Netherlands. By 2016, screening for HCV and HBV had become universal and, as a result, the presence or absence of HBV or HCV infection is now documented for virtually all HIV-positive individuals. Approximately, 12% of individuals had evidence of ever having been exposed to HCV, 6% were documented as being chronically infected with HCV, and 2% were documented as having an acute HCV infection. 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.

Seven percent of individuals were found to have chronic HBV infection. The prevalence of HBV has decreased over time as a result of increased HBV vaccination rates, together with the HBV prophylactic effect of tenofovir disoproxil fumarate/tenofovir alafenamide in cART-treated individuals.

*An estimated 30% of HIV-positive individuals overall and 18% 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.*

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

## 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 750 individuals have received, or are currently receiving, treatment with novel DAAs. Of note, 97% of all individuals treated with DAAs achieved a sustained virological response and 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 (225 as of May 2017 versus 499 as of August 2016), in spite of an increase in the total number of individuals who have ever had HCV co-infection and are currently retained in care (1,439 as of May 2017 versus 1,420 as of August 2016).

Successful treatment of HCV may also prevent onward HCV transmission, which is possibly reflected in a lower number of acute HCV infections in the past year and a rapid reduction in the prevalence of an active HCV infection, with prevalence in MSM declining to less than 1.5% in 2016. However, ongoing transmission of HCV remains, as is apparent from the observation that HCV re-infection still occurs after successful treatment. Nonetheless, the rate of re-infection has declined in the most recent years.

*The rapidly expanding availability of DAA regimens for HCV, together with optimised screening for HCV co-infection with time will probably limit the impact of HCV co-infection on long-term liver-related morbidity and mortality, but needs to be monitored. 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

The absolute number of pregnancies in women living with HIV in the Netherlands has declined over time. The proportion of women with undetectable viraemia on cART at the time of delivery, the most important factor in preventing vertical transmission of HIV, has increased considerably and is now close to 100%. Together with universal first trimester screening for HIV in pregnant women, this has made perinatal transmission of HIV extremely rare in the Netherlands.

*To ensure zero vertical transmissions of HIV, there is a need for continued vigilance for new HIV infections during pregnancy.*

### Children

Of the 590 children diagnosed with HIV before the age of 18 years and ever registered by SHM, the majority are still in care and, of those currently in care, 57% have reached adulthood and have transitioned into adult care. However, at the time of transitioning into adult care, 30% of the children did not have suppressed viraemia.

A substantial proportion of the children newly-registered since 2010 are children who have been adopted by Dutch parents. Outcomes for cART-treated children living with HIV in the Netherlands are generally favourable in terms of a low observed mortality rate and long-term immunological responses to treatment.

The continuum of care shows a high retention in care rate for children currently aged less than 18 years. However, the lost-to-follow-up rate is high in young people aged 18 years or older who have non-vertically-acquired HIV-1. Moreover, young people over 18 years were also less likely to have an undetectable viral load at their most recent clinic visit.

*The large number of children who have inadequately-suppressed viraemia at the time of transitioning 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.*

### 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 individuals presenting late for care. As a consequence, combination antiretroviral therapy is being started at increasingly higher CD4 cell counts. However, although early start of treatment appears to be possible, long-term continuous follow up should be guaranteed to optimise the effect of treatment.

## The Amsterdam Cohort Studies

The Amsterdam Cohort Studies (ACS) on HIV infection and AIDS started in 1984 as a prospective cohort study of men who have sex with men (MSM). 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.

As of 31 December 2016, 2,736 MSM had ever been included in the ACS, of whom 607 were HIV-positive when they entered the study and 251 seroconverted during follow up. In 2016, 630 HIV-negative and 64 HIV-positive MSM were in active follow up within the ACS. Three MSM seroconverted for HIV in 2016, and the observed HIV incidence among MSM remained relatively stable at around 0.5 per 100 person years. As of 31 December 2016, 1,680 PWUD had ever been included in the ACS, 323 of whom were HIV-positive at entry and 99 seroconverted during follow up; the last seroconversion was seen in 2012. Follow up of the cohort of PWUD ended in 2016.

Highlights in 2016 within the ACS research programme include an investigation into the role of IP10 as a marker of HIV-1 disease progression, as well as a study of monoclonal antibodies from an elite neutralizer from the ACS that could offer opportunities for HIV vaccine design. In terms of viral hepatitis, one project used blood plasma samples from HBsAg-positive MSM to trace the origin of the HBV-G variation in Amsterdam, while a second study examined the cost-effectiveness of HCV treatment among people who use injecting drugs (PWID), concluding that HCV treatment with DAA-containing regimens is highly cost-effective in PWID.

# Monitoring programme report

## 1. The HIV epidemic in the Netherlands

Ard van Sighem and Eline Op de Coul

### Introduction

As of May 2017, 26,409 HIV-positive individuals had ever been registered by Stichting HIV Monitoring (SHM). Of those, 25,355 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 263,600 person years. The remaining 1,054 were followed in the St. Elisabeth Hospital in Willemstad, Curaçao (see *Chapter 9*). Of the 25,355 patients, the majority were infected with HIV-1 (25,092; 99%). A small group of patients, 97 in total, were infected with HIV-2, while 60 patients had antibodies against both HIV-1 and HIV-2. Serological results were not yet available in the SHM database for 106 recently-registered individuals.

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

**Box 1.1: Definitions of infection, diagnosis, entry into care, and registration**

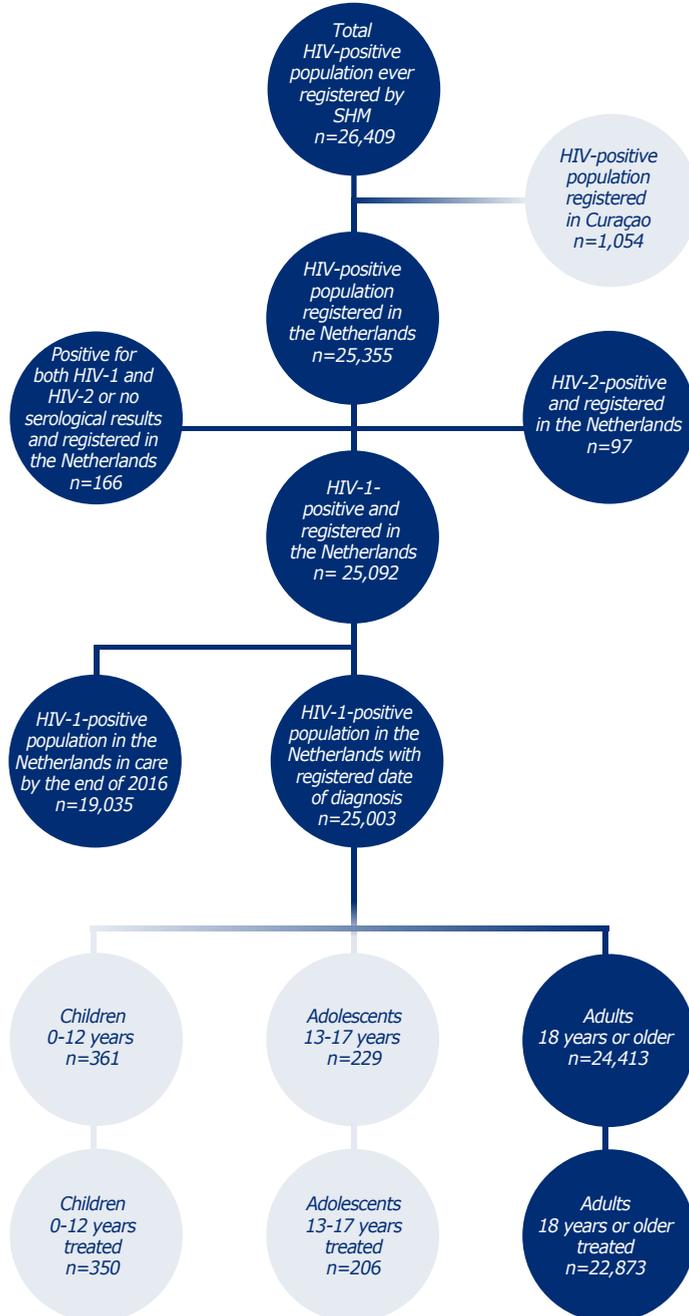
<b>Infection</b>	The moment an individual acquires an HIV infection. The time of infection is often unknown.
<b>Diagnosis</b>	The moment an individual is newly diagnosed with an HIV infection. The time of diagnosis can be weeks, months, or years after infection.
<b>Entry into care</b>	The moment an HIV-positive individual is first seen for care in an HIV treatment centre, which usually is within a few weeks of HIV diagnosis.
<b>Registration</b>	The moment an HIV-positive individual in care is notified to SHM by their treating HIV physician or nurse and registered in the SHM database. Registration is usually within a few months of entering care, but can take longer. Collection of demographic and clinical data from the time of HIV diagnosis can only be done after an HIV-positive individual is registered with SHM.

## Population – HIV-1

### HIV-1-positive individuals

Altogether, 24,413 individuals were ever diagnosed with HIV-1 as adults and had a recorded date of diagnosis (*Figure 1.1*). The majority of these people were men who have sex with men (MSM; 14,652 [60%]), while 3,353 other men (14%) and 4,019 (16%) women reportedly acquired their HIV infection via heterosexual contact (*Appendix Table 1.1*). For 759 (3%) individuals, the reported mode of transmission was injecting drug use, while for 292 (1%) individuals infection occurred through exposure to contaminated blood. Other and unknown modes of transmission accounted for the remaining 5% (1,338) of infections.

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

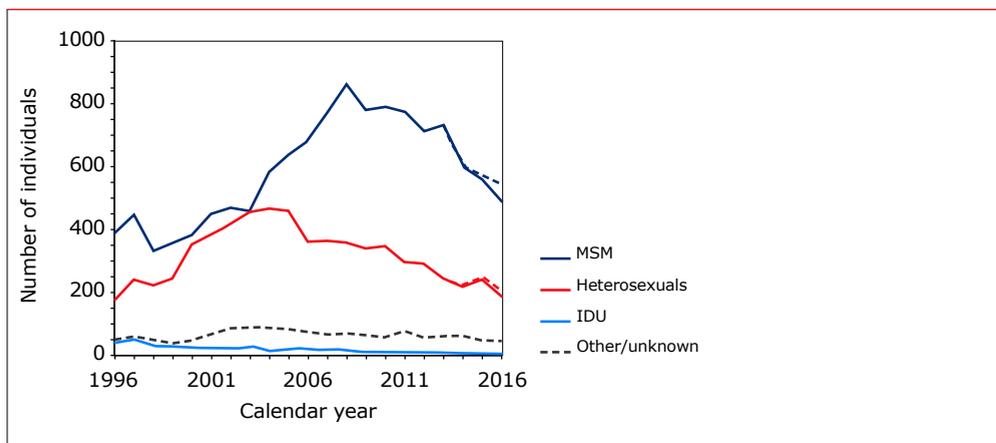


### Decreasing number of diagnoses

From the 1990s until 2008, the annual number of new diagnoses among MSM increased from approximately 400 to well above 800 (Figure 1.2). However, from 2009 onwards, the registered number of new diagnoses has steadily declined. In 2016, the decreasing trend has continued and the projected number of new HIV diagnoses in MSM, taking into account a backlog<sup>A</sup> in registration of HIV cases, was approximately 545. A similar decreasing trend in HIV diagnoses was observed in STI clinics<sup>1</sup>.

In the heterosexual population, the number of new diagnoses has declined to between 200 and 250 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 now rarely reported as the most probable mode of transmission, which reflects the decreasing popularity of injecting drugs.

*Figure 1.2: Annual number of new HIV-1 diagnoses among adults, according to most likely mode of transmission. In 2016, men who have sex with men (MSM) accounted for 68% of new diagnoses, infections via heterosexual contact for 26%, 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 dotted lines indicate the projected number of diagnoses when the backlog in registration of HIV cases (3% in 2015, 11% in 2016) is taken into account.*



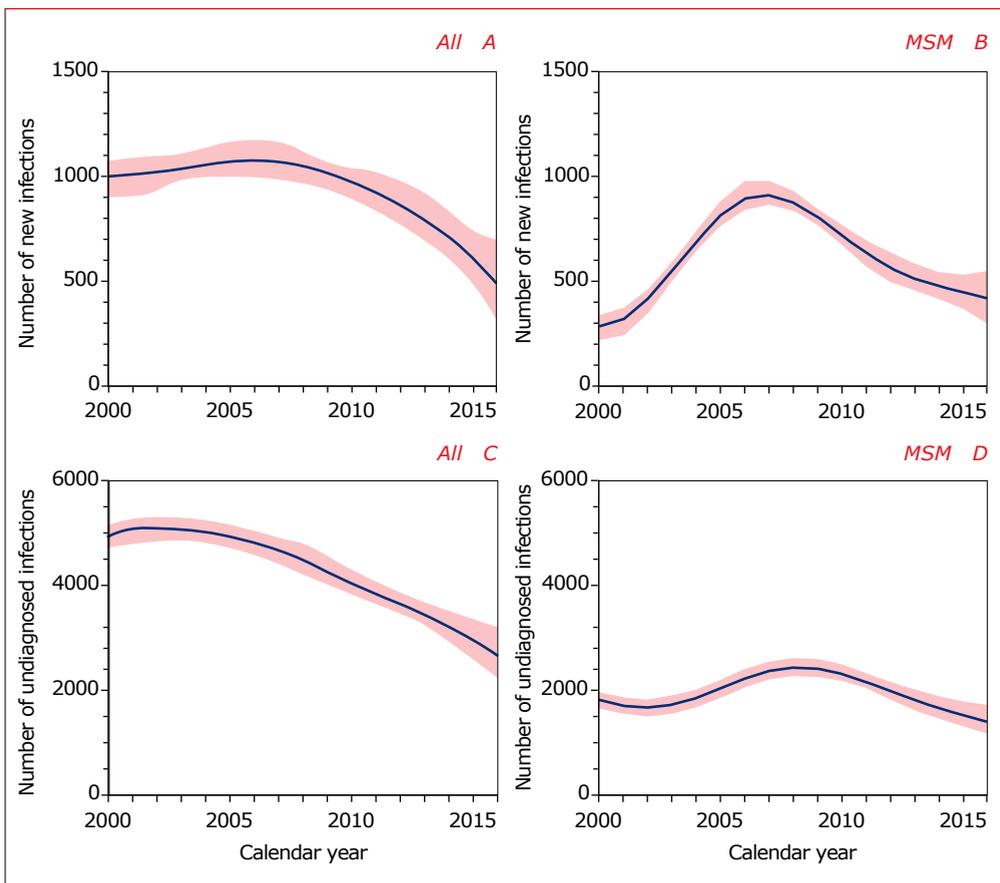
*Legend: MSM=men who have sex with men; IDU=injecting drug users.*

<sup>A</sup> As it may take some time before people living with HIV are registered in the SHM database by their treating physician, there is some backlog for the most recent calendar years. Based on past trends, this backlog is estimated to be 3% in 2015 and 11% in 2016.

### 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 the European Centre for Disease Prevention and Control (ECDC) HIV Modelling Tool, there were approximately 1,000 new HIV infections each year between 2000 and 2010<sup>2</sup>. Thereafter, the number of new infections decreased to 500 (95% CI, 300-700) in 2016 (Figure 1.3A). In MSM, the annual number of new HIV infections reached a peak of approximately 900 around 2007 and then decreased to approximately 400 (95% CI, 300-550) in 2016 (Figure 1.3B). From 2000 onwards, the number of people estimated to be living with undiagnosed HIV has decreased, although this decrease was less pronounced among MSM (Figure 1.3C and 1.3D).

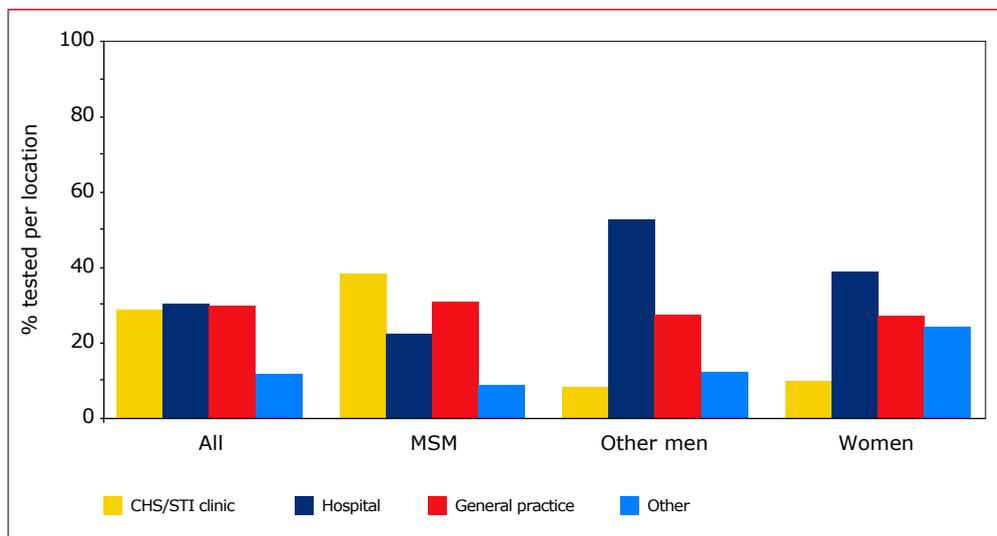
Figure 1.3: Estimated annual number of newly-acquired HIV infections and number of people living with undiagnosed HIV (A, C) in the entire HIV-positive population in the Netherlands and (B, D) in men who have sex with men.



### Testing location

Information on the location of HIV testing was available for 96% of people diagnosed in 2008 or later. Overall, 29% of these individuals received their first HIV-positive test result at a community health service or STI clinic, 30% at a hospital, and 30% at a general practice (*Figure 1.4*). Among those tested at community health services or STI clinics, 90% were MSM, 5% were other men, and 5% were women. These numbers are comparable to those directly reported by STI clinics in 2016: 93% MSM, 4% heterosexual men, and 4% women<sup>1</sup>.

*Figure 1.4: Proportion of individuals 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.*

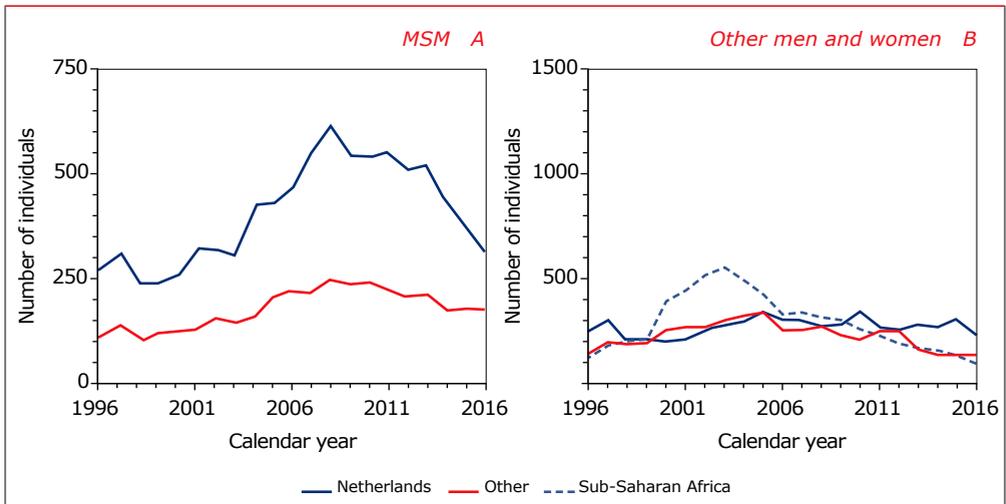
### Geographical region of origin

In total, 70% 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 68% (*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 33% originated from sub-Saharan Africa, 8% from South America, 5% from the Caribbean, and 4% from South and South-East Asia (*Figure 1.5B*). However, the number of new

diagnoses among sub-Saharan Africans dropped sharply after 2003, probably partly as a result of stricter immigration laws that came into effect in the Netherlands around that time. From 2014 onwards, 50% of the diagnosed individuals were of Dutch origin, and 24% 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 14,652 MSM, 10,279 (70%) originated from the Netherlands, 1,576 (11%) from other European countries, 985 (7%) from South America, and 533 (4%) from the Caribbean. Among the other 9,761 patients, 3,260 (33%) originated from sub-Saharan Africa, 3,626 (37%) from the Netherlands, 829 (8%) from South America, 448 (5%) from the Caribbean, and 400 (4%) from South and South-East Asia. Note: data collection for 2015 and 2016 has not yet been finalised.*



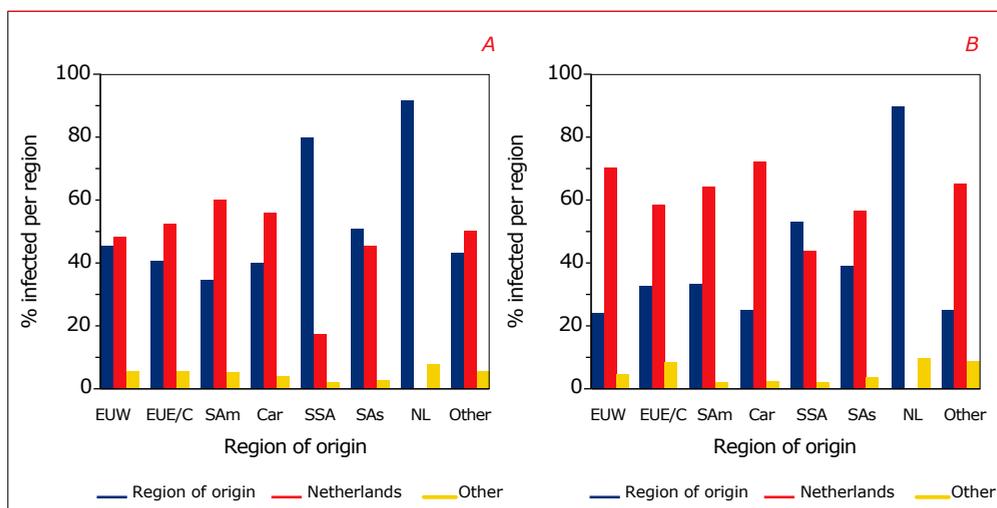
*Legend: MSM=men who have sex with men.*

Overall, 21% of those people newly diagnosed since 2014 were living in the Amsterdam community health service (CHS) region and 13% in the Rotterdam-Rijnmond CHS region. These proportions were 16% and 13%, respectively, for people of Dutch origin and 30% and 15%, respectively, for people originating from other countries. Among MSM, 24% were living in Amsterdam and 14% in Rotterdam, while in other groups these proportions were 16% and 13%. Other CHS regions with at least 4% of new diagnoses were Haaglanden (8%, including Den Haag), Utrecht (6%), 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 17,850 (73%) of the diagnosed adult population. The majority of the people born in the Netherlands (92%) reported having been infected in the Netherlands (*Figure 1.6A*). Most of those born in sub-Saharan Africa reported to likely have been infected in their region of origin (80%), and 17% to probably have been infected in the Netherlands. The majority of individuals from other regions, except those from South and South-East Asia, reported having been infected in the Netherlands. Overall, 41% of foreign-born individuals reported having acquired their HIV infection in the Netherlands. This proportion was 60% among those diagnosed in 2014 or later (*Figure 1.6B*).

*Figure 1.6: Proportion of (A) all HIV-1-positive adults and (B) adults diagnosed in 2014 or later per region of origin who 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; SA=South America; Car=Caribbean; SSA=sub-Saharan Africa; SAs=South and South-East Asia; NL=the Netherlands; Other=other regions of origin.*

As may be expected from the heterogeneity in geographic region of origin, there were also major differences in the regions of infection between the major transmission groups. The majority of MSM (86%) were infected in the Netherlands. Of the other 6,746 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 1,747 Dutch men who reported a country of infection and were not infected via homosexual contact, 80% were infected

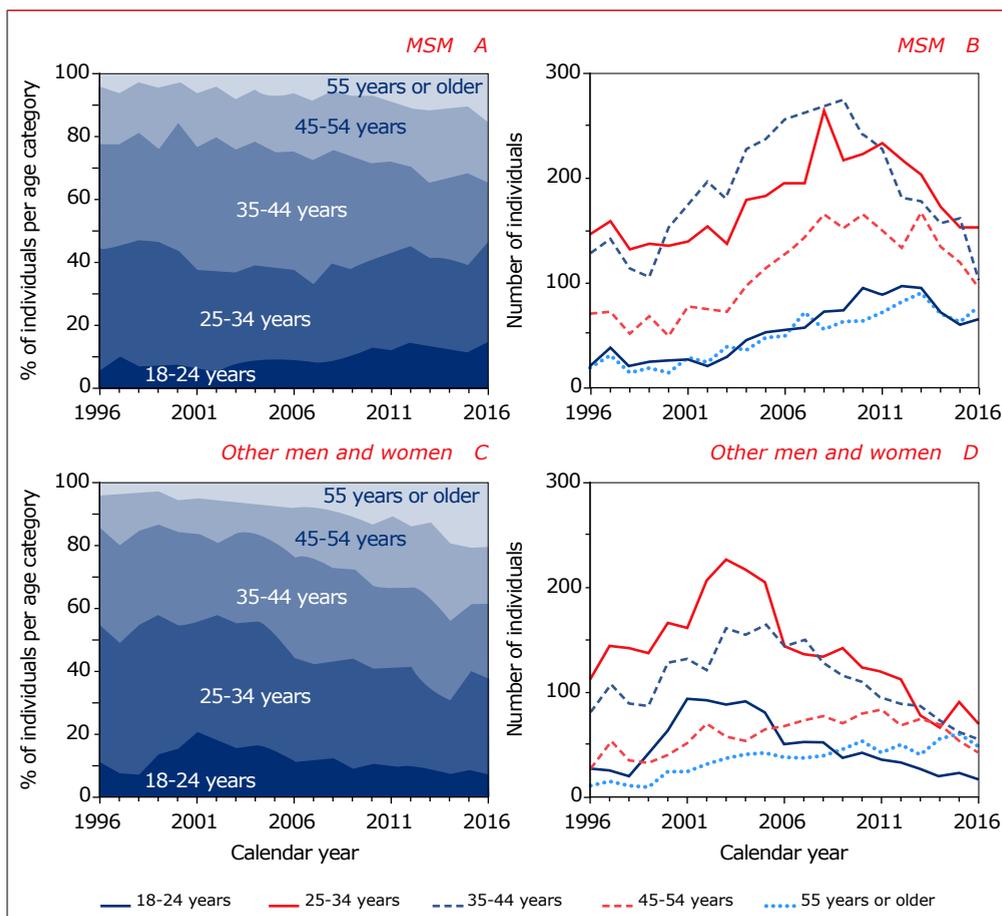
in the Netherlands, 8% in South and South-East Asia, and 7% in sub-Saharan Africa. Of the 1,075 Dutch women, 88% reported having been infected in the Netherlands and 7% in sub-Saharan Africa, whereas less than 1% had been infected in South and South-East Asia.

### **Increasingly older age at time of HIV diagnosis**

The age at which individuals 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] 30-42) years; in 2016, it was 38 (IQR 30-51) years. Over the entire period from 1996 through 2016, 16% of adults who received a diagnosis of HIV were 50 years or older; in 2016, 27% were 50 years or older. There were considerable age differences between MSM, other men and women diagnosed in 2014 or later. MSM born in the Netherlands were diagnosed at a median age of 41 (32-51) years, while those of foreign origin were diagnosed at 32 (27-41) years. Among other patients of Dutch origin, the median age at the time of diagnosis was 45 (30-57) years for women and 46 (34-59) years for men. Patients born in sub-Saharan Africa (women: 36 years; men: 38 years) or elsewhere (women: 36 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 individuals there were no notable changes up to 2003 (*Figure 1.7*). Thereafter, the age of other individuals at diagnosis started to increase concomitantly with the decreasing number of diagnoses among individuals from sub-Saharan Africa, who were generally younger than those of Dutch or other origin.

**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 2016, the proportion of MSM aged 45 years or older at the time of diagnosis increased from 23% to 35%, while these proportions were 15% and 39% for other individuals. During the same period, the proportion of individuals between 25 and 34 years of age decreased from 38% to 31% for MSM and from 43% to 30% for other patients.**



### 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 2016, or to 7% 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 2012, young adults accounted for 14% (97) of the diagnoses. Thereafter, the proportion of diagnoses among young adults remained around this level, although the absolute number has decreased.

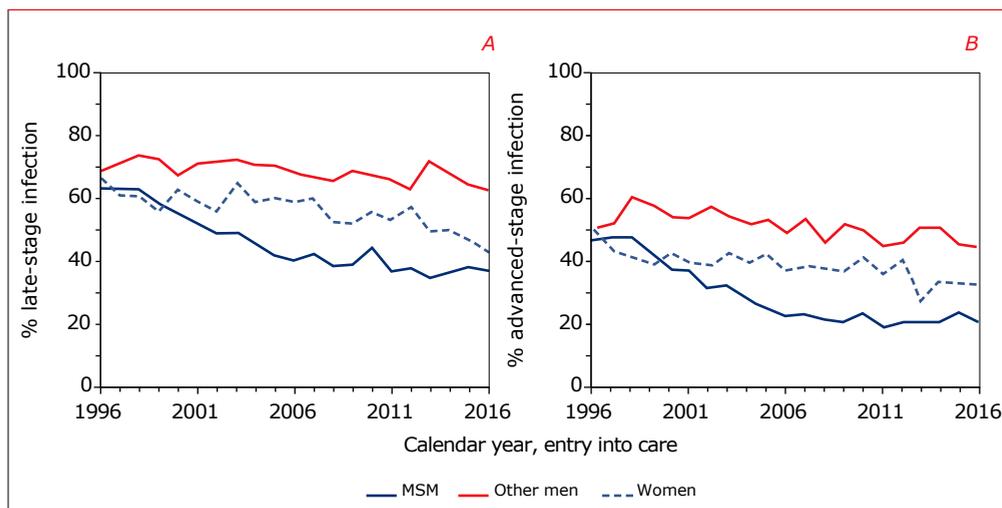
### Entry into care

Of all individuals diagnosed with HIV in 2014 or later for whom the location of testing was known, excluding those diagnosed abroad, 92% had entered care within 4 weeks of receiving their diagnosis and 97% within 6 weeks. The proportion in care within 6 weeks was 97% for individuals who received their first HIV-positive test at a CHS or STI clinic, as well as for those who tested HIV-positive in a hospital and for those diagnosed at a general practice, while the proportion was slightly lower (93%) for those diagnosed at other locations. Overall, the proportion in care within 6 weeks was similar for MSM (97%), other men (96%), and women (96%), and did not differ by age at the time of diagnosis.

### Late presentation

Overall, 52% of the individuals were late presenters, i.e., presenting for care with either a CD4 count below 350 cells/mm<sup>3</sup> or an AIDS-defining event regardless of CD4 count<sup>3</sup>. Although the proportion of late presenters has decreased over time, in 2016, 43% of people entered clinical care late in their infection (*Figure 1.8; Appendix Figure 1.1*). In addition, the proportion of individuals presenting for care with advanced HIV disease, i.e., with a CD4 count below 200 cells/mm<sup>3</sup> or AIDS, has decreased over time and was 26% in 2016.

**Figure 1.8:** Proportion of individuals classified as presenting with (A) late-stage or (B) advanced-stage HIV infection at the time of entry into care. From 1996 (2014) onwards, 52% (44%) presented with late-stage HIV infection: men who have sex with men (MSM) 44% (37%), other men 69% (65%), and women 57% (47%). Overall, 33% (26%) presented with advanced-stage HIV infection: MSM 26% (20%), other men 51% (46%), and women 38% (32%). Late-stage HIV infection: CD4 counts below 350 cells/mm<sup>3</sup> or having AIDS, regardless of CD4 count. Advanced-stage HIV infection: CD4 counts below 200 cells/mm<sup>3</sup> or having AIDS.



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

In total, 29% of the individuals entering care from 1996 onwards had CD4 counts of 500 cells/mm<sup>3</sup> or higher, 20% had CD4 counts between 350 and 499 cells/mm<sup>3</sup>, 20% had CD4 counts between 200 and 349 cells/mm<sup>3</sup>, and 30% had CD4 counts below 200 cells/mm<sup>3</sup>, while 16% had already been diagnosed with AIDS. For patients entering clinical care in recent years (2014 or later), these proportions were 35%, 21%, 19%, and 25%, respectively; 12% had already been diagnosed with AIDS.

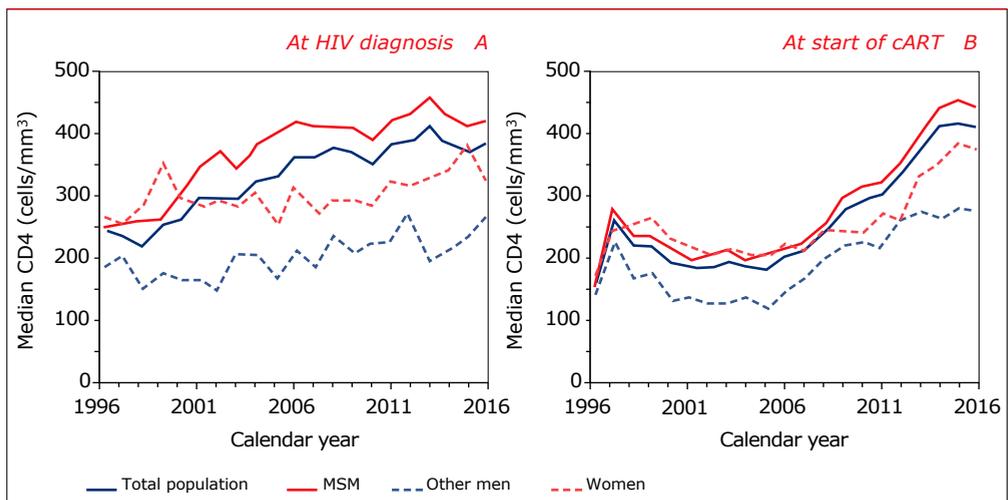
Among individuals entering clinical care in 2014 or later, 37% of MSM, 65% of other men, and 47% of women were late presenters. People of sub-Saharan African origin and not infected via homosexual contact were more likely to be late presenters (60%) than their peers of Dutch origin (57%). Late presentation at the time of entry into care was also often found in non-MSM patients originating from South America (57%) or from South and South-East Asia (69%). In this latter group, 58% presented for care with advanced HIV infection, compared to 36% of South Americans, 38% of sub-Saharan Africans, and 43% of Dutch patients.

Late presentation was also more common in individuals entering care at older ages. Late presentation was seen in 49% of MSM, 70% of other men, and 57% of women entering care in 2014 or later at 45 years of age or older, compared with 21% of MSM, 50% of other men, and 23% 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 presentation was also observed more often in people who received their HIV diagnosis at a hospital (72%) compared with those who were tested at a general practice (43%), a CHS or STI clinic (33%), or another testing location (36%).

### Earlier diagnosis

Between 1996 and 2016, median CD4 counts in the total adult population at the time of diagnosis increased from 240 to 380 cells/mm<sup>3</sup> (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.

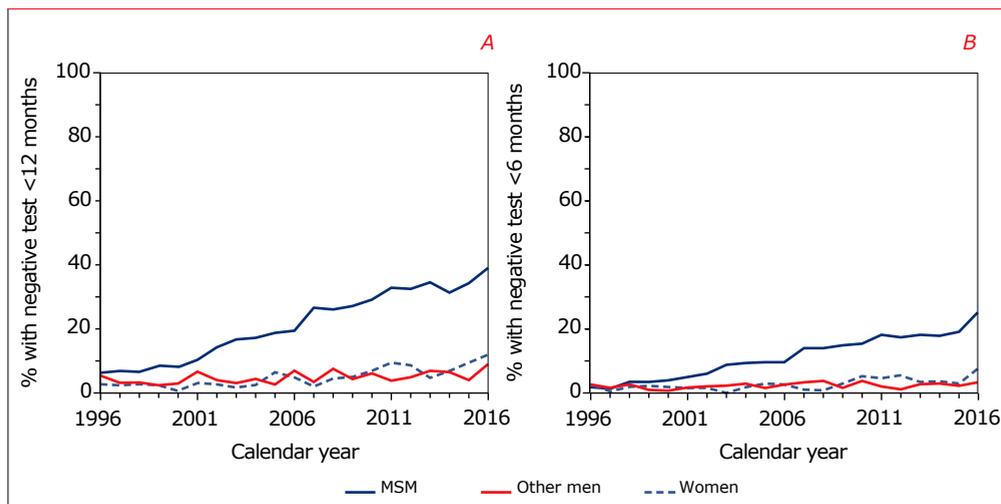
*Figure 1.9: Changes over calendar time in median CD4 counts (A) at HIV diagnosis and (B) at the start of combination antiretroviral therapy (cART). Between 1996 and 2016, CD4 counts at the time of diagnosis increased from 240 (interquartile range [IQR], 80–420) to 380 (IQR, 190–566) cells/mm<sup>3</sup> in the total adult population. The increase was most apparent for men who have sex with men (MSM): 240 (IQR, 80–420) cells/mm<sup>3</sup> in 1996 and 420 (IQR, 250–590) cells/mm<sup>3</sup> in 2016. During the same period, CD4 counts in other men increased from 180 (IQR, 40–400) to 263 (IQR, 90–420) cells/mm<sup>3</sup>, whereas CD4 counts in women increased from 260 (IQR, 94–450) to 320 (IQR, 88–540) cells/mm<sup>3</sup>. (B) In the total adult population, CD4 counts at the start of cART rose to 260 (IQR, 130–396) cells/mm<sup>3</sup> shortly after cART became available, decreased to a plateau of approximately 180 cells/mm<sup>3</sup> between 2000 and 2005, and increased thereafter. In 2016, CD4 counts were 410 (IQR, 230–590) cells/mm<sup>3</sup> in the total population, 450 (IQR, 290–600) cells/mm<sup>3</sup> in MSM, 270 (IQR, 130–500) cells/mm<sup>3</sup> in other men, and 370 (IQR, 110–540) cells/mm<sup>3</sup> in women.*



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

The increase in CD4 counts at diagnosis, in conjunction with a decreasing proportion of late presenters, suggests that, on average, people are being diagnosed increasingly earlier in the course of their HIV infection. Another indication of earlier diagnosis is the increase in the proportion of individuals who were diagnosed with strong evidence of a recent infection, based on a known negative HIV test 6 or 12 months, at most, before their first positive test (Figure 1.10). Among MSM diagnosed between 2010 and 2015, 33% had a negative test in the 12 months before diagnosis, while 18% had a negative test in the 6 months before diagnosis; in 2016, these proportions were 39% and 26%, respectively (see also Box 1.2 *HIV Transmission Elimination Amsterdam*). For other men and for women, the proportions with a recent infection between 2010 and 2015 and in 2016 were considerably lower: only 6% (10%) had a negative test in the 12 months before diagnosis, while 4% (5%) had a negative test in the 6 months before diagnosis.

Figure 1.10: Proportion of people 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, 39% of men who have sex with men (MSM), 9% of other men, and 12% of women diagnosed in 2016 had a last negative test at most 12 months before diagnosis, whereas 26% of MSM, 4% of other men, and 8% of women had a last negative test at most 6 months before diagnosis.

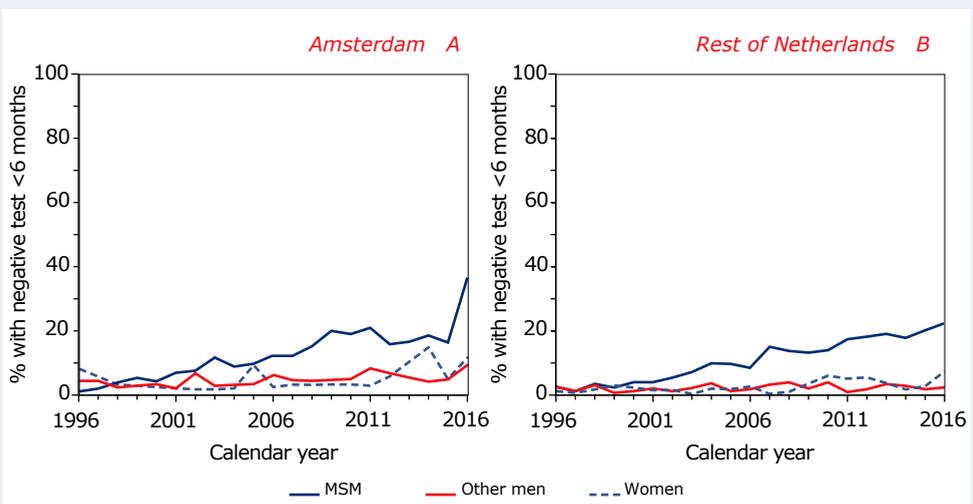


Legend: MSM=men who have sex with men.

**Box 1.2: HIV Transmission Elimination AMsterdam (H-TEAM)**

SHM is one of the participants in the HIV Transmission Elimination AMsterdam (H-TEAM) initiative. H-TEAM is a unique collaboration between all relevant stakeholders involved in the prevention and care concerning HIV in Amsterdam, and was initiated in 2014 ([www.hteam.nl](http://www.hteam.nl)). The objectives of H-TEAM include reducing the proportion of people living with undiagnosed HIV infection and increasing the number of early detected infections by raising awareness of acute HIV infection among MSM. Interestingly, the proportion of MSM with a negative test in the 6 months before diagnosis (indicative of a recent infection) increased from 18% between 2010 and 2015 to 36% in 2016 in Amsterdam, while the increase was more modest (from 18% to 22%) in the rest of the Netherlands (See Figure). In addition, both in Amsterdam and in the rest of the Netherlands, the proportion of MSM with a CD4 count of 350 cells/mm<sup>3</sup> or above at the time of diagnosis was 62% between 2010 and 2015, whereas in 2016 this proportion was 77% in Amsterdam and 58% outside Amsterdam. This increase in the proportion of individuals diagnosed at relatively high CD4 counts is another indication of a more recent infection. For other men and for women, the proportions with a negative test in the 6 months before diagnosis were below 10%, both in Amsterdam and in the rest of the country, while the proportion diagnosed with 350 CD4 cells/mm<sup>3</sup> or more was 40% between 2010 and 2015 as well as in 2016. Although these findings that MSM in Amsterdam are now being diagnosed earlier in their HIV infection compared to MSM in the rest of the country need to be interpreted with caution, they might be an early indicator of the effectiveness of H-TEAM's combined efforts.

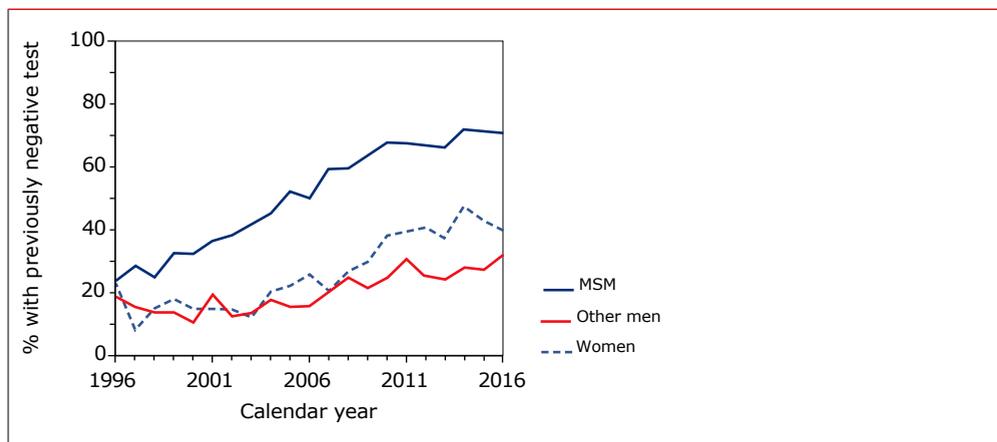
**Figure:** Proportion of people diagnosed with a last negative test in the preceding 6 months for (A) Amsterdam and (B) the rest of the Netherlands.



### 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 people with a known previous negative HIV test (*Figure 1.11*). In 2016, 71% of MSM, 32% of other men, and 40% 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 27% of those diagnosed in a hospital, 61% of those tested at a general practice, and 68% of those diagnosed elsewhere.

*Figure 1.11: Proportion of individuals diagnosed after a previously negative HIV test. Altogether, 71% of men who have sex with men (MSM), 32% of other men, and 40% of women diagnosed in 2016 had a previously negative HIV test.*



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

### Treated population

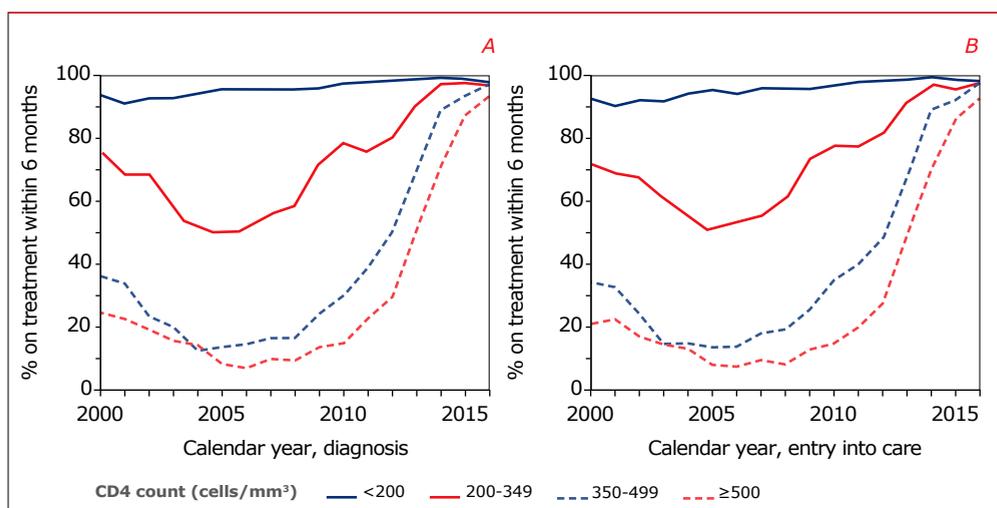
Of the 24,413 adults ever registered with an HIV-1 infection, 22,873 (94%) had started cART by May 2017. The majority of these individuals (88%) started cART while being antiretroviral therapy-naive. For the entire group of adults, the total follow-up time since start of cART was 203,200 person years. 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 2016, median CD4 counts at the start of treatment had increased to 410 cells/mm<sup>3</sup>. Of those starting cART in 2016, 21% of patients started treatment at CD4 counts already below 200 cells/mm<sup>3</sup>, 19% started at CD4 counts between 200 and 349 cells/mm<sup>3</sup>, 22% started at CD4 counts between 350 and 499 cells/mm<sup>3</sup>, and 38% started at CD4 counts of 500 cells/mm<sup>3</sup> or above.

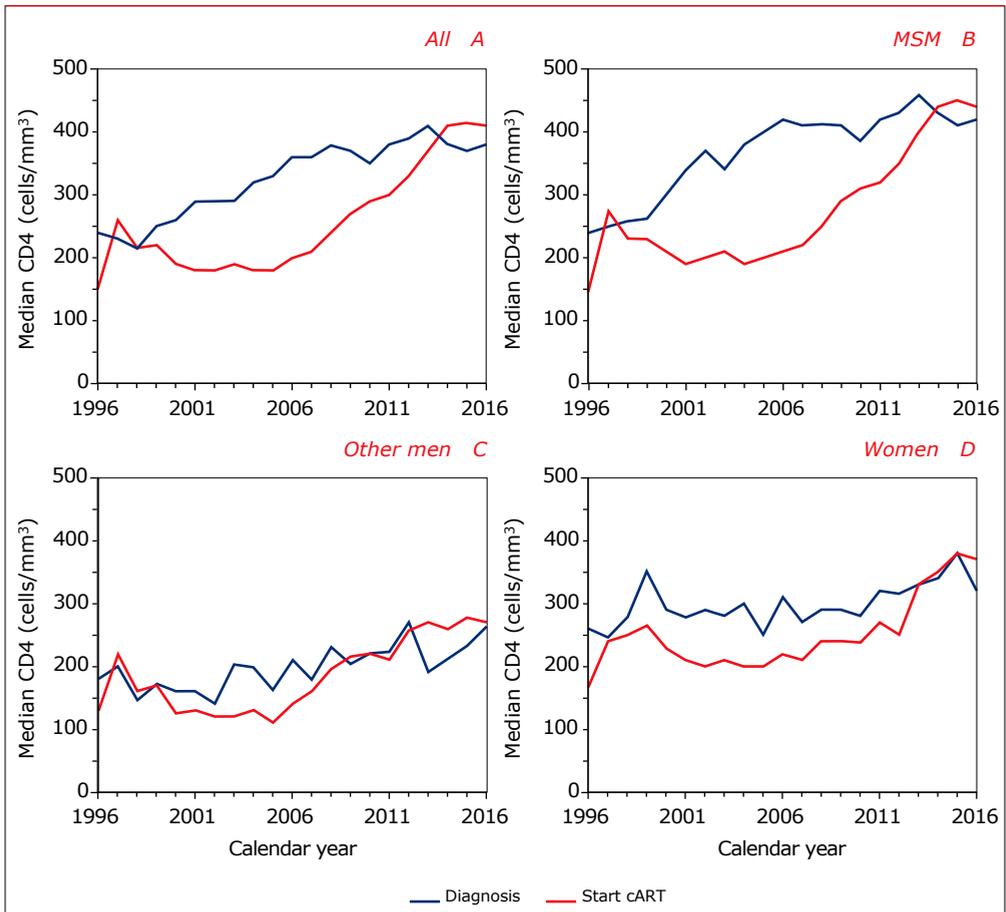
The main reason for starting treatment too late, i.e., at low CD4 counts, appears to be a late diagnosis, because most patients who are able to start treatment on time now do so. Patients with less than 200 CD4 cells/mm<sup>3</sup> at diagnosis or at the time of entry into care almost immediately started treatment: within 6 months after diagnosis, almost everyone had started cART ([Figure 1.12](#); [Appendix Figure 1.2](#)).

**Figure 1.12:** Proportion of individuals who started combination antiretroviral treatment (cART) within 6 months after HIV diagnosis by CD4 count at the time of diagnosis (A). Proportion of individuals who started cART within 6 months after entry into care stratified by CD4 counts at the time of entry into care (B). Individuals were considered only if they had more than 6 months of follow up after diagnosis or entry into care. Of all individuals diagnosed in 2016, 98% of those with CD4 counts below 200 cells/mm<sup>3</sup>, 97% of those with CD4 counts between 200 and 349 cells/mm<sup>3</sup>, 97% of those with CD4 counts between 350 and 499 cells/mm<sup>3</sup>, and 94% of those with CD4 counts of 500 cells/mm<sup>3</sup> or above had started cART within 6 months of diagnosis. In individuals who entered HIV care in 2016, 98% of those with CD4 counts below 200 cells/mm<sup>3</sup>, 98% of those with CD4 counts between 200 and 349 cells/mm<sup>3</sup>, 98% of those with CD4 counts between 350 and 499 cells/mm<sup>3</sup>, and 93% of those with CD4 counts of 500 cells/mm<sup>3</sup> or above had started cART within 6 months of entry.



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 a universal start of treatment regardless of CD4 count. In 2016, for all CD4 strata, at least 90% of people 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 1.13:** Changes over calendar time in median CD4 counts at HIV diagnosis and at the start of combination antiretroviral therapy (cART) for (A) all individuals 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.

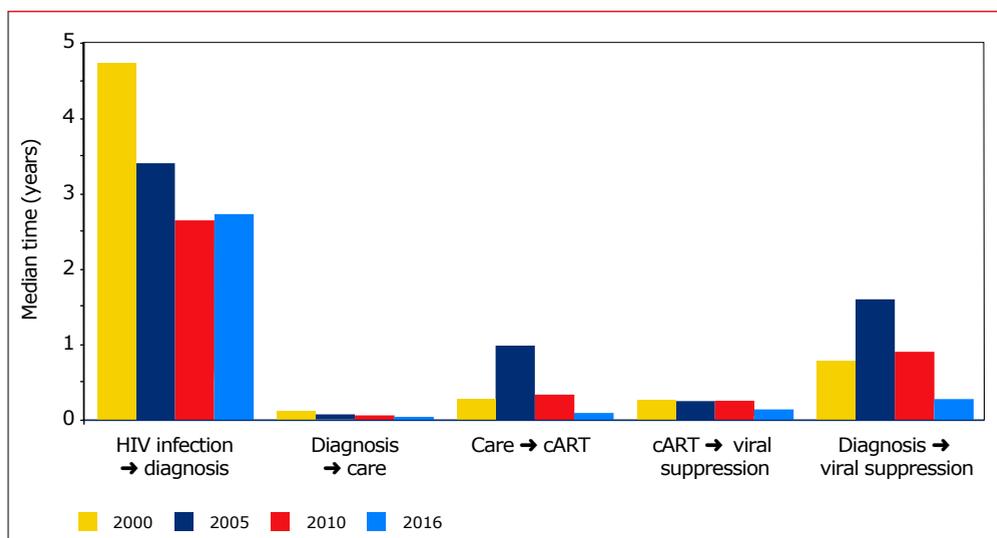


### Time between HIV infection and viral suppression

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 acquires HIV and the moment viral suppression is reached is minimised<sup>4</sup>. After all, people with a suppressed viral load are highly unlikely to transmit their virus to uninfected partners<sup>5,6</sup>. However, 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 2016, the median time

from infection to diagnosis in the entire HIV-1-positive population was estimated to have decreased from 4.7 (IQR, 2.3-8.4) to 2.7 (1.3-5.0) years. During this same period, the median time from diagnosis to viral suppression decreased from 0.78 (IQR, 0.39-3.53) years to 0.27 (0.16-0.54) 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 individuals, 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 200 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 25,355 registered individuals, including 45 men and 52 women, were infected with HIV-2. The majority (78, or 80%) of these people acquired HIV-2 via heterosexual contact. HIV-2 is endemic in West Africa, and 63 people originated from this region, mostly from Ghana (25 people) or Cape Verde (24). Only 20 individuals were born in the Netherlands, 14 of whom reported to have acquired their HIV infection in the Netherlands. A total of 63 people were still in clinical care, 15 people had died, and 6 had moved abroad. The mean age of the people still in care was 58 years, and 78% were 50 years or older.

The median age at the time of diagnosis was 41 years, which is considerably higher than for HIV-1-positive individuals. For the 81 individuals who were diagnosed in 1996 or later, the median CD4 count at the time of diagnosis was 310 (90-681) cells/mm<sup>3</sup>. From 1996 onwards, 46% of the people were late presenters, and 38% presented for care with advanced HIV disease<sup>3</sup>. The distribution of CD4 counts at entry into care appeared to be more bimodal than for HIV-1-positive individuals: 36% had CD4 counts below 200 cells/mm<sup>3</sup>, 41% had CD4 counts of 500 cells/mm<sup>3</sup> or higher, while relatively few people (22%) had CD4 counts between 200 and 499 cell/mm<sup>3</sup>.

### Treatment

In total, 60 HIV-2-positive individuals had ever started cART. Of the 41 of these individuals who were still in care by the end of 2016, 20 used a backbone of abacavir/lamivudine and 12 tenofovir/emtricitabine. Additional drugs in the regimen included cobicistat-boosted or ritonavir-boosted darunavir in 18 individuals, ritonavir-boosted lopinavir in 8 individuals, atazanavir in 4 individuals (all ritonavir-boosted, except one), and dolutegravir in 8 individuals.

At start of cART, 24 individuals had HIV-2 RNA levels above 500 copies/ml, while 16 had levels below this threshold. Of the 63 patients who were still in care, 49 had a most recent viral load measurement below 500 copies/ml, 3 had a viral load above 500 copies/ml, and 11 patients had no available HIV-2 RNA result. The 22 individuals who were still in care and had not, or not yet, started treatment still had high CD4 counts (median 830 (600-1060) cells/mm<sup>3</sup>), and all had an HIV-2 viral load below 500 copies/ml.

## HIV-1-positive people in care

### Patients in clinical care

In total, 19,035 (78%) of the 25,092 registered HIV-1-positive individuals, comprising 18,824 adults and 211 minors less than 18 years of age, were known to be in clinical care (*Figure 1.1; Table 1.1; Appendix Table 1.3*) by the end of 2016. People were considered to be in clinical care if they visited their treating physician in 2016 or had a CD4 count or HIV RNA measurement in that year and they were still living in the Netherlands. Of the 6,057 people who, according to this definition, were not in care, 2,776 (46%) were known to have died, and 1,491 (25%) to have moved abroad, while 125 (2%) were only diagnosed with HIV in 2017.

**Table 1.1: Characteristics of the 19,035 HIV-1-positive individuals in clinical care by the end of 2016. An extended version of this table is available as Appendix Table 1.3.**

	Men (n=15,475, 81%)		Women (n=3,560, 19%)		Total (n=19,035)	
	n	%	n	%	n	%
<b>Transmission</b>						
MSM	11,928	77	-	-	11,928	63
Heterosexual	2,377	15	3,104	87	5,481	29
IDU	224	1	84	2	308	2
Blood (products)	151	1	89	3	240	1
Other/unknown	795	5	283	8	1,078	6
<b>Current age (years)</b>						
0-12	57	0	77	2	134	1
13-17	48	0	29	1	77	0
18-24	264	2	79	2	343	2
25-34	1,762	11	541	15	2,303	12
35-44	3,210	21	1,087	31	4,297	23
45-54	5,345	35	1,055	30	6,400	34
55-64	3,333	22	491	14	3,824	20
65-74	1,259	8	159	4	1,418	7
≥75	197	1	42	1	239	1
<b>Region of origin</b>						
The Netherlands	10,394	67	1,073	30	11,467	60
Sub-Saharan Africa	1,058	7	1,447	41	2,505	13
Western Europe	882	6	126	4	1,008	5
South America	1,009	7	330	9	1,339	7
Caribbean	618	4	168	5	786	4
South and South-East Asia	436	3	227	6	663	3
Other	1,020	7	177	5	1,197	6
Unknown	58	0	12	0	70	0
<b>Years aware of HIV infection</b>						
<1	605	4	94	3	699	4
1-2	1,403	9	248	7	1,651	9
3-4	1,641	11	260	7	1,901	10
5-10	4,359	28	818	23	5,177	27
10-20	5,297	34	1,671	47	6,968	37
>20	2,146	14	452	13	2,598	14
Unknown	24	0	17	0	41	0

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

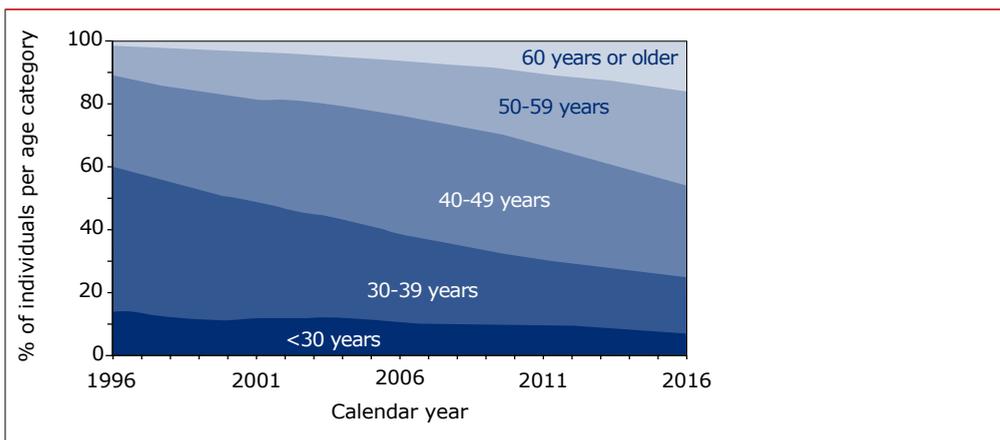
### Loss to care

Of the 11,907 individuals who enrolled in HIV care between 2006 and 2015, 639 (5%) were lost to care before 2016 and were not reported as having died or moved abroad. Loss to care was lowest for people of Dutch origin: 6% were estimated to be lost to care after 10 years. Of the individuals of sub-Saharan African origin, 22% of men and 15% of women were lost to care after 10 years, as were 18% of men and 16% of women originating from other regions. Loss to care improved with increasing age at the time of entry into care: for every additional 5 years of age at the time of entry, individuals were 8% less likely to be lost to care.

### Ageing population

The median age of the population in clinical care by the end of 2016 was 49 (interquartile range [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 people with HIV after the introduction of combination antiretroviral treatment (cART). In addition, people are being diagnosed at increasingly older ages, as has been discussed earlier in this chapter. As a result, more than two out of five people currently in care (46%) are 50 years or older, including 49% of men and 33% of women; 16% of the people 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 individuals 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-1-positive population in clinical care over calendar time. In 1996, 14% of the individuals in care were younger than 30 years of age, whereas 11% were 50 years or older. In 2016, these proportions were 7% and 46%, respectively, while 16% of individuals in care were 60 years of age or older. The proportion of individuals in clinical care as of 31 December 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

People in clinical care by the end of 2016 had been diagnosed with HIV a median of 10.1 (IQR, 5.5-15.9) years ago. Thus, a large group (50%) of those in care have been living with HIV for more than 10 years, while 14% had done so for more than 20 years. The median time since diagnosis was 9.3 years for men who have sex with men (MSM), 11.0 years for other men, and 11.8 years for women. The majority of injecting drug users (91%) 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, 97% of the individuals in care were being treated with cART, compared with 95% in last year's report<sup>7</sup>. The most frequently-prescribed currently-used regimens, which accounted for 69% of all treatment combinations, were a combination of abacavir, lamivudine and dolutegravir (15%), combinations of tenofovir disoproxil fumarate and emtricitabine and either efavirenz (14%), nevirapine (10%), rilpivirine (8%), ritonavir-boosted darunavir (6%), cobicistat-boosted elvitegravir (6%), or ritonavir-boosted atazanavir (4%), and a combination of tenofovir alafenamide, emtricitabine and cobicistat-boosted elvitegravir (7%). The majority of the patients, 90%, used a once-daily regimen. Antiretroviral treatment is discussed in more detail in [Chapter 2](#).

### Clinical condition

The median CD4 count in 2016 of the patients in care was relatively high at 660 (IQR, 480-860) cells/mm<sup>3</sup>, 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 with a viral load measurement in 2016, their last measurement in that year was below 200 copies/ml for 95% and below 100 copies/ml for 94%. 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 2016, including those not yet diagnosed, was estimated at 22,900 (95% confidence interval [CI] 22,400-23,400), of whom 2,600 (2,100-3,200) were still undiagnosed<sup>2</sup>. Adjusted for registration delay, 20,264 patients, or 89% of the total number estimated to be living with HIV, had been diagnosed, linked to care, and registered by SHM, while 19,136 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 2016) ([Figure 1.16A](#)). The majority of these patients (18,599 in total) had started cART, and

17,580 had a most recent HIV RNA measurement below 200 copies/ml<sup>B</sup>, irrespective of treatment. Overall, 77% of the total estimated population living with HIV and 87% of those diagnosed and ever linked to care had a suppressed viral load. Hence the Netherlands is nearing the Joint United Nations Programme on HIV/AIDS (UNAIDS) 90-90-90 target for 2020 with the current estimate standing at 89-92-95 (2015: 87-91-96)<sup>8</sup>. Of the people with a suppressed viral load, 10,861 (62%) had a CD4 count of 500 cells/mm<sup>3</sup> or higher at their last measurement in 2016, equivalent to 75% of those with a CD4 measurement in 2016.

### Box 1.3: International collaborations

This year, SHM participated in a collaboration between the European Centre for Disease Prevention and Control (ECDC) and European HIV cohorts and surveillance agencies. The collaboration constructed a standardised, 4-stage continuum of HIV care for 11 European Union countries for 2013<sup>9</sup>. In total, 674,500 people were estimated to be living with HIV, of whom 84% were diagnosed. Of those diagnosed 84% were on antiretroviral treatment and 85% of those who were treated, or 60% of all people living with HIV, were virally suppressed, i.e. had a most recent viral load below 200 copies/ml.

### Lost to care

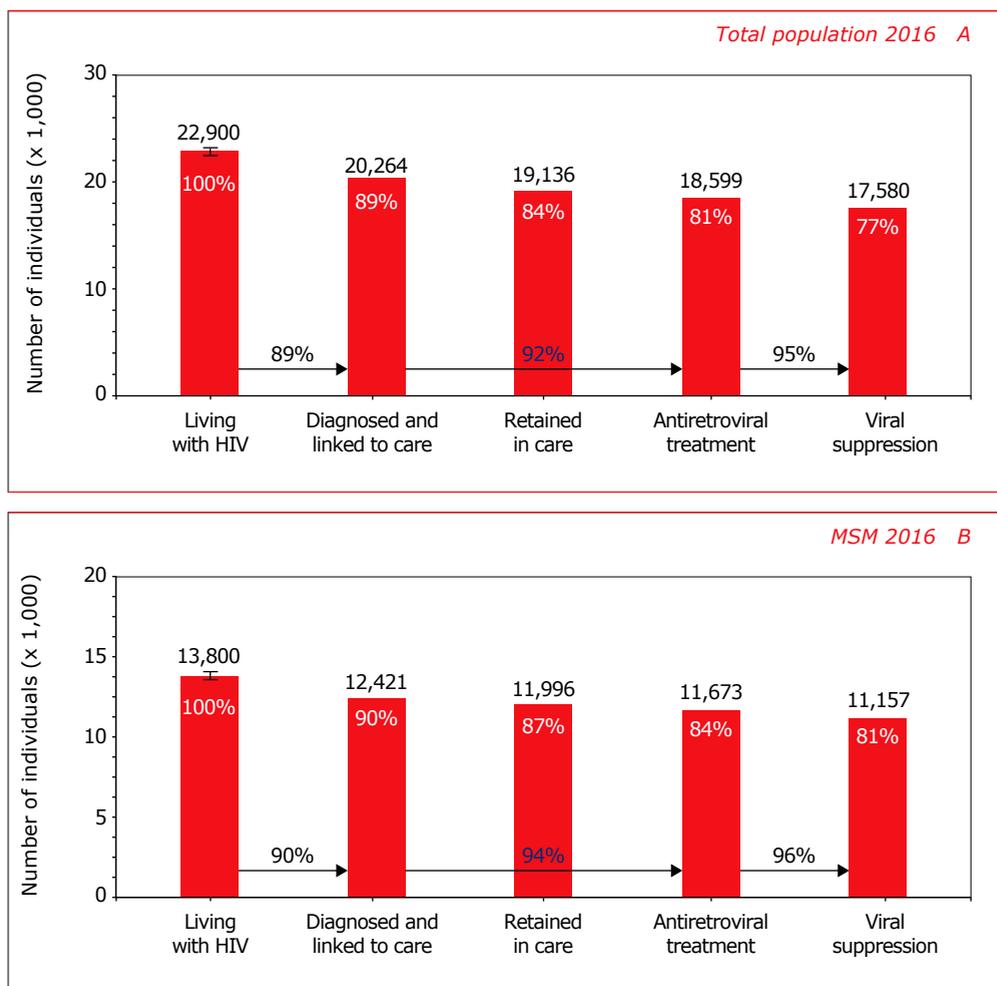
The estimated number of people living with HIV and the number of people diagnosed and linked to care excluded 521 individuals who had been diagnosed and linked to care but were lost to care before the end of 2006, i.e. more than 10 years ago. It is unlikely that these 521 individuals are still living in the Netherlands without needing care or antiretroviral treatment. Of the 1,128 patients lost to care (20,264 minus 19,136), 75% were born outside the Netherlands, whereas this proportion was only 40% for those who were still in care by the end of 2016. This suggests that some of those lost to care may actually have moved abroad, in particular back to their country of birth.

### MSM

The number of MSM living with HIV was estimated to be 13,800 (13,600-14,200), of whom 1,400 (1,200-1,700) were still undiagnosed. Of these MSM estimated to be living with HIV, 12,421 (90%) had been diagnosed and linked to care, 11,996 (87%) were still in care, 11,673 (84%) had started cART, and 11,157 (81%) had a most recent HIV RNA below 200 copies/ml, or 90-94-96 in terms of the UNAIDS 90-90-90 target (*Figure 1.16B*). In total, 7,222 (65%) of MSM with a suppressed viral load had a CD4 count of 500 cells/mm<sup>3</sup> or higher at their last measurement in 2016, equivalent to 78% of those with a CD4 measurement in 2016.

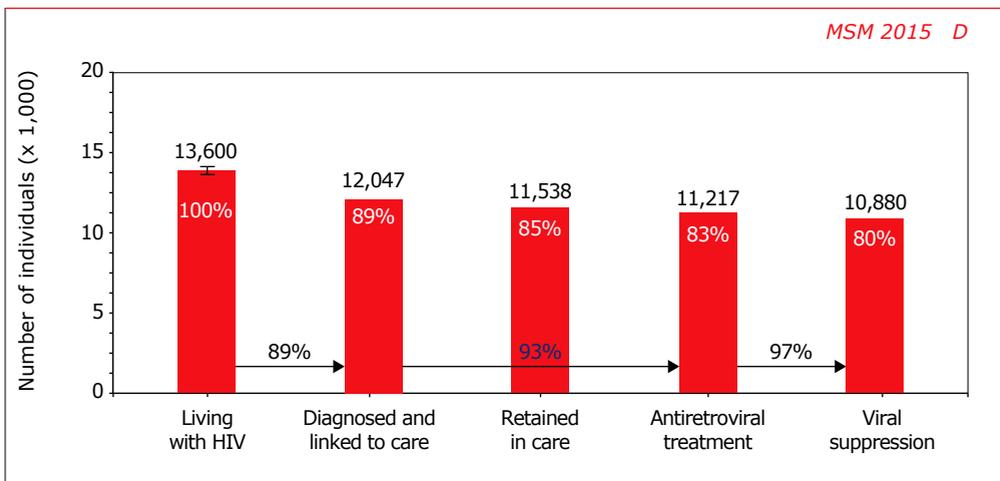
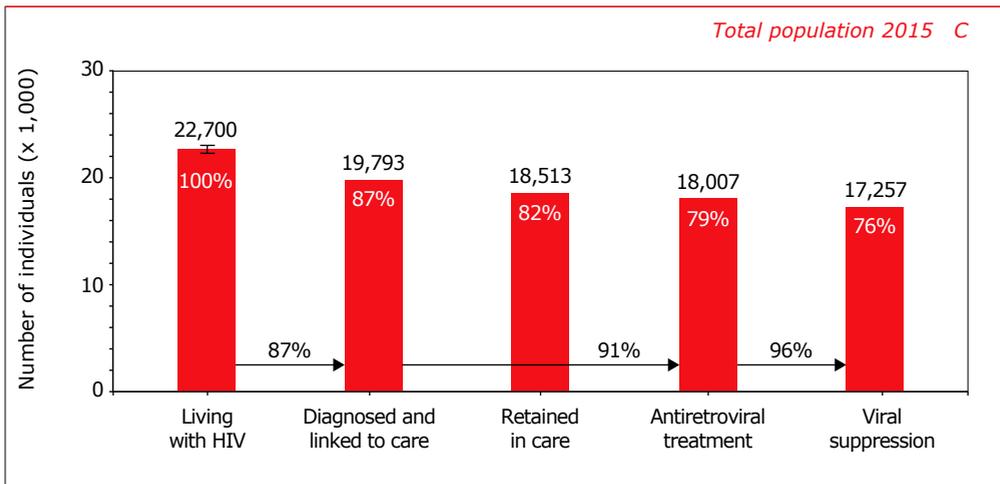
<sup>B</sup> Note that this is different from the threshold of 100 copies/ml used up to last year. The threshold of 200 copies/ml is in line with recommendations by ECDC.

**Figure 1.16: Continuum of HIV care for (A, C) the total estimated HIV-1-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 2016 and by the end of 2015. 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 2015, 11% in 2016).**



Among MSM the proportion with a most recent HIV RNA below 200 copies/ml in 2016 was higher than among other men and women (*Appendix Figure 1.3*). Also, patients of Dutch origin generally reached higher proportions of engagement in the various stages of the care continuum than people originating from abroad

(Appendix Figure 1.4). The proportion of patients who were still in care by the end of 2016 was similar between age groups, while the proportion who had started cART increased from 82% of those diagnosed and linked to care among 18 to 24 year olds to 96% of those aged 65 years or above (Appendix Figure 1.5). As a consequence, the proportion of people with viral suppression increased with age and was 72% among those aged 18 to 24 years and 91% in patients 65 years of age or older, or 88% and 95%, respectively, of those who had started cART.



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

### Continuum of care 2015

We also re-estimated the continuum of HIV care for 2015 and found that, by the end of that year, 22,700 (22,300-23,100) people were living with HIV in the Netherlands, which was similar to the estimated 22,900 (22,300-23,500) reported in last year's Monitoring Report (Figures 1.16C and 1.16D)<sup>7</sup>. The main reason that the estimate for 2015 is lower in this year's report is that people who had not been in care for more than 10 years were excluded from the continuum. If these people were included in the continuum, the number of people living with HIV would be 23,100. 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 (18,007 compared to 17,721 last year) and the number with viral suppression (17,257 compared to 16,456) were considerably higher in this year's report. This is due to a backlog in the collection of data on start of treatment and on viral load measurements that may also be present in the reported continuum of HIV care for 2016.

### Conclusion

Since 2008 there has been a steady decrease in the annual number of new HIV diagnoses to approximately 900 new diagnoses in most recent years. This decreasing trend continued in 2016 with approximately 820 new diagnoses in that year, although there is some uncertainty concerning this number of diagnoses because not all people diagnosed in 2016 have yet been included in the SHM database at the time of writing. 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 individuals are diagnosed with CD4 counts below 350 cells/mm<sup>3</sup>. 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 presenting with late or advanced 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 community health centre or 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 people

tested at CHSs or STI clinics are more likely actively seeking testing for HIV on a regular basis than people diagnosed in a hospital, who are more likely to be tested because they have a condition that may be caused by HIV.

People tested early in their infection generally start treatment earlier and with CD4 counts above 350 cells/mm<sup>3</sup>. In the most recent years, treatment uptake has also increased in patients with high CD4 cells such that, in 2016, more than 90% of patients diagnosed with CD4 cells above 500 cells/mm<sup>3</sup> were on cART within 6 months after entering HIV care. As a result, at least 90% of patients in care and 77% of the total estimated population of persons living with HIV in the Netherlands in 2016, including those not yet diagnosed, have a suppressed viral load.

Approximately 5% of individuals who enrolled in HIV care between 2006 and 2015 were lost to care before 2016. Loss to care is low for people of Dutch origin, but appears much higher for foreign-born individuals. Some of the individuals who are lost to care may in fact have moved abroad and may now be in care elsewhere. However, SHM does not have information on transfer of care to hospitals abroad.

### Recommendations

A re-assessment of the continuum of HIV care for 2015 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 (LabLink) 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, prevention, 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 HIV disease progression, improve clinical outcomes and limit transmission<sup>6,10</sup>. The HPTN 052, Temprano ANRS 12136 and START randomised clinical trials on when to start cART showed that when cART is started while CD4 cell counts are still above 500 CD4 cells/mm<sup>3</sup>, HIV-related and non-HIV related morbidity and mortality are greatly reduced by 44% to 57% as compared with waiting until CD4 counts have declined further<sup>11,12,13</sup>. These findings have resulted in treatment guidelines across the globe now recommending that all HIV-positive individuals should be advised to start cART immediately after diagnosis.

Besides preventing clinical events, AIDS and tuberculosis, immediate start of cART is also more effective at preventing transmission of HIV than deferral of treatment until the CD4 count has dropped to  $\leq 350$  cells/mm<sup>3</sup><sup>5,13</sup>. People living with HIV and receiving cART with an undetectable viral load in their blood have a negligible to non-existent risk of sexual transmission of HIV; undetectable equals untransmittable (U=U)<sup>6,14,15,16,17,18</sup>. Depending on the drugs employed, it may take as long as six months for the viral load to become undetectable. Sustained HIV suppression requires selection of appropriate treatment and continued adherence to treatment. Thus, HIV viral suppression should be continuously monitored and documented to assure both personal health and public health benefits.

The US Department of Health and Human Services (DHHS), European AIDS Clinical Society, International AIDS Society-USA and World Health Organization's guidelines on when to start cART currently all recommend starting cART in all HIV-positive individuals, irrespective of CD4 cell count<sup>19,20,21,22</sup>. In general, the Dutch Association of HIV Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*, NVHB) follows the DHHS guidelines. Furthermore, in these guidelines, preferred first-line cART regimens include an integrase inhibitor as the third agent, along with the options of boosted darunavir, as either ritonavir-

boosted or cobicistat-boosted (DRV/b; DRV/r or DRV/c, respectively), as a boosted protease inhibitor or rilpivirine (RPV) as a non-nucleoside reverse transcriptase inhibitor (NNRTI) option (the latter if viral load is <100,000 copies/mL), all in combination with a double nucleoside backbone (either tenofovir/emtricitabine or abacavir/lamivudine)<sup>21</sup>. Additionally, tenofovir can be prescribed in two formulations: either as tenofovir disoproxil fumarate (TDF) or tenofovir alafenamide fumarate (TAF), which has been available and reimbursed in the Netherlands since April 2016. TDF use should be avoided in people with either reduced, or a risk of reduced, renal function and in those with osteoporosis or at risk for osteoporotic fractures<sup>23,24</sup>. While still frequently used, efavirenz is no longer recommended as the preferred, but instead as the alternative, first-line cART regimen in the Netherlands<sup>19,21</sup>.

Treatment with cART generally results in sustained suppression of HIV viral load to levels below the reported threshold. Low-level viraemia above the reported threshold, however, may be associated with the development of drug resistance. Moreover, high-level viraemia can lead to selection and accumulation of mutations in the HIV genome that are associated with drug resistance, which prevent successful viral suppression and thereby increase the risk of poor clinical outcomes<sup>25,26,27,28,29,30,31</sup>.

This chapter reports the impact of HIV treatment guidelines on the prescription of cART and its outcome in the Netherlands. We describe trends over time in the use of cART and trends in the virological and immunological responses to cART in HIV-1 positive adults registered by Stichting HIV Monitoring (SHM) and enrolled in the AIDS Therapy Evaluation in the Netherlands (ATHENA) cohort. We also analyse the presence of HIV drug resistance. *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 in Chapter 2.*

**Of the 24,413 HIV-1 positive adults (aged  $\geq 18$  years at the time of diagnosis) registered in the ATHENA cohort by May 2017:**

**1. Starting combination antiretroviral therapy**

22,611 individuals were known to have initiated cART between January 1995 and December 2016\*.

**2. Population in care and on cART in 2016**

Out of 22,611 individuals known to have initiated cART between January 1995 and December 2016\*,

→ 17,898 were in care and had a clinical visit in 2016; of those, 538 were diagnosed with HIV before 1990 (i.e. long-term survivors).

**3. Changes in the use of antiretroviral therapy**

Out of 22,611 individuals known to have initiated cART between January 1995 and December 2016\*,

→ 7,322 initiated cART between January 2011 and December 2016,

→ 5,723 initiated cART between January 2011 and December 2016 with a regimen composed of TDF/FTC in combination with EFV, RPV, DRV/b, ATV/r, EVG/c, or DTG, or ABC/3TC/DTG.

**4. Viral response**

Out of 22,611 individuals known to have initiated cART between January 1995 and December 2016\*,

→ 18,545 individuals were ART-naïve, not pregnant at cART initiation, and had a viral load result  $\geq 3$  months after cART initiation.

*Initial virological success*

→ 15,894 individuals were ART-naïve, not pregnant at cART initiation, and had a viral load result 6 ( $\pm 3$ ) months after cART initiation; 5,305 of those initiated TDF/FTC in combination with EFV, RPV, DRV/b, ATV/r, EVG/c, DTG, or RAL, or ABC/3TC/DTG or TAF/FTC/EVG/c in 2011-2016; and 4,286 of those also had viral load data available at the time of cART initiation.

*Viral rebound*

→ 17,044 were ART-naïve, not pregnant at cART initiation, and had a viral load test result after 6 or more months ( $>180$  days) of continuous cART; 6,228 of those had initiated cART in 2011 or thereafter.

## 5. HIV drug resistance

Out of 22,611 individuals known to have initiated cART between January 1995 and December 2016<sup>\*</sup>,

### *Screening for drug-resistant HIV before treatment initiation*

5,971 antiretroviral (ARV)-naive individuals had an HIV-1 sequence available within a year of diagnosis and before initiating cART in the period 2003-2016; 1,345 of those individuals had a recent infection and 4,626 had a long-standing (i.e., non-recent) infection<sup>\*\*</sup>.

→ 11 individuals had pre-treatment integrase sequences available.

### *Acquired drug resistance*

4,584 HIV-1 sequences were obtained from 2,837 individuals who received cART for at least 4 months in the period 2000-2016.

→ 1,502 sequences from 832 people who were pre-treated with monotherapy or dual therapy before initiating cART.

→ 3,082 sequences from 2,005 people who were ARV-naive before initiating cART.

→ 87 integrase sequences were available from 73 people.

## 6. Immunological response

Out of the 22,611 individuals known to have initiated cART between January 1995 and December 2016<sup>\*</sup>;

→ 21,563 had CD4 cell count data available after initiating cART.

→ 18,928 had CD4 cell count data available at and after initiating cART; 6,040 of those had CD4 cell count data available at and after initiating cART between January 2011 and December 2016.

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

*\*\*An infection was considered recent when there was less than 12 months between the last known negative HIV test and the first known positive HIV test. Individuals without a previously negative test or with a negative test more than 12 months before the first positive test were considered non-recent.*

*Legend: ARV=antiretroviral therapy (antiretroviral drug use that may prevent HIV from damaging the immune system by blocking the replication of HIV); cART=combination antiretroviral therapy (defined as a combination of three antiretroviral drugs from two different antiretroviral drugs classes). 3TC=lamivudine; b=boosted (cobicistat or ritonavir); ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RAL=raltegravir; RPV=rilpivirine; /r=ritonavir-boosted; TDF=tenofovir disoproxil fumarate; NRTI=non-nucleoside reverse transcriptase inhibitor.*

## Starting combination antiretroviral therapy

Of the 24,413 HIV-1 positive adults ever registered by SHM and followed in the ATHENA cohort who were aged 18 years or older at the time of diagnosis, 22,611 were known to have initiated cART (defined as a combination of at least 3 antiretroviral agents) between January 1995 and December 2016 (*Box 2.1*). Of these, 2,630 (11.6%) had prior exposure to mono or dual ART at the start of cART and 19,981 (88.4%) were ART-naïve. The proportion of pre-treated individuals initiating cART has decreased over time to approximately 1% to 1.5% since 2009; the majority of these pre-treated individuals originated from outside of the Netherlands, predominantly sub-Saharan Africa. In *Table 2.1*, we grouped individuals according to calendar year of starting cART: 4,477 started between 1995 and the end of 1999, 4,943 between 2000 and the end of 2005, 5,869 between 2006 and the end of 2010, and 7,322 between 2011 and the end of 2016. Individuals starting cART in 2017 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 treatment.

Of the 22,611 individuals who initiated cART since January 1995, 18,463 were men (81.7%), of whom 13,756 (74.5%) were men who have sex with men (MSM). Overall, 13,157 (58.2%) originated from the Netherlands. While 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. Over the past 20 years, there has been a slight increase in individuals from eastern and central Europe. During the period from 1995-1999, 1.2% originated from eastern and central Europe compared to 6.5% in 2016. Simultaneously, there was a decrease in individuals from western Europe/North America/Australia, from 12.2% in 1995-1999 to 5.4% in 2016, and a decrease in individuals from sub-Saharan Africa; from 24.7% in 2000-2005, to 14.3% in 2006-2010, and 9.1% in 2011-2016.

Table 2.1: Characteristics of HIV-positive individuals starting combination antiretroviral therapy in 1995–2016.

Calendar year of cART initiation		1995–1999	2000–2005	2006–2010	2011–2016	Total
		n (%)	n (%)	n (%)	n (%)	n (%)
<b>Total n</b>		4,477	4,943	5,869	7,322	<b>22,611</b>
<b>DEMOGRAPHIC CHARACTERISTICS</b>						
<b>Age at start cART</b>	Median	37.7	37.6	40.4	40.1	<b>39</b>
	Q1 / Q3	32.6 / 44.8	31.4 / 44.6	33.3 / 47.5	31.5 / 49.0	<b>32 / 47</b>
<b>Male</b>		3,751 (83.8)	3,561 (72.0)	4,810 (82.0)	6,341 (86.6)	<b>18,463 (81.75)</b>
<b>Transmission risk group</b>						
Men who have sex with men		2,806 (62.7)	2,237 (45.2)	3,631 (61.9)	5,084 (69.4)	<b>13,758 (60.9)</b>
Heterosexual contact		1,041 (23.3)	2,126 (43.0)	1,796 (30.6)	1,811 (24.7)	<b>6,774 (23.0)</b>
Injecting drug use		327 (7.3)	200 (4.1)	104 (1.8)	40 (0.6)	<b>671 (3.0)</b>
Blood or blood products		84 (1.9)	77 (1.6)	47 (0.8)	62 (0.9)	<b>270 (1.2)</b>
Vertical transmission		.	.	1 (0.02)	3 (0.04)	<b>4 (0.02)</b>
Other/unknown		219(4.9)	303 (6.1)	290 (4.9)	322 (4.4)	<b>1,134 (5.0)</b>
<b>CLINICAL CHARACTERISTICS</b>						
<b>Region of origin</b>						
The Netherlands		2,887 (64.5)	2,305 (46.6)	3,377 (57.54)	4,588 (62.7)	<b>13,157 (58.2)</b>
Western Europe/North America/Australia		546 (12.2)	391 (7.9)	452 (7.7)	420 (5.7)	<b>1,809 (8)</b>
Eastern/central Europe		54 (1.2)	110 (2.23)	189 (3.22)	361 (4.9)	<b>714 (3.2)</b>
South America and the Caribbean		397 (8.9)	620 (12.5)	677 (11.5)	841 (11.5)	<b>2,535 (11.2)</b>
Sub-Saharan Africa		400 (8.9)	1,223 (24.7)	840 (14.3)	663 (9.1)	<b>3,126 (13.8)</b>
Other*		193 (4.3)	294 (6.0)	334 (5.7)	449 (6.1)	<b>1,270 (5.6)</b>
<b>Socio-economic status<sup>(2)</sup></b>						
1 – high		223 (5.0)	221 (4.5)	280 (4.8)	365 (5.0)	<b>1,089 (4.8)</b>
2		955 (21.3)	974 (19.7)	1,319 (22.5)	1,534 (21.0)	<b>4,782 (21.2)</b>
3		1,041 (23.3)	1,393 (28.2)	1,680 (28.6)	2,185 (29.8)	<b>6,299 (27.9)</b>
4		1,076 (24.0)	1,224 (24.8)	1,427 (24.3)	1,720 (23.5)	<b>5,447 (24.1)</b>
5 – low		669 (14.9)	979 (19.8)	1,044 (17.8)	1,390 (19.0)	<b>4,082 (18.1)</b>
Missing		513 (11.5)	152 (3.1)	119 (2.0)	128 (1.8)	<b>912 (4.0)</b>
<b>CD4 at start cART (cells/mm<sup>3</sup>)</b>	Median	200	180	242	360	<b>260</b>
	Q1 / Q3	80 / 340	72 / 294	140 / 328	22 / 510	<b>120 / 390</b>
<b>HIV RNA at start cART log<sub>10</sub> cps/ml</b>	Median	4.8	5.0	5.0	4.8	<b>4.9</b>
	Q1 / Q3	4.0 / 5.3	4.5 / 5.4	4.4 / 5.4	4.3 / 5.4	<b>4.3 / 5.4</b>
<b>AIDS diagnosis at start of cART</b>		1,469 (32.8)	1,335 (27.0)	1,031 (17.6)	888 (12.1)	<b>4,723 (20.9)</b>

Calendar year of cART initiation	1995-1999	2000-2005	2006-2010	2011-2016	Total
	n (%)				
<b>Hepatitis B status at start of cART<sup>(1)</sup></b>					
HBV-	3,974 (88.8)	4,470 (90.4)	5,401 (92.0)	6,753 (92.2)	<b>20,598 (91.1)</b>
HBV+	291 (6.5)	299 (6.1)	318 (5.4)	233 (3.2)	<b>1,141 (5.1)</b>
Unknown	212 (4.7)	174 (3.5)	150 (2.6)	336 (4.6)	<b>872 (3.9)</b>
<b>Hepatitis C status at start of cART<sup>(2)</sup></b>					
HCV-	3,939 (88.0)	4,469 (90.4)	5,518 (94.0)	6,892 (94.1)	<b>20,818 (92.1)</b>
HCV RNA+	51 (1.1)	120 (2.4)	136 (2.3)	121 (1.7)	<b>428 (1.9)</b>
HCV Ab+	108 (2.4)	89 (1.8)	41 (0.7)	39 (0.5)	<b>277 (1.2)</b>
Unknown	379 (8.5)	265 (5.4)	174 (3.0)	270 (3.7)	<b>1,088 (4.8)</b>
ART-naïve at start cART	2,423 (54.1)	4,577 (92.6)	5,747 (97.9)	7,234 (98.8)	<b>19,981 (88.4)</b>
cART started during pregnancy	37 (0.8)	345 (7.0)	215 (3.7)	100 (1.4)	<b>697 (3.1)</b>
cART started during recent infection	31 (0.7)	95 (1.9)	183 (3.1)	753 (10.3)	<b>1,062 (4.7)</b>

(1) The 50 individuals from other regions of origin who started in 2016 were from South-East Asia (n=26), North Africa and the Middle East (n=12), and Oceania and the Pacific (n=3), while the region of origin was unknown for 9 individuals.

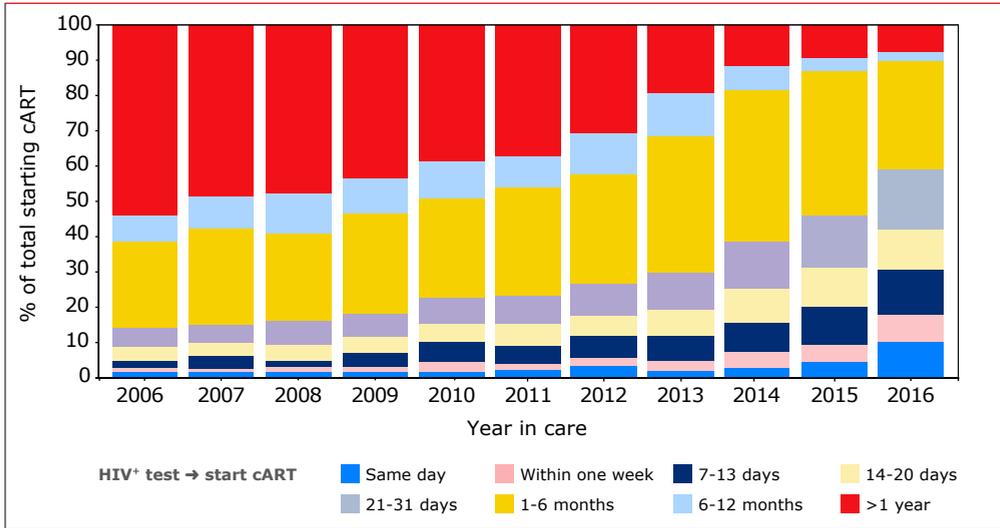
(2) Socio-economic status (SES): a combined measure based on income, employment, and level of education obtained by interviewing one household in each six-position postal code and aggregated into a single score for each four-position postal code by principal component analysis. Scores were classified 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](#).

(3) Chapter 4 gives more detailed information on viral hepatitis co-infection.

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

Prompt initiation of cART following an HIV-positive diagnosis has increased over time, reflecting implementation and uptake of evolving 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 shifted from 133 days (IQR 34-655) for those who entered care in 2011 to 95 days (interquartile range [IQR] 30-469) in 2012, 64 days (IQR 27-259) in 2013, 41 days (IQR 21-97) in 2014 and 35 days (IQR 18-73) in 2015. In 2016, the majority of individuals entering care and initiating cART did so within a month after diagnosis (median 26 days, IQR 12-45). Likewise, the time between entering care and starting cART decreased over time (Appendix Figure 2.1). Of all individuals initiating cART in 2016, less than 1% spent more than 6 months in care before starting cART; their median CD4 count at entry into care was also relatively high, i.e. 547 cells/mm<sup>3</sup> [IQR 460-710].

Figure 2.1: Time between HIV diagnosis and initiation of combination antiretroviral therapy (cART) for those starting cART in 2006–2016\*.



\*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.

Furthermore, an increasing proportion of individuals starting cART had evidence of recent infection (i.e., within 12 months of a last negative HIV test). The percentage of individuals with an AIDS diagnosis at the start of cART declined over time. This trend was accompanied by an increase in the median CD4 cell count at the start of cART from 180 cells/mm<sup>3</sup> (IQR 72-294) in 2000-2005 to 242 cells/mm<sup>3</sup> (IQR 140-328) in 2006-2010 and 360 cells/mm<sup>3</sup> (IQR 220-510) in 2011-2016 (p-value for trend <.0001). In 2016, the median CD4 cell count at the start of cART was 410 cells/mm<sup>3</sup> (IQR 230-590). *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.

## Population in care and on cART in 2016

Out of the 22,611 HIV-positive individuals who were known to have initiated cART between January 1995 and December 2016, 17,898 were alive, in care, and had a clinical visit in the Netherlands in 2016. *Table 2.2* shows their treatment and clinical characteristics in 2016. Overall, 82.2% were men, and 64.2% were MSM. The median age on 31 December 2016 was 49 (IQR 41-56) years. The majority (61.4%) originated from the Netherlands, followed by sub-Saharan Africa (12.2%) and South America and the Caribbean (11.1%).

**Table 2.2: Characteristics of HIV-positive individuals who ever started combination antiretroviral therapy and known to be in care in 2016.**

Calendar year of cART initiation		1995–2001	2002–2008	2009–2015	2016	All
		n (%)	n (%)	n (%)	n (%)	n (%)
<b>n</b>		3,851	4,979	8,320	748	<b>17,898</b>
<b>Male</b>		3,107 (80.6)	3,773 (75.8)	7,180 (86.3)	647 (86.5)	<b>14,707 (82.2)</b>
<b>Age on 31 December 2016</b>	Median	55.3	50.2	45.2	39.7	<b>49.4</b>
	Q1 / Q3	50.3 / 61.5	43.9 / 56.9	36.6 / 53.1	30.6 / 51.6	<b>41.0 / 56.6</b>
<b>Transmission risk group</b>						
Men who have sex with men		2,384 (61.9)	2,754 (55.3)	5,823 (70.0)	531 (71.0)	<b>11,492 (64.2)</b>
Heterosexual contact		1,104 (28.7)	1,822 (36.6)	2,093 (25.2)	172 (23.0)	<b>5,191 (29)</b>
Injecting drug use		150 (3.9)	92 (1.9)	50 (0.6)	5 (0.7)	<b>297 (1.7)</b>
Blood or blood products		72 (1.9)	61 (1.2)	58 (0.7)	8 (1.1)	<b>199 (1.1)</b>
Vertical transmission		.	.	3 (0.04)	.	<b>3 (0.02)</b>
Other/unknown		141 (3.7)	250 (5.0)	293 (3.5)	32 (4.3)	<b>716 (4)</b>
<b>Region of origin</b>						
The Netherlands		2,413 (62.7)	2,766 (55.6)	5,356 (64.4)	448 (59.9)	<b>10,983 (61.4)</b>
Western Europe/North America/Australia		355 (9.2)	297 (6.0)	454 (5.5)	41 (5.5)	<b>1,147 (6.4)</b>
Eastern/central Europe		51 (1.3)	125 (2.5)	342 (4.1)	49 (6.6)	<b>567 (3.2)</b>
South America and the Caribbean		385 (10)	614 (12.3)	891 (10.7)	100 (13.4)	<b>1,990 (11.1)</b>
Sub-Saharan Africa		444 (11.5)	884 (17.8)	788 (9.5)	60 (8.0)	<b>2,176 (12.2)</b>
Other		203(5.3)	293 (5.9)	489 (5.9)	50 (6.7)	<b>1,035 (5.8)</b>
<b>Last cART regimen in 2016</b>						
TDF/FTC/EFV		333 (8.7)	972 (19.5)	1,262 (15.2)	22 (2.9)	<b>2,589 (14.5)</b>
TDF/FTC/NVP		645 (16.8)	660 (13.3)	664 (8.0)	8 (1.1)	<b>1,977 (11.1)</b>
TDF/FTC/RPV		156 (4.1)	343 (6.9)	966 (11.6)	22 (2.9)	<b>1,487 (8.3)</b>
TDF/FTC/DRV/b		227 (5.9)	341 (6.9)	767 (9.2)	30 (4.0)	<b>1,365 (7.6)</b>
TDF/FTC/ATV/r		124 (3.2)	251 (5.0)	334 (4.0)	8 (1.1)	<b>717 (4.0)</b>
TDF/FTC/LPV/r		16 (0.4)	39 (0.8)	18 (0.2)	.	<b>73 (0.4)</b>
TDF/FTC/EVG/c		86 (2.2)	169 (3.4)	759 (9.1)	55 (7.4)	<b>1,069 (6.0)</b>
TDF/FTC/DTG		88 (2.3)	155 (3.1)	377 (4.5)	79 (10.6)	<b>699 (3.9)</b>
TDF/FTC/RAL		71 (1.8)	83 (1.7)	147 (1.8)	4 (0.5)	<b>305 (1.7)</b>
ABC/3TC/DTG		301 (7.8)	565 (11.4)	1,470 (17.7)	289 (38.6)	<b>2,625 (14.7)</b>
TAF/FTC/EVG/c		125 (3.3)	219 (4.4)	559 (6.7)	173 (23.1)	<b>1,076 (6.0)</b>
TAF/FTC/RPV		6 (0.)	21 (0.4)	52 (0.6)	2 (0.3)	<b>81 (0.5)</b>
TAF/FTC/DTG		11 (0.3)	12 (0.2)	32 (0.4)	12 (1.6)	<b>67 (0.4)</b>

Calendar year of cART initiation	1995-2001	2002-2008	2009-2015	2016	All
	n (%)	n (%)	n (%)	n (%)	n (%)
<b>Last cART regimen in 2016</b>					
Other: 2NRTI+NNRTI	522 (13.6)	419 (8.4)	189 (2.3)	2 (0.3)	<b>1,132 (6.3)</b>
Other: 2NRTI+PI	212 (5.5)	243 (4.9)	220 (2.6)	9 (1.2)	<b>684 (3.8)</b>
Other: 2NRTI+INST	48 (1.3)	49 (1.0)	45 (0.5)	.	<b>142 (0.8)</b>
Other: NNRTI+INST	4 (0.1)	5 (0.1)	3 (0.04)	.	<b>12 (0.1)</b>
Other: PI+INSTI	96(2.5)	56 (1.1)	68 (0.8)	2 (0.3)	<b>222 (1.2)</b>
Other: NRTI+PI+INSTI (3 ARVs)	80 (2.1)	36 (0.7)	23 (0.3)	1 (0.1)	<b>140 (0.8)</b>
Other: NRTI+PI+INSTI (4 ARVs)	93 (2.4)	36 (0.7)	42 (0.5)	12 (1.6)	<b>183 (1.0)</b>
Other	561 (14.6)	211 (4.2)	196 (2.4)	8 (1.1)	<b>976 (5.5)</b>
Not on cART in 2016	46 (1.2)	94 (1.9)	127 (1.5)	10 (1.3)	<b>277 (1.6)</b>
<b>Last CD4:CD8 ratio <sup>(1)</sup></b>					
<0.50	694 (21.0)	766 (18.0)	1,432 (20.0)	291 (44.5)	<b>3,183 (20.7)</b>
≥0.50 - 1.00	1,717 (27.2)	2,421 (56.8)	3,979 (55.6)	271 (41.4)	<b>8,388 (54.5)</b>
≥1.00	899 (27.2)	1,076 (25.2)	1,740 (24.3)	92 (14.1)	<b>3,807 (24.8)</b>
<b>Last CD4 cell count (cells/mm<sup>3</sup>) <sup>(2)</sup></b>					
<50	9 (0.2)	6 (0.1)	10 (0.1)	15 (2.0)	<b>40 (0.2)</b>
50-199	76 (2.0)	103 (2.1)	149 (1.8)	68 (9.2)	<b>396 (2.2)</b>
200-349	267 (7.1)	321 (6.6)	580 (7.0)	110 (14.9)	<b>1,278 (7.3)</b>
350-499	604 (16.1)	782 (16.0)	1,259 (15.3)	132 (17.9)	<b>2,777 (15.8)</b>
500-749	1,250 (33.3)	1,911 (39.2)	3,012 (36.6)	223 (30.3)	<b>6,396 (36.3)</b>
≥750	1,545 (41.2)	1,756 (36.0)	3,229 (39.2)	189 (25.6)	<b>6,719 (38.2)</b>
<b>Last VL&lt;50 cps/ml <sup>(3)</sup></b>					
	3,178 (85.6)	4,136 (84.5)	7,053 (85.7)	418 (56.9)	<b>14,785 (84.1)</b>
<b>Last VL&lt;200 cps/ml <sup>(3)</sup></b>					
	3,618 (97.5)	4,732 (96.7)	8,041 (97.7)	526 (71.7)	<b>16,917 (96.3)</b>

(1) Last CD4:CD8 ratio data available for n=15,378

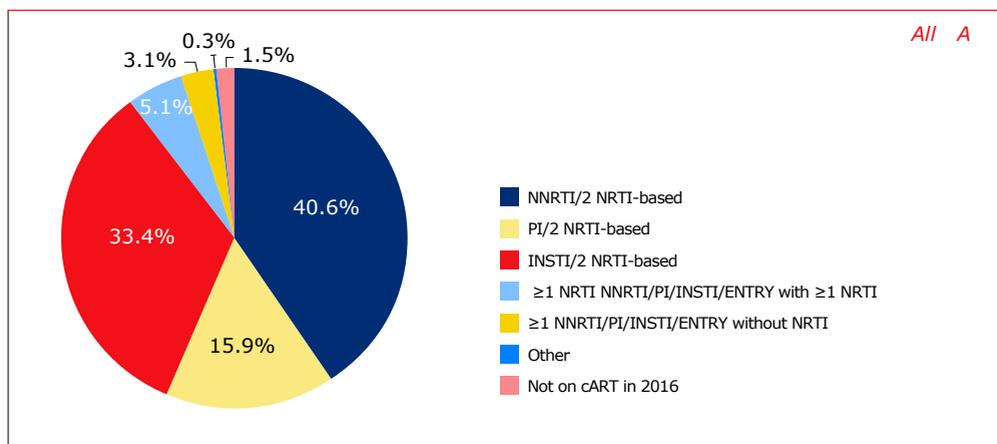
(2) Last CD4 cell count data available for n=17,606

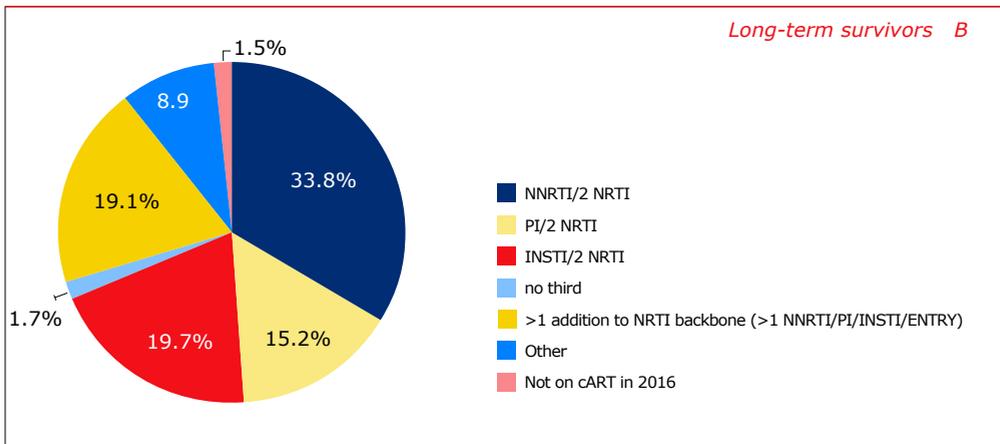
(3) Last VL data available for n=17,575

**Legend:** 3TC=lamivudine; b=boosted (cobicistat or ritonavir); Ir=ritonavir-boosted; Ic=cobicistat-boosted; cART=combination antiretroviral therapy; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir; NVP=nevirapine; PI=protease inhibitor; RAL=raltegravir; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; NNRTI=nonnucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; INSTI=integrase inhibitor; VL=viral load.

Among the 17,898 individuals in care in 2016, the majority received a regimen based on 2 nucleoside reverse transcriptase inhibitor (NRTIs), combined with either an NNRTI (40.6%), an integrase inhibitor (33.4%) or a protease inhibitor (15.9%). The distribution of cART use among the population in care in 2016 is presented in *Figure 2.2A*. Overall, and irrespective of other regimen components, integrase inhibitor-based cART was used by 39.4% of those in care in 2016; 22.3% received dolutegravir (DTG), 12.1% cobicistat-boosted elvitegravir (EVG/c), and 5.0% raltegravir (RAL). The most common regimens were abacavir (ABC)/lamivudine (3TC)/DTG (14.7%) and TDF/emtricitabine (FTC) combined with efavirenz (EFV) (14.5%) or nevirapine (NVP) (11.1%). Overall, TDF was still used by the majority of in care (62.1%). However, TAF was prescribed to 7.9% of persons in care in 2016; 75.7% of all TAF-based regimens were TAF/FTC/EVG/c. Furthermore, 277 (1.6%) individuals who had initiated cART previously had no documentation of using cART in 2016. Of those receiving cART in 2016, 84.9% had a viral load <50 copies/ml and 97.1% had a viral load <200 copies/ml. Based on the last available CD4 and CD8 cell count measurements in 2016, 74.5% had a CD4 cell count of 500 cells/mm<sup>3</sup> or higher, and 24.8% had a CD4:CD8 ratio of 1 or higher.

*Figure 2.2: Combination antiretroviral therapy use in 2016 by (A) all HIV-positive individuals who ever started cART and (B) HIV-positive individuals who ever started cART and were diagnosed before 1990 (i.e. long-term survivors). See Appendix Table 2.1 for a more detailed overview of the regimen used by HIV-positive who were diagnosed before 1990.*





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

### Long-term survivors

Out of the 17,898 HIV-1 positive adults alive and in care in the Netherlands in 2016, 538 (3.0%) were diagnosed with HIV before the year 1990 and can be considered long-term survivors. Their median age at diagnosis was 29 years (IQR 25-34). The majority were men (84.8%), and the main HIV transmission risk group was MSM (70.6%), followed by groups with heterosexual contact (12.1%), injecting drug use (11.2%), and contaminated blood or blood products (3.2%); the remaining 2.9% acquired HIV through another or unknown transmission route. Most long-term survivors (68.8%) originated from the Netherlands, followed by western Europe, North America and Australia (17.7%), South America and the Caribbean (8.4%), sub-Saharan Africa (2.2%), and other regions (3.0%). At the start of cART, the median HIV viral load was 4.5 [IQR 3.8-5.1]  $\log_{10}$  copies/ml, the median CD4 cell count was 129 [IQR 210-330] cells/mm<sup>3</sup>, and the CD4:CD8 ratio was <0.5 for 29.8%,  $\geq 0.5$ -1.0 for 49.3%, and  $\geq 1$  for 21.0%. The majority (58.3%) had initiated cART in 1996 or 1997 (37.7% and 20.6%, respectively), and 58.7% had used antiretroviral drugs as monotherapy or dual therapy before initiating cART.

As of 31 December 2016, the median age of the long-term survivors was 59 years (IQR 55-65). In 2016, 98.5% were receiving cART; 1.5% were currently not using cART, but had previously initiated cART. Two-thirds received a dual NRTI backbone in combination with a NNRTI (33.8%), integrase inhibitor (19.7%), or protease inhibitor (12.5%). The most common regimens were TDF/FTC/NVP

(13.0%), ABC/3TC/DTG (7.1%), TDF/FTC/EFV (5.8%), TDF/FTC/DRV/b (5.8%), and TAF/FTC/EVG/c (4.1%). Importantly, 29.2% received a non-standard regimen. The cART regimens are presented in *Figure 2.2B* and *Appendix Table 2.1*.

Based on the last available CD4 and CD8 cell count measurements in 2016, 2.5% had a CD4 cell count <200 cells/mm<sup>3</sup>, 9.2% between 200 and 349 cells/mm<sup>3</sup>, 20.8% between 350 and 499 cells/mm<sup>3</sup>, 33.8% between 500 and 749 cells/mm<sup>3</sup>, and 33.8% had 750 cells/mm<sup>3</sup> or higher. Furthermore, 21.0% had a CD4:CD8 ratio of 1 or higher. Of all long-term survivors receiving cART with a viral load measurement in 2016, viral suppression was high and comparable to the overall population in care: 88.4% had a viral load <50 copies/ml and 98.1% had a viral load <200 copies/ml.

### Changes in the use of initial antiretroviral therapy

Data from recent clinical trials on new antiretroviral drugs, such as DTG, EVG/c, and TAF, have shown good outcomes in terms of viral suppression, convenience, tolerability and toxicity. Over past years, these new antiretroviral drugs and once-daily fixed-dose combinations have been approved (*Box 2.2*). In this section, we evaluate the implementation after approval of these new drugs in the Netherlands.

**Box 2.2: Approval dates of new antiretroviral drugs in the Netherlands in 2011–2017.**

Medicine	Authorisation date
RPV (Edurant®), TDF/FTC/RPV (Eviplera®)	November 28, 2011
TDF/FTC/EVG/cobicistat (Stribild®)	May 24, 2013
Cobicistat (Tybost®)	September 19, 2013
DTG (Tivicay®)	January 16, 2014
ABC/3TC/DTG (Triumeq®)	September 1, 2014
DRV/cobicistat (Rezolsta®)	November 19, 2014
TAF/FTC/EVG/cobicistat (Genvoya®)	November 19, 2015
TAF/FTC (Descovy®)	April 21, 2016
TAF/FTC/RPV (Odefsey®)	June 21, 2016
TAF (Vemlidy®)	January 9, 2017

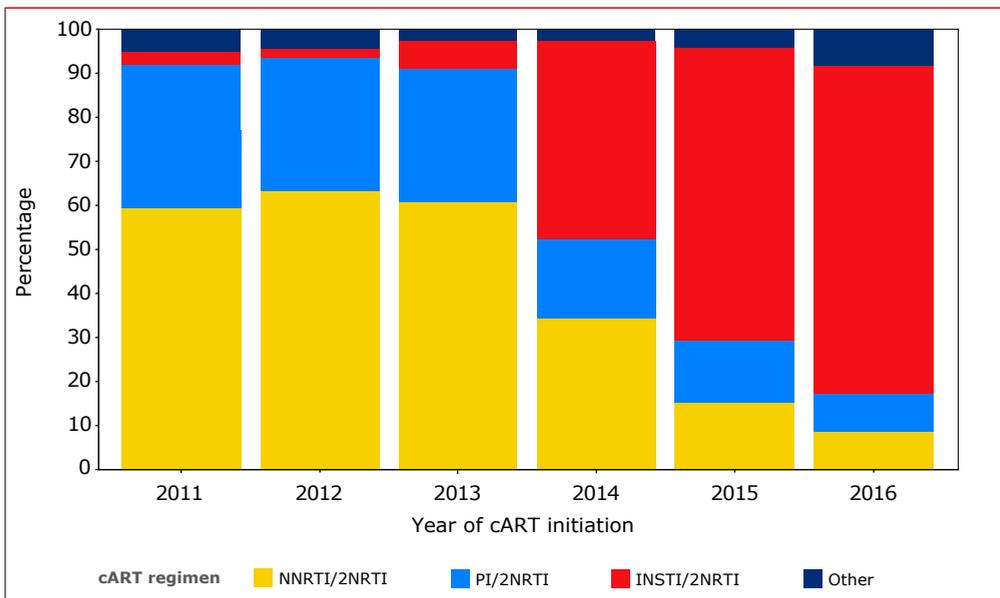
Source: *Medicines Evaluation Board*

Legend: 3TC=lamivudine; ABC=abacavir; DTG=dolutegravir; EVG=elvitegravir; FTC=emtricitabine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.

### Initial regimen

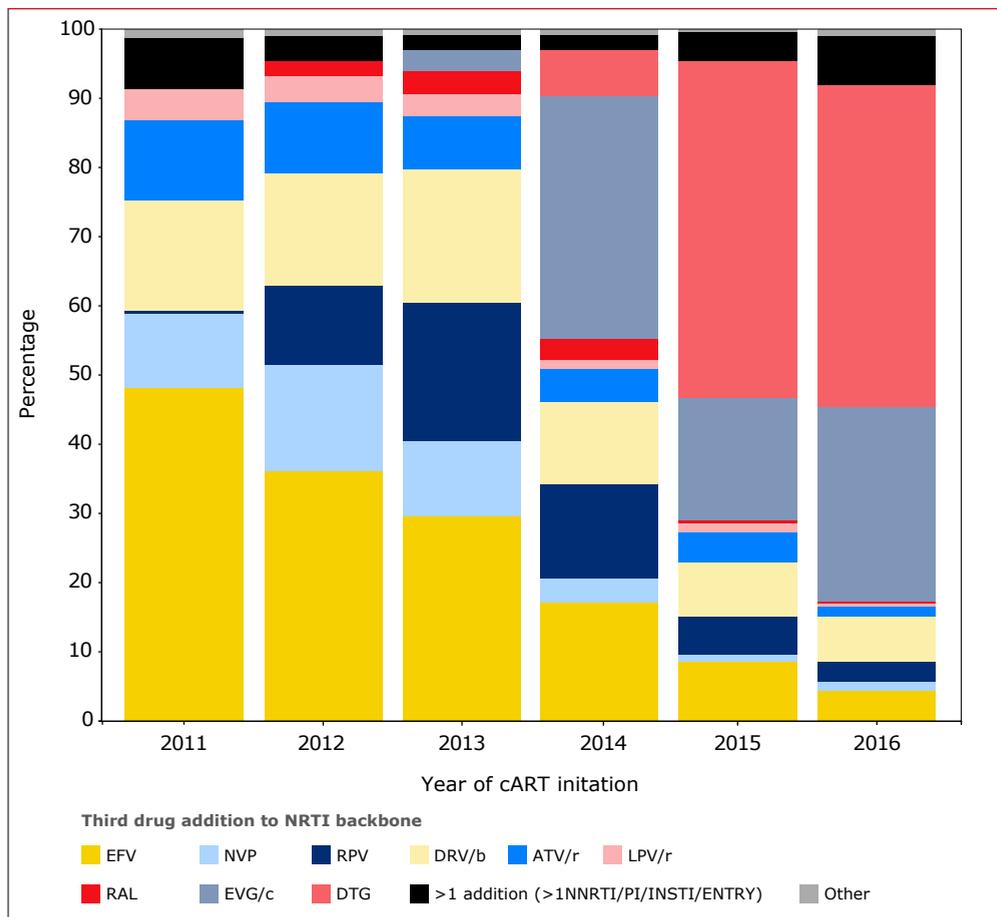
Out of 22,611 HIV-positive individuals who were known to have initiated cART between January 1995 and December 2016, 7,322 (32.5%) initiated cART between January 2011 and December 2016. *Figure 2.3 and 2.4* show the trends over time in third-drug additions to the NRTI backbone that was part of the initial cART regimen in these individuals. The use of integrase inhibitors in combination with an NRTI backbone as initial therapy has risen sharply from 2% to 3% in 2011-2012, to 6.6% in 2013, 44.8% in 2014, 67.1% in 2015, and 74.6% in 2016. EVG/c was introduced in the Netherlands at the end of 2013 and was used in 4.9%, 52.3%, 20.6%, and 22.3% of the initial regimens in 2013, 2014, 2015, and 2016, respectively. Since its introduction in 2014, DTG was prescribed as part of the initial regimen in 6.6% in 2014, increasing to 46% to 49% in 2015-2016. With the introduction of EVG/c and DTG, the use of NNRTIs in the initial regimen decreased from  $\geq 60\%$  in 2011-2013, to 34.3% in 2014, 15.2% in 2015, and 8.6% in 2016. The use of protease inhibitors in the initial regimen decreased from  $>30\%$  in 2011-2013 to 18.2% in 2014, 13.5% in 2015 and 8.6% in 2016. In 2011-2016, 3% to 5% of persons received more than one addition to the NRTI backbone in their initial cART regimen, the majority of whom initiated cART during an acute HIV infection.

*Figure 2.3: Third-drug class additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2011-2016.*



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

Figure 2.4: Individual third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial regimen in 2011–2016.

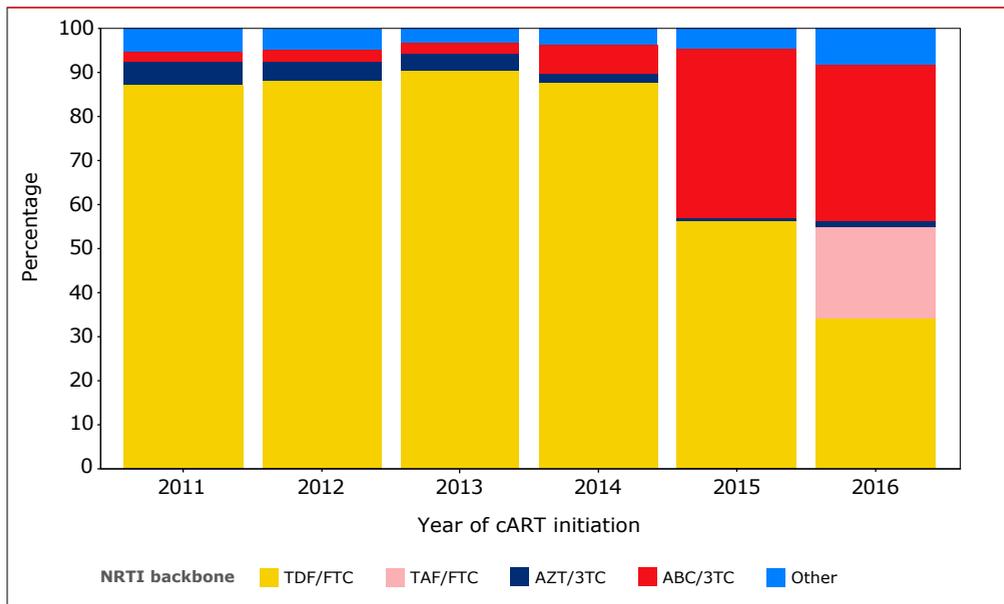


Legend: cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; ENTRY=entry inhibitor; INSTI=integrase inhibitor; LPV=lopinavir; NRTI=nucleoside reverse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

Figure 2.5 provides an overview of the initial components of the NRTI backbone used between 2011 and 2016. The combination of tenofovir (TDF or TAF) and FTC was the predominant backbone prescribed in initial cART regimens. TDF was

prescribed in 87-90% of the initial regimen in 2011-2014, 56.0% in 2015 and 34.0% in 2016; TAF with emtricitabine was prescribed in 20.5% of initial regimens in 2016. The use of abacavir in combination with lamivudine, which was introduced as a once daily fixed-dose combination with dolutegravir by the end of 2014, increased from 3% of all initial regimens in 2011-2013, to 6.7% in 2014, and 36-38% in 2015-2016. The combination of zidovudine and lamivudine further decreased over time, from 5.1% in 2011 to <1% since 2015.

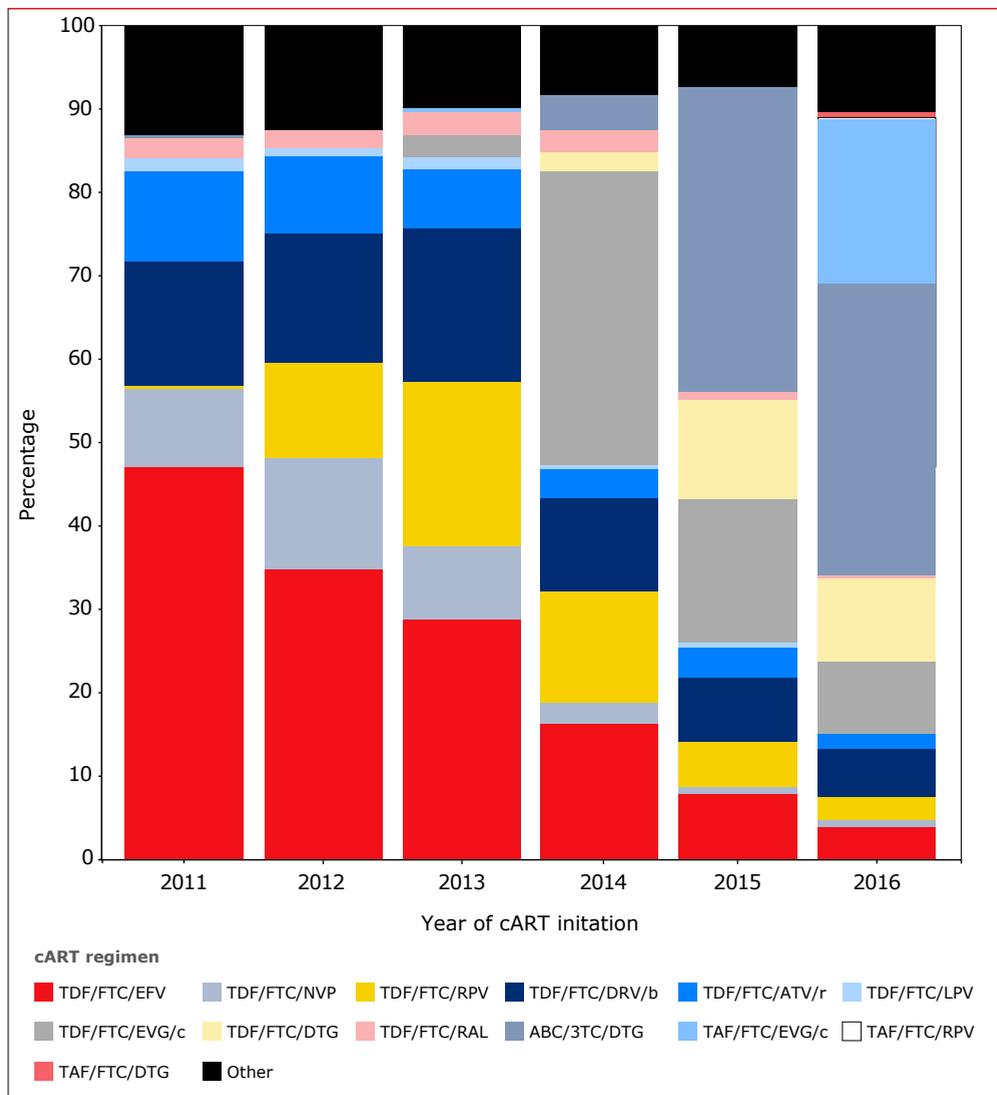
Figure 2.5: Nucleoside reverse transcriptase backbone used as part of the initial regimen in 2011–2016.



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

The full cART regimens initiated between 2011 and 2016 are presented in Figure 2.6. In 2016, the majority started a DTG-based regimen combined with either ABC and 3TC as part of the once-daily fixed-dose combination (35.0%), or provided separately with FTC and tenofovir (10.8%; TDF 10.1%/TAF 0.7%). Additionally, 28.3% initiated an EVG/c-containing once-daily fixed-dose combination with FTC and tenofovir (TDF 8.6%/TAF 19.7%). RAL is not recommended in starting regimens because it needs to be taken twice daily, and its use in an initial regimen has decreased further from 2-3% in 2011-2014 to less than 1% since 2015. The combination of DRV/b with TDF and FTC was used in 5.8% of initial cART regimens in 2016.

Figure 2.6: Initial combination antiretroviral therapy regimen use in 2011–2016.



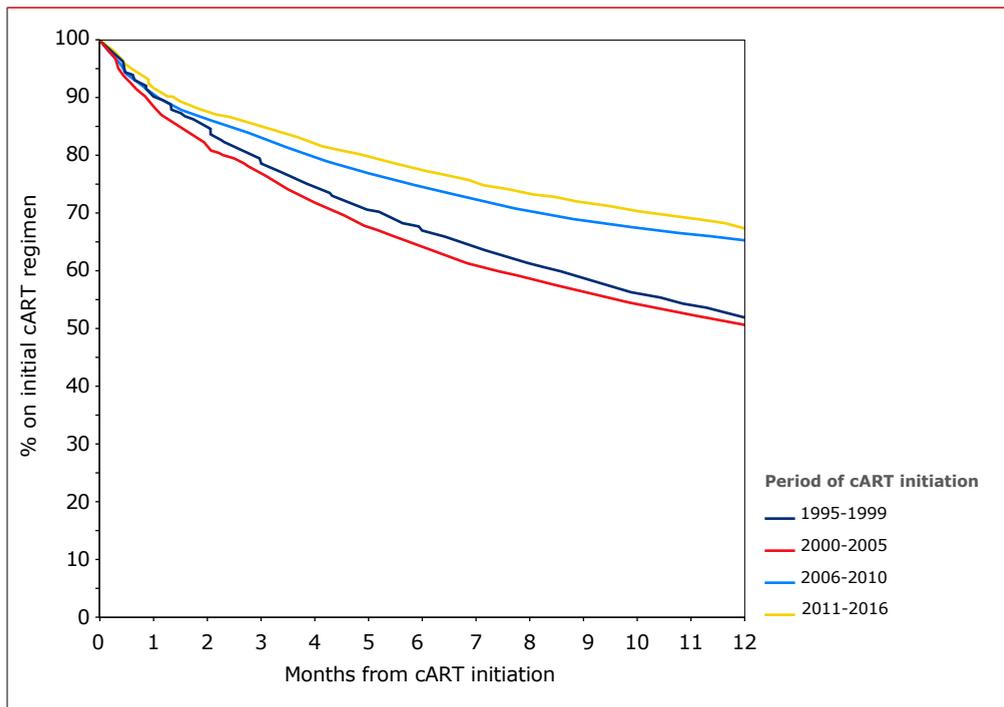
Legend: cART=combination antiretroviral therapy; lb=boosted (cobicistat or ritonavir); lr=ritonavir-boosted; lc=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir; NVP=nevirapine; RPV=rilpivirine; RAL=raltegravir; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.

In 2011-2016, 10.3% initiated an ‘other’ initial regimen not further specified. These regimens consisted of a dual NRTI backbone in combination with a different third drug (6.3%: 3.5% protease inhibitor; 2.5% NNRTI, and 0.3% integrase inhibitor); a triple class regimen containing 3 or 4 drugs (2.0%); or another antiretroviral drug combination (2.0%).

### Discontinuation of the initial regimen

We assessed the time spent on the initial cART regimen among the 22,611 individuals who ever started cART. Discontinuation of the initial cART regimen was defined as a change in, or discontinuation of, one or more of the drugs included in the regimen. Simplification to a fixed drug combination formulation containing the same drugs was not considered a discontinuation. For example, a switch from efavirenz with TDF/FTC (Truvada®) to the fixed-drug combination EFV/TDF/FTC (Atripla®) was not considered discontinuation of the initial regimen, but a change from efavirenz/TDF/emtricitabine to EVG/c/TDF/FTC was. One-year discontinuation rates presented are based on the Kaplan-Meier estimates.

Figure 2.7: Kaplan-Meier estimate of the time on initial regimen by calendar year period of initiation (log-rank test  $p < 0.001$ ).



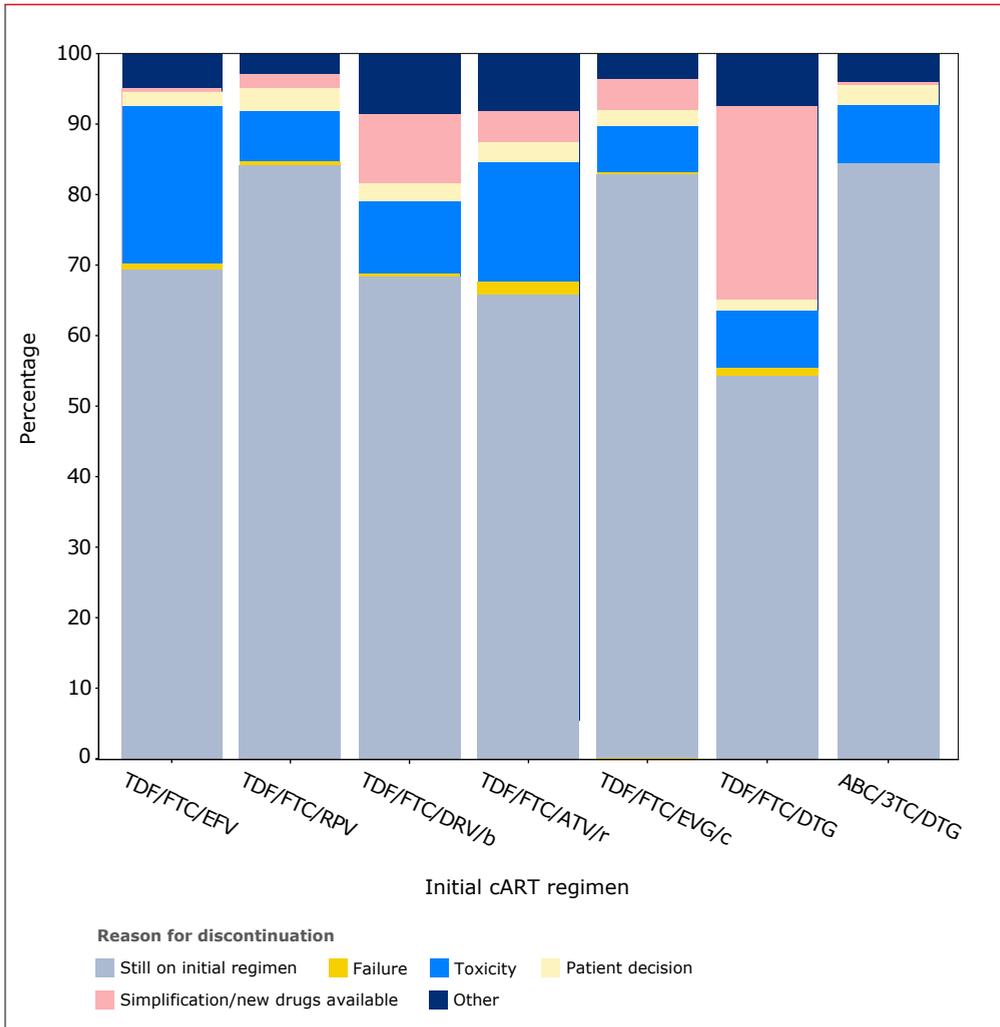
In the period 1995-2016, 40.1% (95% confidence interval [CI] 40.2-41.5) discontinued their initial regimen within one year. The time on the initial regimen improved over the years: in the period 1995-2005, half of the individuals discontinued their original regimen within a year, compared with approximately one third who discontinued their initial regimen in 2006-2016. The time spent on the initial regimen during the first year of cART stratified by 5-year periods is shown in *Figure 2.7*.

### **Discontinuation of the initial regimen: 2011-2016**

We further assessed the time to discontinuation of the initial regimen during the first year of treatment among 5,723 individuals who started common initial regimens in 2011 and beyond. Common regimens considered in this analysis were: TDF/emtricitabine combined with EFV (TDF/FTC/EFV; 31.7%), RPV (TDF/FTC/RPV; 12.4%), DRV/b (TDF/FTC/DRV/b; 16.3%), ritonavir-boosted atazanavir (TDF/FTC/ATV/r; 8.2%), EVG/c (TDF/FTC/EVG/c; 14.1%), DTG (TDF/FTC/DTG; 4.3%), or ABC-3TC combined with dolutegravir (ABC/3TC/DTG; 13.0%). Numbers were too small and follow up time too limited to provide reliable one-year discontinuation rates and reasons for TDF/TDF/RAL and TAF/FTC/EVG/c.

One year after cART initiation, 1,522 (26.6%) out of 5,723 individuals who initiated one of these regimens had discontinued their initial regimen. The main reason for regimen discontinuation was toxicity (n=764; 50.2%), followed by simplification and/or availability of new drugs (n=237; 15.6%). The availability of new once-daily fixed-dose combinations contributed to an increase in initial regimen discontinuation due to simplification and/or availability of new drugs, especially for those receiving TDF/FTC/DTG, and TDF/FTC/DRV/b (*Figure 2.8*). Of all discontinuations, 5.7% discontinued their initial regimen for simplification reasons and/or availability of new drugs in 2011, compared to 9.9% in 2012, 7.2% in 2013, 15.2% in 2014, 28.9% in 2015 and 30.3% in 2016.

Figure 2.8: Reasons for discontinuation of the initial regimen during the first year of treatment 2011–2016, by regimen.



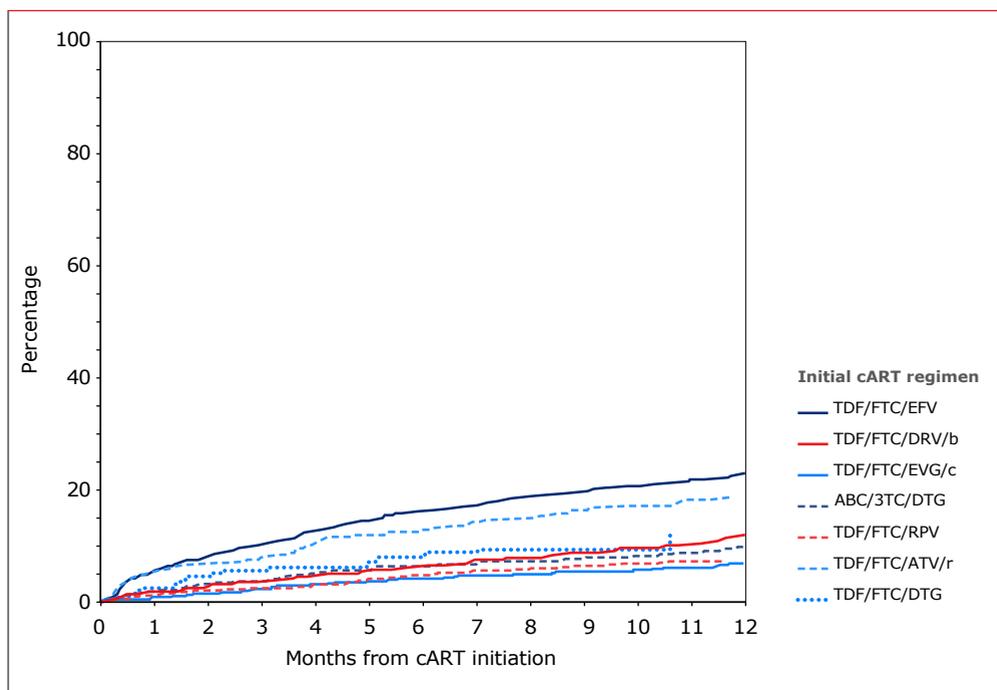
**Legend:** cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TDF=tenofovir disoproxil fumarate.

### Discontinuation of the initial regimen due to toxicity

Figure 2.9 presents the time until discontinuation of the initial regimen due to toxicity during the first year of treatment, by regimen. The discontinuation rate due to toxicity was significantly higher for those initiating TDF/FTC/EFV than for those

initiating any of the other regimens: 23.4% (95% CI 21.5-25.5) discontinued within one year ( $p < 0.001$ ). Of those receiving a protease inhibitor-based regimen, toxicity-driven discontinuations in the first year were more frequent among those receiving TDF/FTC/ATV/r (19.0%; 95% CI 15.5-23.1), than among those receiving TDF/FTC/DRV/b (12.2%; 95% CI 10.1-14.7;  $p < 0.001$ ). In general, discontinuation due to toxicity was least frequent among individuals who received TDF/FTC/EVG/c (6.9%; 95% CI 5.3-9.0). Of those who initiated TDF/FTC/RPV, 7.5% (95% CI 5.7-9.7) discontinued their regimen due to toxicity in the first year. Toxicity-driven discontinuation of DTG combined with TDF/FTC or ABC/3TC occurred at a rate of 11.7% (95% CI 7.5-18.0) and 10.1% (95% CI 7.9-12.8), respectively. The type of backbone did not have a significant influence on toxicity-driven discontinuation of DTG-based cART ( $p = 0.408$ ).

**Figure 2.9:** Kaplan–Meier estimate of the time till discontinuation of the initial regimen due to toxicity 2011–2016 by regimen. Time was censored when the initial regimen was discontinued due to reasons other than toxicity (log-rank  $p < 0.001$ ).

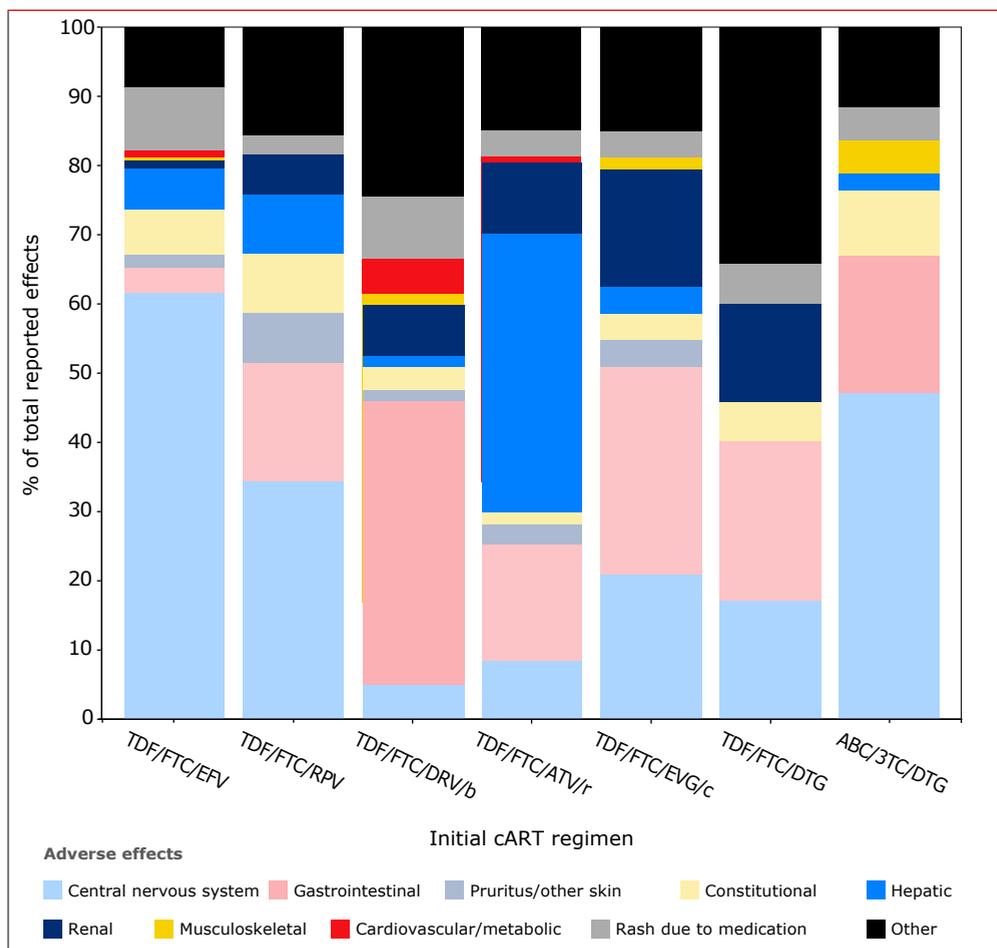


**Legend:** cART=combination antiretroviral therapy; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; RPV=rilpivirine; TDF=tenofovir disoproxil fumarate.

### Adverse effects

Among the 764 individuals who discontinued their initial cART regimen due to toxicity within a year, 1,063 adverse effects were recorded. The predominant effects recorded were: 43.1% central nervous system-related (mainly insomnia, mood changes, dizziness, and depression), 13.6% gastrointestinal (mainly diarrhoea and nausea), 8.5% hepatic and 7.4% rash due to medication. These adverse effects are stratified by cART regimen in *Figure 2.10*. Central nervous system-related effects were associated with TDF/FTC/EFV, ABC/3TC/DTG (but less for TDF/FTC/DTG), and TDF/FTC/RPV. Hepatic effects were reported mainly by individuals discontinuing TDF/FTC/ATV/r. Renal effects were reported only by individuals who discontinued TDF-based cART.

Figure 2.10: Adverse effects associated with regimen discontinuation due to toxicity within the first year of treatment for those initiating treatment between 2011 and 2016. The bars represent the distribution of 1,063 reported effects among 764 individuals by regimen.



Legend: cART=combination antiretroviral therapy; 3TC=lamivudine; /b=boosted (cobicistat or ritonavir); /r=ritonavir-boosted; /c=cobicistat-boosted; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; TDF=tenofovir disoproxil fumarate; RPV=rilpivirine.

Note: The presented discontinuation rates and reasons for discontinuation are descriptive by nature, and should be interpreted with caution. The choice of initial cART regimen depends on patient characteristics, which might explain differences in discontinuation unrelated to the regimen (i.e., confounding by indication).

Furthermore, follow-up time for some of the newer cART regimens was fairly short, which also influences discontinuation rates.

## Virological response

In the Netherlands, a total of 22,611 individuals have started cART since January 1995. For the current analysis of virological outcomes, we will focus on the 19,981 individuals who were ART-naïve at the time of starting cART. Since 2009, more than 98% of the individuals starting cART were ART-naïve. We subsequently excluded 672 women who were pregnant at the time of cART initiation, because cART may have been interrupted at the end of the pregnancy. Subsequently, we excluded 756 individuals without any viral load test result after at least three months of cART initiation. Results in the following section on viral response to cART are therefore restricted to the remaining 18,545 individuals. The main definitions for virological outcomes used in this chapter are summarised in *Box 2.3*.

### Initial virological success

Out of 18,545 included individuals with a viral load test result after at least 3 months of cART initiation, 15,894 (85.7%) had a viral load measurement 6 ( $\pm$  3 months) months after cART initiation. Of these individuals, 13,622 (85.7%) 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 61.7% (95% CI 59.6-63.8) in those starting cART between 1995 and 2001, to 87.5% (95% CI 86.6-88.4) in those starting between 2002 and 2008, 90.3% (95% CI 89.6-90.9) in those starting between 2009 and 2015, and 91.4% (95% CI 88.8-93.9) in those starting in 2016.

### Initial virological success of common initial cART regimens (2011-2016)

We analysed the initial virological success among the 5,305 individuals who started a common cART regimen in 2011-2016 (TDF/FTC with EFV, RPV, DRV/b, ATV/r, EVG/c, DTG, RAL, ABC/3TC/DTG or TAF/FTC/EVG/c; described under 'Changes in use of initial antiretroviral therapy 2011-2016'), and had a viral load result after 6 ( $\pm$  3) months of cART initiation. In total, 92.6% (95% CI 91.9-93.3) showed initial virological suppression, after a mean of 179 (standard deviation [SD] 38) days. Overall, individuals on an integrase-inhibitor based regimen showed significantly higher rates of initial virological success: 94.7% (95% CI 92.1-94.1) of individuals on an integrase-inhibitor based regimen had initial virological success, compared to 88.7% (95% CI 86.9-90.4) on a protease-inhibitor based regimen and 93.1% (95% CI 92.1-94.1) on a NNRTI-based based regimen. These differences are in line with results from randomised clinical trials.

We further evaluated the initial virological success rates stratified by viral load at cART initiation, cART regimen, and regimen class through logistic regression analysis. Out of 5,305 individuals, 4,286 also had viral load data available at the time of cART initiation. Stratified analysis of initial virological success based on viral load at cART initiation showed similar differences between cART regimens as described in the previous paragraph. The effect of cART regimen on the initial virological suppression rates was strongest in individuals with a viral load  $\geq 100,000$  copies/ml at cART initiation, see *Table 2.3*.

### **Viral suppression**

We assessed longitudinal viral suppression rates (i.e., viral load  $< 200$  copies/ml) over time on cART during six-monthly intervals among the 18,545 individuals with a viral load test result after cART initiation. The viral load measurement after at least three months of cART closest to each six-monthly time point ( $\pm 3$  months) was included in the analysis, irrespective of the viral load of that time point.

**Box 2.3: Definitions of virological response and HIV drug resistance.****Virological response****Initial virological success**

HIV viral load <100 copies/ml within 6 months after starting cART. The viral load measurement closest to 6 months ( $\pm 3$ ) after cART initiation was included in the analysis, irrespective of the viral load of that measurement.

**Viral suppression**

Any viral load measurements <200 copies/ml, at least 3 months after cART initiation.

**Viral rebound**

First of two consecutive viral load measurements  $\geq 200$  copies/ml after 6 months (>180 days) of cART.

**HIV drug resistance****Transmitted drug resistance**

At least one resistance-associated major mutation detected within a year of HIV diagnosis, among recently infected\* people who had never previously received antiretroviral drugs and had not started cART. The 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations<sup>32</sup>.

*\*Recent infection:* An infection was considered recent when there was less than 12 months between the last known negative HIV test and the first known positive HIV test. Individuals without a previously negative test or with a negative test more than 12 months before the first positive test were excluded.

**Acquired drug resistance**

High-level resistance to at least one antiretroviral drug detected at the time of virological failure (viral load >500 copies/ml) among people receiving cART for at least 4 months. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.3) was used to infer antiretroviral drug susceptibility and resistance scores<sup>33,34</sup>.

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

**Table 2.3: Initial virological success rates (see definition in Box 2.3) by initial regimen, and initial viral load at cART start. Population characteristics, which can be associated with the initial prescribed regimen, were not taken into account in this analysis.**

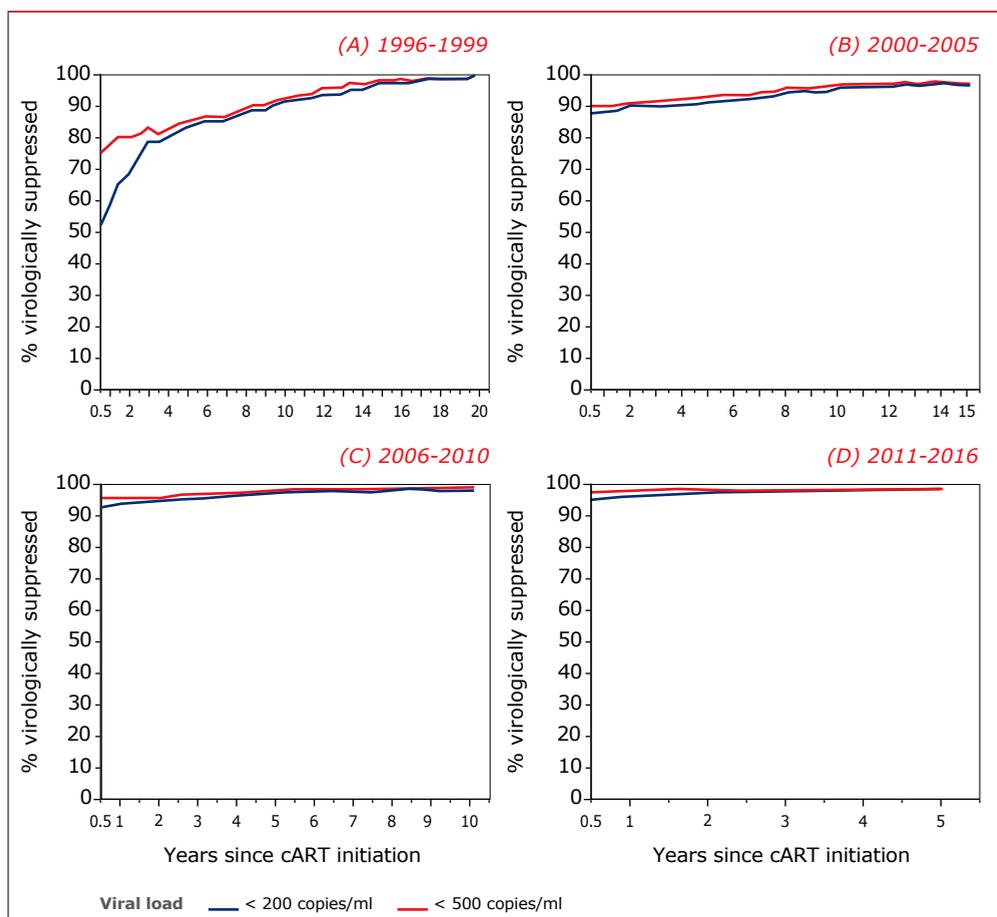
	Total		By initial viral load at cART start					
	(n=4,286; 100%)		<100,000 copies/ml (n=2,559; 59.7%)					
	n	%	n	%	Initial viral success	95% CI low	95% CI high	p-value
<b>cART regimen</b>								
TDF/FTC/EFV	1,274	29.7	675	26.4	97.0	95.8	98.3	reference
TDF/FTC/RPV	483	11.3	483	18.9	95.2	93.3	97.1	0.220
TDF/FTC/DRV/b	752	17.6	306	12.0	95.1	92.7	97.5	0.236
TDF/FTC/ATV/r	325	7.6	148	5.8	93.2	89.2	97.3	0.042
TDF/FTC/EVG/c	585	13.7	405	15.8	97.0	95.4	98.7	0.559
TDF/FTC/DTG	177	4.1	92	3.6	96.7	93.1	100.0	0.880
TDF/FTC/RAL	104	2.4	58	2.3	96.6	91.9	100.0	0.970
ABC/3TC/DTG	513	12.0	343	13.4	97.4	95.7	99.1	0.373
TAF/FTC/EVG/c	73	1.7	49	1.9	98.0	94.0	100.0	0.535
<b>cART regimen class</b>								
NNRTI/2NRTI	1,757	41.0	1,158	45.3	96.3	95.2	97.4	reference
PI/2NRTI	1,077	25.1	454	17.7	94.5	92.4	96.6	0.022
INSTI/2NRTI	1,452	33.9	947	37.0	97.1	96.1	98.2	0.040
<b>All regimens</b>					<b>96.3</b>	<b>95.6</b>	<b>96.2</b>	

**Legend:** cART=combination antiretroviral therapy; 3TC=lamivudine; ABC=abacavir; ATV/r=ritonavir–boosted atazanavir; CI=confidence interval; DRV/b=cobicistat/ritonavir–boosted darunavir; DTG=dolutegravir; EFV=efavirenz; EVG/c=cobicistat–boosted elvitegravir; FTC=emtricitabine; INSTI=integrase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non–NRTI; PI=protease inhibitor; RPV=rilpivirine; RAL=raltegravir; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate.

		By initial viral load at cART start ≥100,000 copies/ml (n=1,727; 40.3%)					
		n	%	Initial viral success	95% CI low	95% CI high	p-value
<b>cART regimen</b>							
TDF/FTC/EFV		599	34.7	87.1	84.5	89.8	reference
TDF/FTC/RPV	not recommended						
TDF/FTC/DRV/b		446	25.8	83.9	80.4	87.3	0.171
TDF/FTC/ATV/r		177	10.3	83.6	78.2	89.1	0.265
TDF/FTC/EVG/c		180	10.4	91.7	87.6	95.7	0.037
TDF/FTC/DTG		85	4.9	89.4	82.9	96.0	0.398
TDF/FTC/RAL		46	4.9	82.6	71.6	93.6	0.393
ABC/3TC/DTG		170	9.8	90.6	86.2	95.0	0.108
TAF/FTC/EVG/c		24	1.4	79.2	62.9	95.4	0.242
<b>cART regimen class</b>							
NNRTI/2NRTI		599	34.7	87.1	84.5	89.8	reference
PI/2NRTI		623	36.1	83.8	80.9	86.7	0.007
INSTI/2NRTI		505	29.2	89.5	86.8	92.2	0.029
<b>All regimens</b>				<b>86.6</b>	<b>85.0</b>	<b>88.2</b>	

Figure 2.11 shows viral suppression rates by calendar period of cART initiation: 1995-1999, 2000-2005, 2006-2010 and 2011-2016. In line with the initial virological success rates, the long-term viral suppression rates likewise improved over time. In those initiating cART in or after 2011, suppression rates ranged from 96.3% (95% CI 95.8-96.8) after one year of cART use to 98.1% (95% CI 97.5-98.7) after four years. The viral suppression rates over time of the full period (1995-2016) are shown in [Appendix Figure 2.2](#).

Figure 2.11: Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1996-1999, (B) 2000-2005, (C) 2006-2010, (D) 2011-2016.



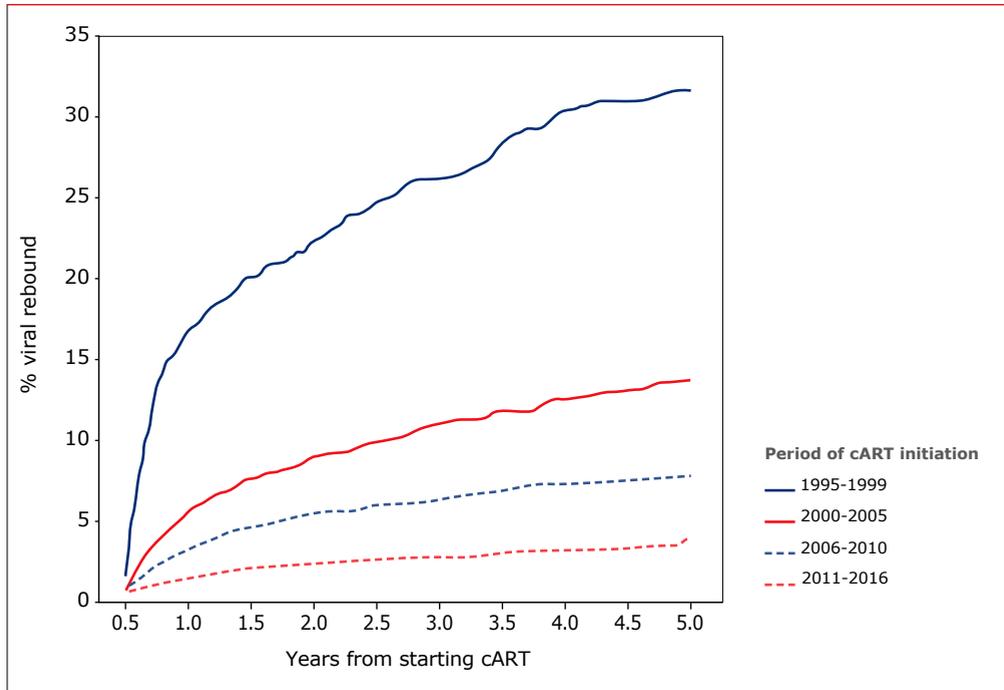
Legend: cART=combination antiretroviral therapy.

Note: To some extent, the increasing trend in viral suppression over time after the start of cART may reflect a bias towards individuals who do well and remain in follow up (i.e., survivor bias).

### Viral rebound

We further assessed the incidence of viral rebound, i.e., the first of two consecutive viral load measurements  $\geq 200$  copies/ml after six months of cART (Box 2.3). Time was censored at the date of last contact with HIV care or at the last date of cART when individuals interrupted cART for longer than two weeks. In total, 17,044 individuals were ART-naïve, not pregnant at cART initiation, and had a viral load test result after six months of continuous cART. In total, 1,807 (10.6%) individuals experienced a viral rebound after a median of 1.4 (IQR 0.7-3.4) years on cART. The incidence of the viral rebound decreased substantially by year of cART initiation (Figure 2.12).

Figure 2.12: Kaplan-Meier estimates of viral rebound\* according to calendar period of starting combination antiretroviral therapy in previously treatment-naïve individuals (log-rank  $p < 0.001$ ).



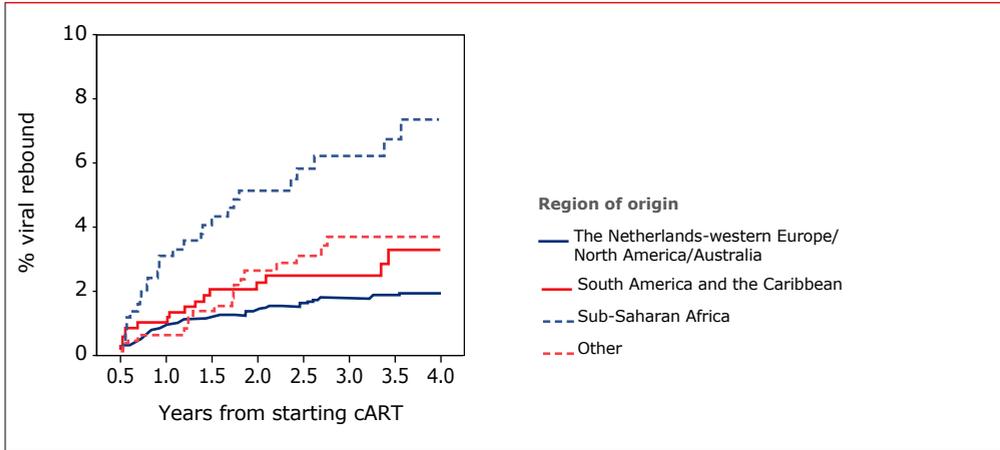
\*Viral rebound is defined as the first of two consecutive viral load measurements  $\geq 200$  copies/ml after 6 months (>180 days) of cART (see Box 2.3).

Legend: cART=combination antiretroviral therapy.

Among the 6,228 individuals who initiated cART in 2011 or thereafter, 133 (2.1%) experienced a viral rebound after a median of 1.6 (IQR 0.7-2.0) years on cART. The Kaplan-Meier curves in *Figure 2.13 and 2.14* show the incidence of viral rebound by region of origin and risk group, respectively. MSM were found to have an overall lower risk of viral rebound, compared to heterosexual males and females. Among heterosexuals, the risk of viral rebound was lowest among those originating from western Europe/North America/Australia. In *Appendix Figure 2.3*, the curves are plotted by a combination of region of origin and risk group.

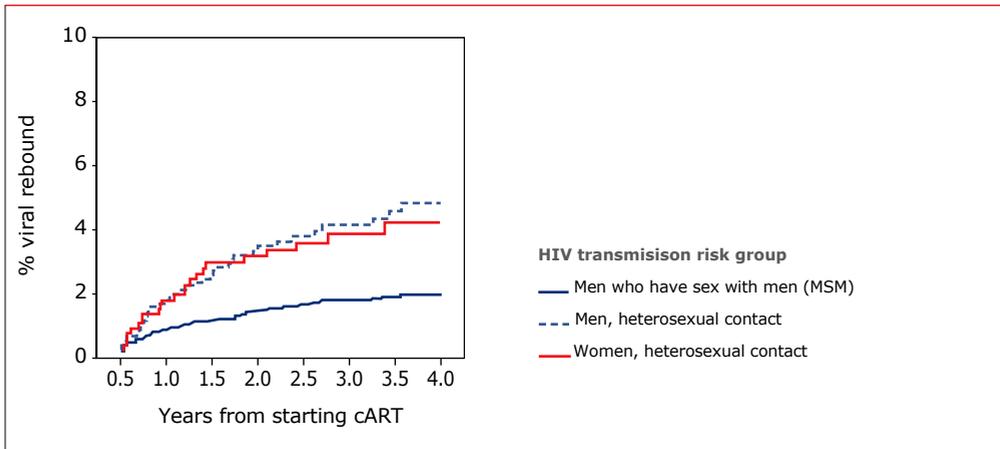
Additionally, we assessed the factors associated with time-to-viral rebound since cART initiation in 2011-2016, with univariable and multivariable Cox models (*Table 2.4*). The multivariable analysis confirmed that the incidence of viral rebound was higher among heterosexual men than among MSM, and higher among those who originated from sub-Saharan Africa than from western Europe/North America/Australia. Furthermore, those with a higher HIV viral load at the start and those starting with CD4 cell counts below 200 cells/mm<sup>3</sup> also had an increased risk of viral rebound compared with those with a lower HIV viral load or higher CD4 cell count, respectively.

Figure 2.13: Kaplan-Meier estimates of viral rebound according to region of origin among previously ART-naïve individuals receiving cART since 2011 (log-rank  $p < 0.001$ ).



Legend: Viral rebound=the first of two consecutive viral load measurements  $\geq 200$  copies/ml after 6 months (>180 days) of cART.

Figure 2.14: Kaplan-Meier estimates of viral rebound according to HIV-transmission risk group among previously ART-naïve individuals receiving cART since 2011 (log-rank  $p < 0.001$ ).



Legend: Viral rebound=the first of two consecutive viral load measurements  $\geq 200$  copies/ml after 6 months (>180 days) of cART.

**Table 2.4:** Factors independently associated with time to viral rebound after combination antiretroviral therapy (cART) initiation since 2011. 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, and also for age and year of cART initiation. Individuals included initiated cART as of 2000. Time was censored when individuals interrupted therapy for longer than two weeks.

	Unadjusted hazard ratio	95% CI		p-value	Adjusted hazard ratio	95% CI		p-value
		low	high			low	high	
<b>Risk group</b>								
Men who have sex with men	Reference				Reference			
Men, heterosexual contact	2.57	1.74	3.81	<.001	1.65	1.00	2.71	0.049
Women, heterosexual contact	2.54	1.61	3.99	<.001	1.58	0.88	2.85	0.126
<b>Region of origin</b>								
The Netherlands/western Europe/ North America/Australia	Reference				Reference			
South America and the Caribbean	1.82	1.08	3.06	0.025	1.53	0.82	2.86	0.183
Sub-Saharan Africa	2.29	2.79	6.60	<.001	2.32	1.31	4.12	0.004
Other	1.94	1.15	3.26	0.013	1.58	0.87	2.90	0.135
<b>CD4 cell count at cART initiation (cells/mm<sup>3</sup>)</b>								
<50	5.55	2.85	10.81	<.001	2.30	1.03	5.13	0.041
50–199	4.22	2.24	7.95	<.001	2.14	1.01	4.51	0.046
200–349	1.62	0.84	3.13	0.153	1.25	0.56	2.63	0.554
350–499	1.090	0.53	2.25	0.816	0.88	0.39	2.00	0.755
≥500	Reference				Reference			
<b>HIV RNA load at cART initiation</b>								
By log <sub>10</sub> copies/ml (continuous)	1.78	1.41	2.24	<.001	1.54	1.79	2.00	0.001
<b>Recent infection</b>								
No	Reference				Reference			
Yes	0.39	0.23	0.66	<.001	0.55	0.28	1.12	0.099
<b>Hepatitis C virus status at cART initiation</b>								
HCV negative	Reference				Reference			
HCV RNA positive	4.50	1.43	4.14	0.010	0.96	0.23	4.00	0.957
HCV Ab positive	0.96	0.24	3.88	0.954	2.66	0.64	1.08	0.180
Unknown	0.95	0.35	2.57	0.918	1.45	0.52	4.00	0.480
<b>Hepatitis B virus status at cART initiation</b>								
HBV negative	Reference				Reference			
HBV positive	2.25	1.14	4.43	0.019	1.93	0.96	3.87	0.065
Unknown	0.37	0.09	1.51	0.166	0.33	0.05	2.44	0.277

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

## HIV drug resistance

Preventing, monitoring and responding to HIV drug resistance is a key component of comprehensive and effective HIV care. HIV drug resistance is caused by the selection of mutations in the genetic structure of HIV that affects the ability of a particular drug or combination of drugs to block replication of the virus due to unsuccessful viral suppression. All current antiretroviral drugs, including newer classes, are at risk of becoming partially or fully inactive due to the emergence of drug-resistant virus<sup>35</sup>.

We assessed the occurrence of HIV drug resistance in the Netherlands among individuals with a viral load >500 copies/ml who had genotypic test results available. The genotypic test results presented in this section relate to the HIV-1 reverse transcriptase and protease gene; HIV-1 sequences of the integrase gene were rare. Therefore, the results of integrase inhibitor resistance testing are described in a separate section. Of note, SHM does not have drug resistance data from all HIV treatment centres and laboratories. Consequently, the presented figures might not be representative for the full HIV-positive population in the Netherlands.

We evaluated the presence of mutations in the HIV genome that are associated with drug resistance. The 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations<sup>32</sup>. Furthermore, we assessed the association between these mutations and the susceptibility to antiretroviral drugs. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.3) was used to infer antiretroviral drug susceptibility scores for each sequence according to a five-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance<sup>33,34</sup>. The definitions of transmitted and acquired HIV drug resistance used in our analyses are summarised in *Box 2.3*.

### Screening for drug resistant HIV before treatment initiation

In the Netherlands, screening for HIV drug resistance at the time of entry into care has been incorporated in the Dutch treatment guidelines since 2003. Transmitted HIV drug resistance occurs when previously uninfected individuals acquired HIV that harbours drug resistance mutations. Although a drug-resistant virus strain may revert to a drug-susceptible virus, drug-resistant variants of HIV may remain dormant in resting CD4 cells, awaiting more favourable conditions for replicating after treatment has started<sup>36,37,38</sup>. Therefore, the presence of transmitted resistance needs to be detected in antiretroviral (ARV)-naive persons before the initiation of cART, as close to the moment of infection as possible.

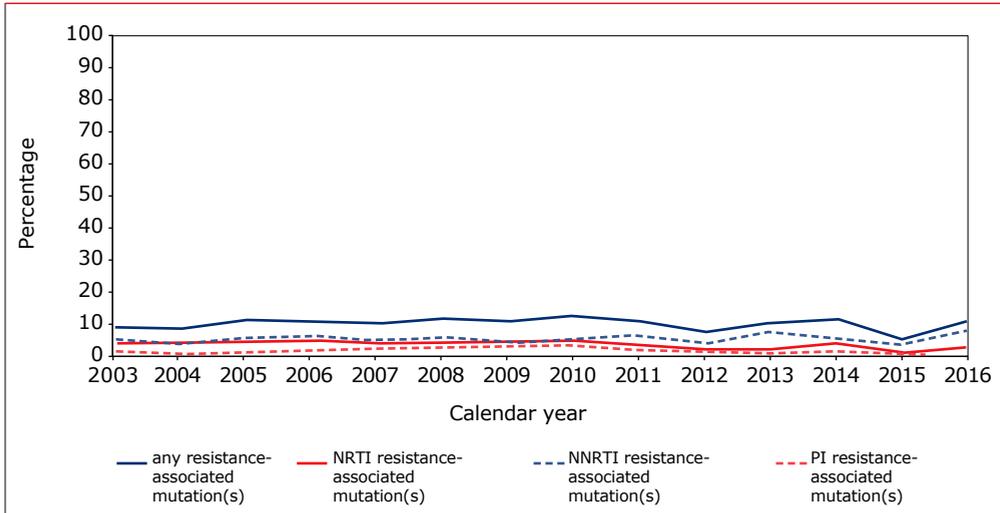
During 2003-2016, HIV-1 sequences were obtained from 5,971 ARV-naive individuals within a year of their HIV diagnosis and before the initiation of cART. If an individual had more than one sequence available before cART initiation, we selected the first available sequence (closest to the date of HIV diagnosis) for further analysis to limit the effect of back mutation. Subsequently, we stratified the results for sequences obtained at the time of a recent and non-recent infection. An infection was considered recent when the time between the last negative HIV test and the first positive test was no longer than 12 months. Those without a previously negative test or with a negative test more than 12 months before the first positive test were considered to have long-standing (i.e., non-recent) infections. The number of sequences and individuals included in each of the analysis is outlined in [Box 2.1](#).

Of 5,971 individuals, 22.5% had a recent infection at the time of genotype resistance testing; 77.5% had a long-standing infection. These two groups differed markedly regarding patient characteristics and HIV-1 subtype. Individuals with a resistance test at the time of a recent infection were more likely to be MSM (90.3% vs 61.5%) and originally from the Netherlands (71.9% vs 57.0%), and less likely to be female (4.2% vs 17.9%), to have acquired HIV through heterosexual contact (8.3% vs 31.9%) or to originate from sub-Saharan Africa (2.8% vs 14.7%) than individuals with a long-standing infection. The main HIV-1 subtypes were B (76.1% in total; 86.8% vs 73.0% for recent and long-standing infections, respectively), followed by recombinant form CRF\_02AG (7.1%: 3.8% vs 8.1%) and subtype C (5.0%: 1.7% vs 5.9%).

### Transmitted drug resistance

In total, one resistance-associated major mutation or more<sup>32</sup> was found in 620 (10.4%) of those who tested for resistance within one year of diagnosis, including 230 (3.9%) with NRTI-associated resistance mutations, 328 (5.5%) with NNRTI-associated resistance mutations, and 114 (1.9%) with protease inhibitor-associated resistance mutations. This prevalence of transmitted drug resistance was low and stable between 2003 and 2016 (*Figure 2.15*).

**Figure 2.15:** The annual proportion of individuals with evidence of transmitted drug resistance over time. Transmitted drug resistance was defined as the presence of at least one resistance-associated mutation detected within a year of HIV diagnosis and before initiating cART. The 2017 IAS-USA HIV drug resistance mutation list was used to score major resistance-associated mutations<sup>32</sup>.



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

In total, 201 (3.4%) individuals screened for transmitted drug resistance harboured high-level resistance<sup>33,34</sup> to at least one antiretroviral drug; 101 (1.7%) to at least one NRTI, 105 (1.8%) to at least one NNRTI and 26 (0.4%) to at least one protease inhibitor. Moreover, the level of transmitted drug resistance detected was similar among individuals with a recent infection and those with a long-standing infection. On the basis of the available resistance data, more than 95% of persons were fully susceptible to all antiretroviral drugs; 3.0% (n=176) harboured high-level resistance in one drug class, 0.3% (n=18) in two drug classes, and 0.1% (n=7) to all three drug classes (i.e., NRTIs, NNRTIs and PIs). It should be emphasised that this does not mean that entire drug classes are rendered unsuitable for use in antiretroviral combinations. Even for those with resistance to all three classes, fully efficacious cART combinations can often still be constructed.

### Integrase inhibitor resistance before HIV treatment initiation

Eleven people had an integrase sequence available prior to cART initiation; all of them were ARV-naïve, and one had recently acquired HIV. No major or minor integrase-resistance associated mutations were detected.

### Acquired drug resistance

The overall viral suppression rates of the HIV-positive population receiving cART are very high, and continue to improve in the Netherlands (see section *Virological response*; *Figure 2.11*). However, acquired HIV drug resistance can still be detected in a subset of individuals receiving cART.

In this section, we describe the level of acquired drug resistance detected among the treated population with both a viral load >500 copies/ml and resistance test results available after at least four months of cART in 2000-2016. If cART was interrupted more than two weeks before the test, the sequence was excluded from the analysis. For analyses over time, we reported the results based on the last available sequence in cases where an individual had more than one sequence available in any given calendar year.

In total, 4,584 HIV-1 sequences were obtained from 2,837 individuals who received cART for at least four months. The number of sequences and individuals included in each subsequent analysis are outlined in *Box 2.1*. The median time between initial cART initiation and resistance testing was 5.1 years [IQR 2.8-8.0]. The main HIV-1 subtype was B (71.2%), followed by recombinant form CRF\_02AG (8.1%) and subtype C (6.7%).

Overall, sequences from persons pre-treated with monotherapy and dual therapy were disproportionately represented: 1,502 (32.8%) sequences were obtained from 832 (31.7%) pre-treated persons, and 3,082 (67.2%) sequences were obtained from 2,005 (68.3%) ARV-naive persons. However, over time this diversion became less distinct. In 2000, 71.5% of sequences was obtained from pre-treated persons, compared to 53.2% in 2005, 14.1% in 2010 and <10% since 2015.

Out of all 4,584 sequences obtained at the time of virological failure, 2,964 (64.7%) harboured high-level resistance<sup>33,34</sup> to at least one antiretroviral drug. High-level NRTI resistance was detected in 2,588 (56.5%) sequences, 2,077 (80.3%) of which harboured high-level resistance to emtricitabine or lamivudine. In addition, 1,732 (37.8%) harboured high-level resistance to at least one NNRTI, and 1,131 (24.7%) to at least one protease inhibitor.

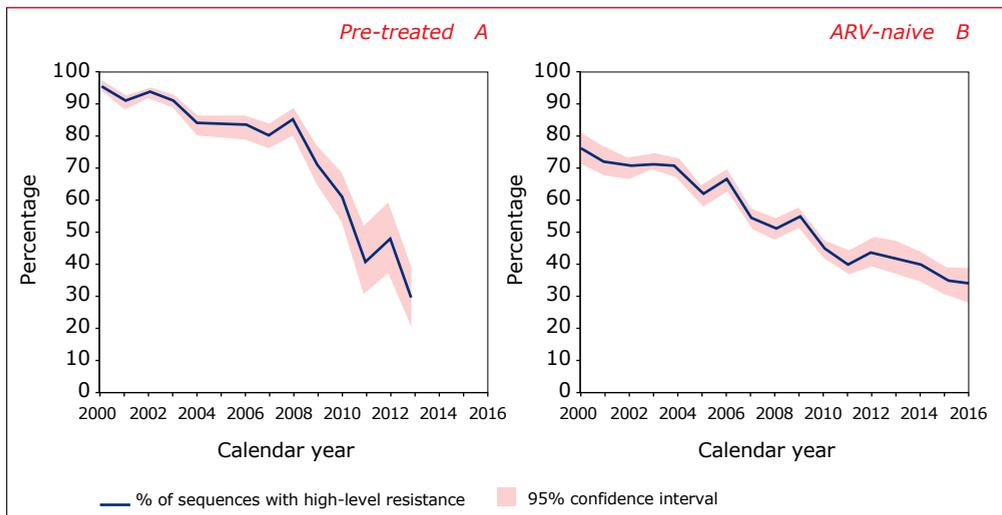
### Previous antiretroviral drug exposure

The occurrence of acquired resistance was different for sequences obtained from previously pre-treated people compared with those obtained from people who were ARV-naïve before initiating cART.

Among pre-treated people, the annual proportion of sequences harbouring high-level resistance to at least one drug was detected among 95.3% (95% CI 93.7-96.0) in 2000, 82.9% (95% CI 79.6-86.3) in 2004, 70.9% (95% CI 64.7-77.1) in 2009, 40.9% (95% CI 30.2-51.6) in 2011, and 28.6% (95% CI 8.5-38.7) in 2013 (Figure 2.16A). The availability of new drugs both in existing and new drug classes largely explains the decline since mid-2000<sup>39</sup>. In recent years (2014-2016), both the number of pre-treated individuals and the number of sequences from pre-treated individuals was too low to provide meaningful proportions.

Among previously ARV-naïve persons, high-level resistance to at least one drug was detected among 75.5% (95% CI 70.6-80.9) of sequences in 2000, 53.8% (95% CI 50.4-57.1) in 2007, 41.4% (95% CI 36.4-46.4) in 2013, and 32.9% (95% CI 27.7-38.1) in 2016 (Figure 2.16B). Over time, the difference in acquired drug resistance detected among pre-treated and ARV-naïve people has disappeared.

**Figure 2.16:** The annual proportion of sequences with evidence of high-level resistance to any antiretroviral drug obtained at the time of virological failure while receiving cART by prior exposure to antiretroviral drugs: (A) Individuals who were pre-treated and (B) individuals who were previously antiretroviral-drug naïve. The shaded area represents the 95% confidence interval.



**Legend:** ARV=antiretroviral drug.

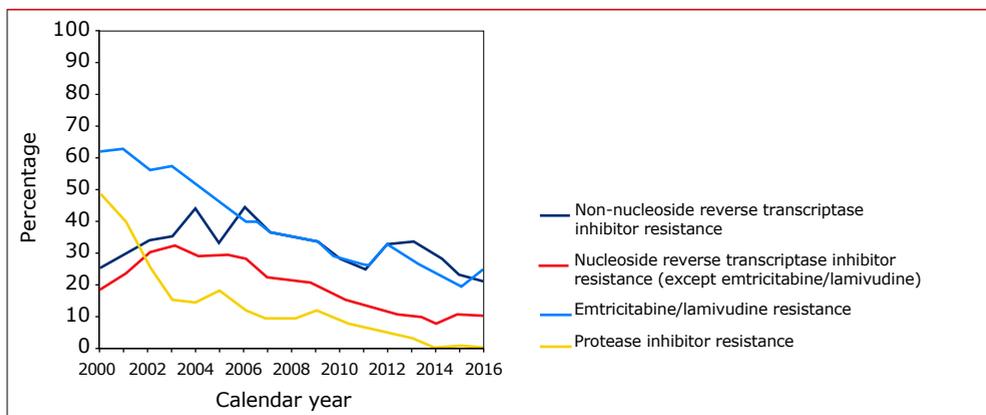
### Acquired drug resistance among previously ARV-naive people

In the remainder of our analysis, we focus on the 2,005 people who were ARV-naive before cART initiation only. Overall, 1,817 (59.0%) out of all 3,082 sequences from previously ARV-naive people receiving cART harboured at least one major resistance mutation associated with NRTI (n=1,435; 46.6%), NNRTI (n=1,143; 37.1%), or protease inhibitor (n=442; 14.3%) resistance.

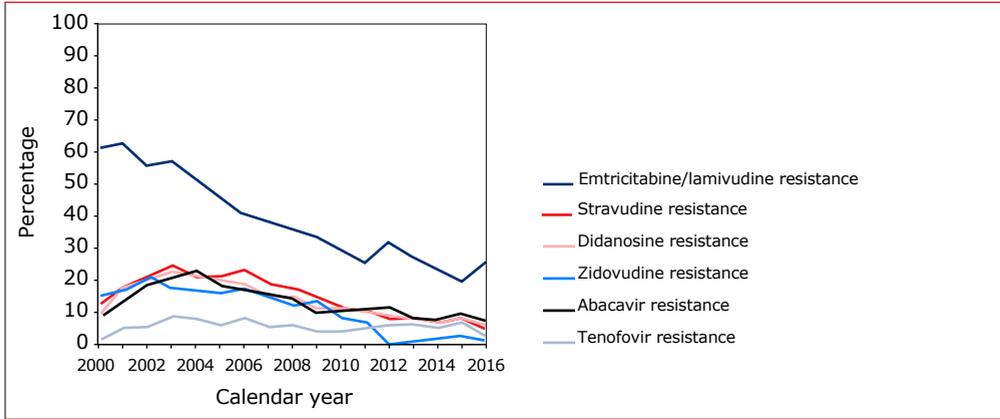
Figure 2.17A and Table 2.5 present the annual proportion of sequences harbouring high-level resistance for each antiretroviral drug class. In 2000, 65.7% (95% CI 60.0-71.4) of sequences harboured high-level resistance to at least one NRTI, 24.3% (95% CI 19.1-29.5) to at least one NNRTI, and 48.6% (95% CI 42.6-54.6) to at least one protease inhibitor. The highest level of resistance was found for the NRTIs emtricitabine and lamivudine (Figure 2.17A and B).

Figure 2.17: The annual proportion of sequences with evidence of high-level resistance by (A) antiretroviral drug class and (B,C,D) antiretroviral drug obtained at the time of virological failure while receiving cART among previously antiretroviral drug-naive persons. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.3) was used to infer antiretroviral drug susceptibility scores for each sequence, according to a five-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance<sup>33,34</sup>.

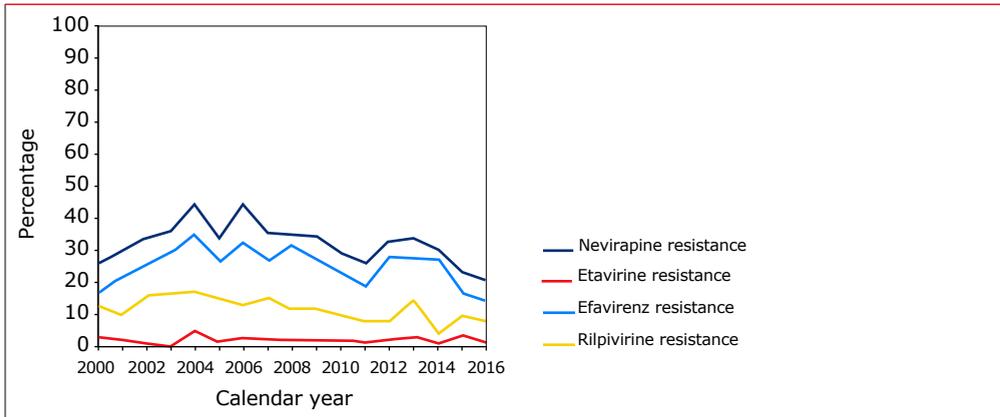
A) By antiretroviral drug class: high-level resistance to at least one drug per class.



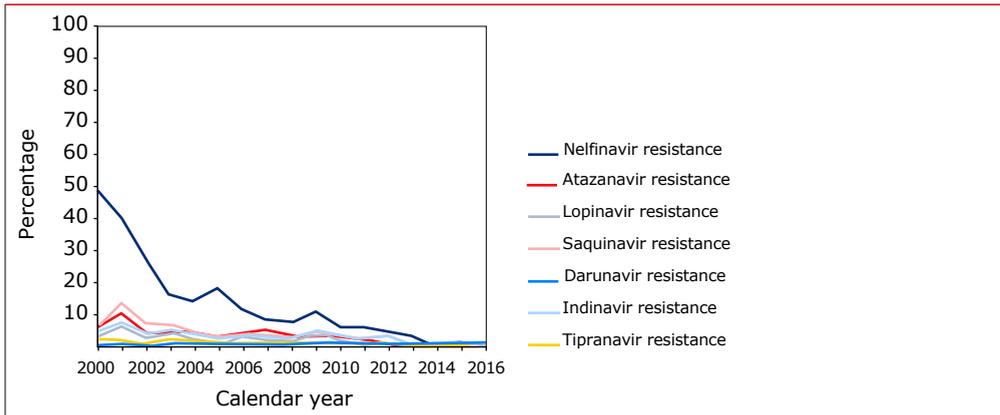
**B) By antiretroviral drug: high-level resistance to at least one nucleoside reverse transcriptase inhibitor.**



**C) By antiretroviral drug: high-level resistance to at least one non-nucleoside reverse transcriptase inhibitor.**



**D) By antiretroviral drug: high-level resistance to at least one protease inhibitor.**



*Table 2.5: Annual proportion of available sequences with evidence of high-level resistance to at least one antiretroviral drug class after virological failure from individuals who received combination antiretroviral therapy and were previously antiretroviral drug-naïve.*

Drug class	NNRTI			NRTI			PI		
	%	95% CI		%	95% CI		%	95% CI	
		low	high		low	high		low	high
2000	24.3	19.1	29.5	65.7	60.0	71.4	48.6	42.6	54.6
2001	28.1	23.5	32.7	68.8	64.0	73.5	40.6	35.6	45.7
2002	33.0	29.4	36.5	65.9	62.3	69.5	26.7	23.4	30.1
2003	35.5	32.4	38.5	66.1	63.1	69.1	15.7	13.4	18.0
2004	44.0	40.7	47.4	57.8	54.5	61.2	14.7	12.3	17.1
2005	32.5	29.3	35.8	54.4	50.9	57.9	17.5	14.8	20.1
2006	44.3	40.8	47.8	50.7	47.2	54.3	11.8	9.6	14.1
2007	35.6	32.4	38.8	44.4	41.1	47.8	8.4	6.6	10.3
2008	34.0	31.0	37.1	42.7	39.6	45.9	8.3	6.5	10.1
2009	33.5	30.5	36.5	40.8	37.7	44.0	11.8	9.8	13.9
2010	27.9	24.9	30.8	33.8	30.7	36.8	8.0	6.3	9.8
2011	25.2	21.6	28.7	31.1	27.4	34.9	6.0	4.0	7.9
2012	32.2	27.8	36.6	32.2	27.8	36.6	4.4	2.4	6.3
2013	33.3	28.6	38.1	29.3	24.7	33.9	3.0	1.3	4.8
2014	29.1	24.6	33.6	26.2	21.9	30.6	0.0	0.0	0.0
2015	22.7	18.8	26.5	21.9	18.0	25.7	0.8	0.0	1.7
2016	20.7	16.2	25.2	26.8	21.9	31.8	0.0	0.0	0.0

*Legend: NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor; CI=confidence interval.*

The proportion of sequences with high-level of resistance declined over time for all drug classes. In 2010, 33.8% (95% CI 30.7-36.8) of sequences harboured high-level resistance to at least one NRTI, 27.9% (95% CI 24.9-30.8) to at least one NNRTI, and 8.0% (95% CI 6.3-9.8) to at least one protease inhibitor. In 2016, 26.8% (95% CI 21.9-31.8) and 20.7% (95% CI 16.2-25.2) of sequences harboured high-level resistance to at least one NRTI and NNRTI, respectively. The annual proportion of sequences with high-level resistance to at least one protease inhibitor has dropped to less than 1% since 2014. The annual proportions of sequences harbouring high-level resistance for each antiretroviral drug are presented in *Figure 2.17B-D* and *Appendix Table 2.3*. Of note, drug resistance does not disappear when viral replication is successfully suppressed or re-suppressed.

### Acquired integrase inhibitor resistance

HIV-1 integrase gene sequencing after virological failure on cART was rare: 87 integrase sequences were available. The sequences originated from 73 persons who received cART for at least four months; 10 were pre-treated with monotherapy or dual therapy before initiating cART, and 63 were ARV-naïve before initiating cART. Most people had initiated cART years before; the median time between initial cART initiation and integrase inhibitor resistance testing was 9.1 years [IQR 2.3-13.4]. For each person, we used the most recent sequence for further analysis.

At least one acquired integrase inhibitor resistance-associated major mutation was detected in 16 out of 73 people, which resulted in high level resistance to at least one integrase inhibitor<sup>32,33</sup>. Among these 16 persons, the following mutations were detected: N155H (n=7) and N155HN (n=1), associated with resistance to EVG and RAL; Y143YC (n=2) and Y143R (n=2), associated with resistance to RAL; and E92Q (n=1), associated with resistance to EVG. One sequence harboured the Q148H mutation in combination with the G140S minor mutation, which is associated with resistance to all three currently available integrase inhibitors: DTG, SVG and RAL. Minor mutations detected were at position L74 (any mutation, n=7; L74I, n=4; L74LM, n=1; L74ILM, n=1; L74M, n=1), Y97A (n=4), G140S (n=1), and R263K (n=1).

**Box 2.4: International collaborations****CD4 cell count monitoring strategies in virally suppressed individuals on cART<sup>54</sup>**

The HIV Cohorts Analyzed Using Structural Approaches to Longitudinal data (HIV-CAUSAL) Collaboration and The Centers for AIDS Research Network of Integrated Clinical Systems investigated the CD4 monitoring strategies in virally suppressed individuals on cART in Europe and North and South America<sup>54</sup>. This study included 47,635 individuals who initiated cART between January 2000 and January 2015, and included data from the ATHENA cohort.

The study compared three monitoring strategies that differed in the threshold used to measure CD4 cell count and HIV RNA viral load every 3–6 months (when below the threshold) or every 9–12 months (when above the threshold). The strategies were defined by the threshold CD4 counts of 200, 350, and 500 cells/ $\mu$ L. Using inverse probability weighting to adjust for baseline and time-varying confounders, the researchers estimated the risk of AIDS-defining illness or death, virological failure, and mean differences in CD4 cell count.

The study showed that a decrease to annual monitoring when the CD4 count is  $>200$  cells/ $\mu$ L, when compared with  $>500$  cells/ $\mu$ L, did not worsen the short-term clinical and immunological outcomes of virally suppressed HIV-positive individuals. However, more frequent virological monitoring might be necessary to reduce the risk of virological failure. Further follow-up studies are needed to establish the long-term safety of these strategies.

**Immediate cART initiation and acquired HIV drug resistance<sup>55</sup>**

The Drug Resistance Working Group of the HIV-CAUSAL Collaboration investigated the effect of immediate cART initiation on the risk of acquired HIV drug resistance<sup>55</sup>. The study included 50,981 ART-naive and AIDS-free adults from Europe and the Americas, including the ATHENA cohort.

This study quantified the risk of acquired drug resistance with use of different cART strategies since baseline (as a proxy of entry into HIV care), rather than since cART initiation. Acquired drug resistance was defined as resistance to any antiretroviral drug that was clinically identified at least 6 months after cART initiation. The parametric g-formula was used to adjust for baseline and time-varying characteristics.

The estimated 7-year risk of acquired drug resistance with different cART strategies was:

- 3.2% (95%CI: 2.8-3.5) for immediate cART initiation;
- 3.1% (95%CI: 2.7-3.3) for cART initiation with  $<500$  CD4 cells/mm<sup>3</sup>, and
- 2.8% (95%CI: 2.5-3.0) for cART initiation with  $<350$  CD4 cells/mm<sup>3</sup>.

In analyses restricted to individuals with baseline in 2005-2015, the corresponding estimates were 1.9% (95%CI: 1.8-2.5), 1.9% (95%CI: 1.7-2.4) and 1.8% (95%CI: 1.7-2.2).

These findings suggest that the risk of acquired drug resistance is very low, especially in recent calendar periods, and that immediate ART initiation only slightly increases the risk. It is unlikely that drug resistance will jeopardize the proven benefits of immediate cART initiation in Europe and the Americas.

## Immunological response

After initiation of cART, most HIV-positive individuals suppress HIV RNA to levels below the limit of detection, and this is accompanied by an increase in CD4 cell count. Normal CD4 cell counts in the general HIV-negative population are, on average, approximately 800 cells/mm<sup>3</sup>, but vary according to factors such as age, ethnicity, sex, and smoking behaviour<sup>40</sup>. Failure to suppress viraemia is associated with poorer recovery of CD4 cell count<sup>27,41</sup>. However, incomplete recovery of CD4 cell count may also occur despite sustained viral suppression, a situation reported to be associated with an increased risk of progression to AIDS and development of non-AIDS-related diseases<sup>28</sup>.

Furthermore, although the CD4 cell count is considered the key prognostic factor for mortality and AIDS-defining endpoints, some but not all studies have suggested that the CD4:CD8 ratio may have additional prognostic value<sup>42,43,44,45,46,47</sup>. As the clinical benefit of cART is strongly related to the level of recovery of the immune status (also see *Chapter 3*)<sup>48,49,50,51,52</sup>, in this section we describe long-term CD4 cell count and CD4:CD8 ratio responses after the start of cART.

### Immunological response – by calendar year

Out of the 21,677 individuals who were known to have initiated cART between January 1995 and December 2016, 21,563 had CD4 cell count data available after

cART initiation. *Figures 2.18* and *2.19* show the last known CD4 cell count and CD4:CD8 ratio of all individuals in care for each calendar year. After starting cART, the percentage of individuals with CD4 cell counts <350 cells/mm<sup>3</sup> dropped from 82.3% in 1996 to 34.4% in 2000, to 18.7% in 2010, and to 11.6% in 2016 (*Figure 2.18*). Likewise, the absolute number of individuals with CD4 cell counts <350 cells/mm<sup>3</sup> at the end of each calendar year decreased from 2,106 in 2010 to 1,829 in 2012 and 1,470 in 2016; see *Appendix Figure 2.4*. The drop in the 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.

The percentage of those with a CD4:CD8 ratio of 1 or more increased from 1.8% in 1995-1999, to 7.9% in 2000-2005, to 14.3% in 2006-2010 and 22.1% in 2011-2016 (*Figure 2.19*). The absolute number of individuals in these CD4:CD8 categories is plotted in *Appendix Figure 2.5*. Of all CD4:CD8 ratio measurements equal to or greater than 1, 12.2% had a CD4 count of less than 500 cells/mm<sup>3</sup>, 34.5% had a CD4 count between 500-749 cells/mm<sup>3</sup> and 53.3% had a CD4 count of  $\geq$ 750 cells/mm<sup>3</sup>. When the CD4:CD8 ratio was  $\geq$ 1, the median CD4 count was 760 cells/mm<sup>3</sup> [IQR 590-962] and remained fairly stable over time, with a median of 740 cells/mm<sup>3</sup> [IQR 590-1,000] in 1995-1999, 750 cells/mm<sup>3</sup> [IQR 570-970] in 2000-2005, 730 cells/mm<sup>3</sup> [IQR 560-930] in 2006-2010 and 770 cells/mm<sup>3</sup> [IQR 600-980] in 2011-2016.

Figure 2.18: Last available CD4 cell count (cells/mm<sup>3</sup>) of the treated population by calendar year. For each individual, the last available CD4 cell count between January and December of each year after the start of cART was selected.

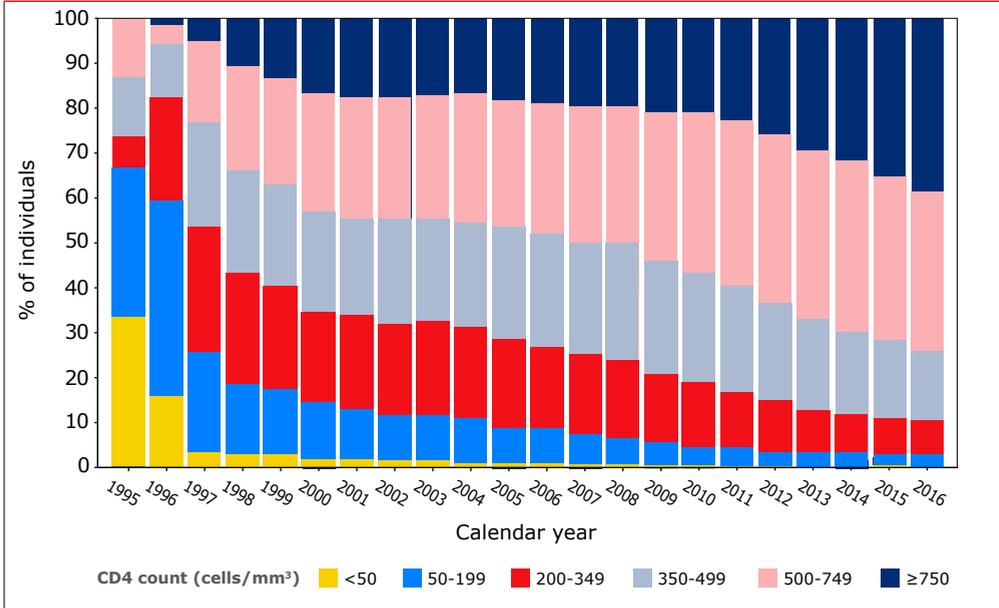
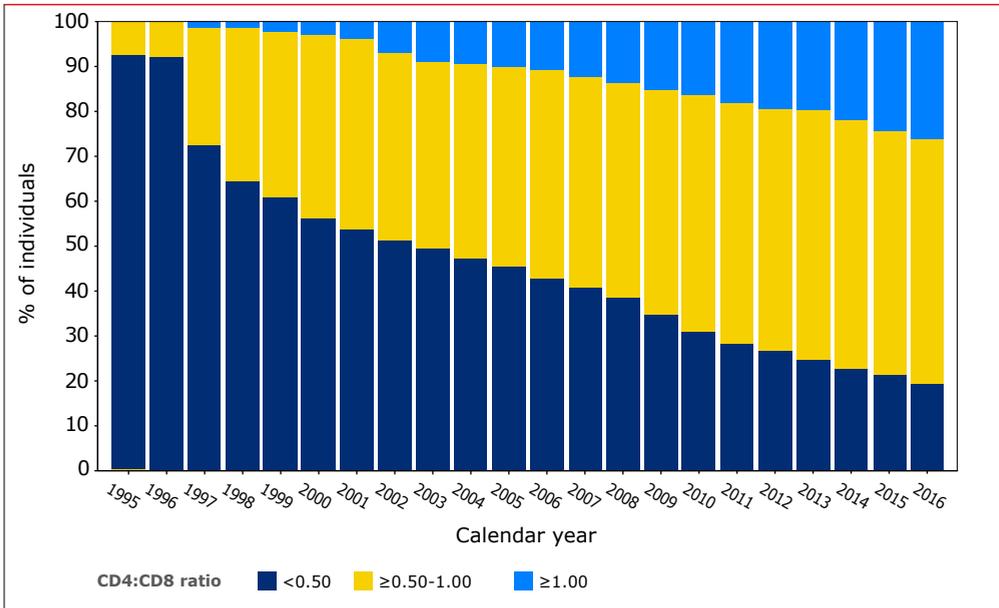


Figure 2.19: Last available CD4:CD8 ratio of the treated population by calendar year of CD4 cell count (cells/mm<sup>3</sup>). For each individual, the last available CD4 cell count between January and December of each year after starting cART was selected.



### Immunological response – after cART initiation

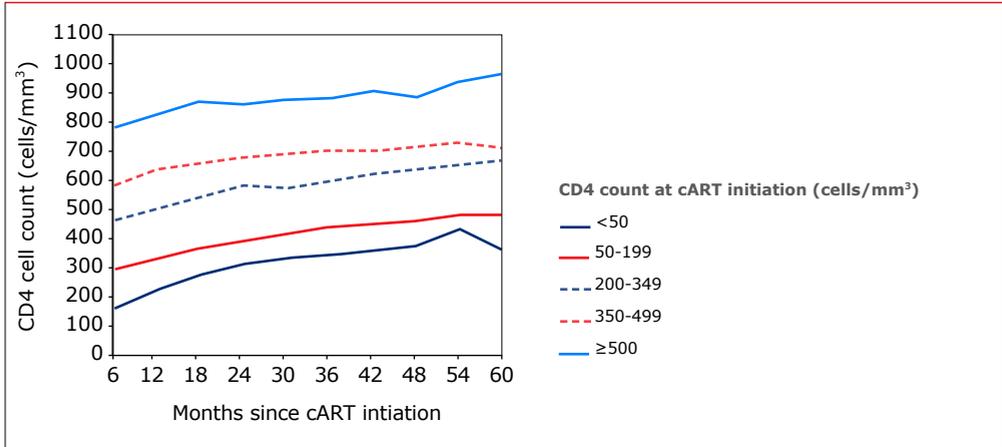
Out of the 21,677 individuals who were known to have initiated cART between January 1995 and December 2016, 18,928 had immunology data available both at and after cART initiation. At cART initiation, 12.6% had CD4 <50 cells/mm<sup>3</sup>, 25.3% had between 50 and 199 cells/mm<sup>3</sup>, 32.2% had between 200 and 349 cells/mm<sup>3</sup>, 16.8% had between 350 and 499 cells/mm<sup>3</sup>, and 13.1% had 500 or more cells/mm<sup>3</sup>. Importantly, and in line with the changes in treatment guidelines, CD4 cell counts at cART initiation have increased over time, as described in *Chapter 1*.

#### 2011–2016

We further assessed the immunological response in individuals who started cART in more recent years: 6,040 individuals started cART in 2011–2016 and had CD4 cell count data available at and after cART initiation. The level of viral suppression and treatment interruptions after initiating cART were not taken into account in this analysis. Of the 6,040 individuals who started cART in 2011–2016, 8.1% had CD4 <50 cells/mm<sup>3</sup>, 15.0% had between 50 and 199 cells/mm<sup>3</sup>, 26.4% had between 200 and 349 cells/mm<sup>3</sup>, 26.0% had between 350 and 499 cells/mm<sup>3</sup>, and 24.5% had 500 or more CD4 cells/mm<sup>3</sup> at time of cART initiation. The CD4 cell count at cART initiation increased over the years (*Appendix Table 2.2*).

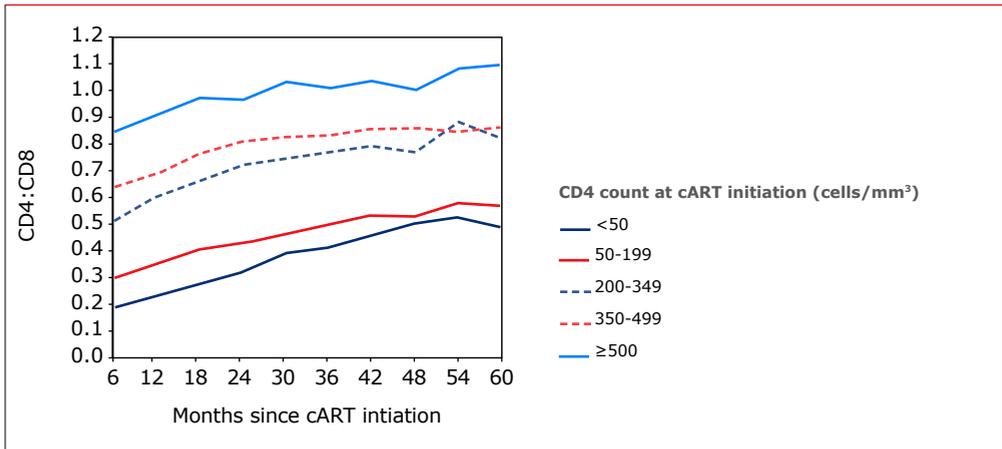
The CD4 cell count and CD4:CD8 ratio trajectories following cART initiation are plotted in *Figures 2.20* and *2.21* by CD4 cell count at cART initiation. The median CD4 cell count and CD4:CD8 ratios increased after cART initiation. Both depended on the CD4 cell count at cART initiation and did not converge between the five baseline CD4 cell count strata.

Figure 2.20: CD4 cell count over time after the start of combination antiretroviral therapy in 2011–2016.



Legend: cART=combination antiretroviral therapy.

Figure 2.21: CD4:CD8 ratio over time after the start of combination antiretroviral therapy in 2011–2016.



Legend: cART=combination antiretroviral therapy.

Note: The presented immunological outcomes are based on available test results. For individuals with a low to moderate CD4 cell count (<350 cells/mm<sup>3</sup>), CD4 cell count testing is recommended at least twice a year. When a person has a reasonable CD4 cell count (>350 cells/mm<sup>3</sup>), the testing frequency may be reduced<sup>53</sup>. Therefore, CD4 data from people achieving higher CD4 cell counts are disproportionately underrepresented and their true CD4 responses may be even better.

## Summary and conclusions

### Starting cART & the initial regimen

- Rapid initiation of cART following a diagnosis of HIV infection, irrespective of CD4 cell count, continues to improve over time.
- The CD4 cell count at cART initiation has increased over time. Among HIV-positive individuals starting cART in 2016, the median CD4 cell count was 410 cells/m<sup>3</sup> [IQR 230-590]. Immunological recovery was strongly related to the CD4 cell count at the start of cART.
- In 2016, the majority of individuals initiating cART did so within a month after diagnosis. Most persons who initiated cART in 2016 received ABC/3TC/DTG or TAF/FTC/EVG/c.
- Discontinuation of the initial regimen has become less common over time, with regimen switches occurring mainly because of intolerance, simplification, or the availability of new drugs.
- Toxicity-associated discontinuations of the initial regimen were often related to the central nervous system, gastrointestinal tract or liver, or a rash due to medication.

### In care and receiving cART in 2016

- Integrase inhibitor-based cART has been further implemented on a large scale in the Netherlands. Integrase inhibitor-based cART was prescribed to 39% of those in care in 2016, compared to 27% in 2015<sup>56</sup>.
- While two-thirds of the population on cART received TDF, newly available fixed-dose combinations led to an increase in the prescription of ABC/3TC and TAF/FTC as the backbone.
- Of those receiving cART who had a plasma HIV RNA measurement in 2016, 97% had a viral load less than 200 copies/ml. Long-term survivors (i.e., individuals in care in 2016 who were diagnosed with HIV prior to 1990) had equally high levels of viral suppression.

### Virological response and drug resistance

- The overall viral suppression rates of the HIV-positive population receiving cART is high and continues to improve. Among those who experience virological failure, the annual proportion of persons with acquired drug resistance continues to decline; this is in line with findings from other high-income settings<sup>57,58</sup>.
- Transmitted drug resistance is rare, and the overall prevalence is low and stable over time, in line with reported rates from other European countries<sup>59</sup>.
- Integrase inhibitor resistance data are limited. No transmitted integrase inhibitor resistance was detected. Detected rates of acquired integrase inhibitor resistance among available sequences were very low, with virtually no resistance to dolutegravir.

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

Ferdinand Wit, Marc van der Valk, Peter Reiss

### Introduction

Of the 24,922 HIV-1-positive adults and children ever registered in the Dutch national HIV registration and monitoring database up to 31 December 2016, 93.9% are currently on combination antiretroviral therapy (cART). Since the introduction of cART, the life expectancy of HIV-1-positive individuals has markedly improved and, in a subgroup of recently diagnosed, effectively-treated individuals, has been shown to be similar to that of the general population in the Netherlands<sup>60</sup>.

Whereas the incidence of AIDS-defining infections and malignancies has markedly decreased<sup>61</sup>, 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 positive individuals during the cART era<sup>62,63,64,65,66,67</sup>.

Various reports suggest that the risk of non-AIDS morbidity may be higher among HIV-positive individuals treated with antiretroviral therapy (ART) than among HIV-negative individuals of comparable age<sup>68,69,70</sup>. For example, pulmonary hypertension<sup>71</sup>, bone disease, and non-traumatic bone fractures<sup>72,73,74</sup> have been reported to be more common in HIV-1-positive individuals. There is also a concern that HIV-related neurocognitive impairment may persist or even progress, despite otherwise effective long-term cART<sup>75,76,77</sup>. Furthermore, as in HIV-negative individuals, traditional risk factors (e.g., tobacco use<sup>78</sup>, alcohol abuse, and viral hepatitis co-infection<sup>79</sup>) are likely to also importantly contribute to the increased risk of certain non-AIDS comorbidities in people living with HIV.

Importantly, one of the most prevalent comorbidities in HIV-1 is cardiovascular disease (CVD). In addition to traditional risk factors such as smoking, probable additional risk factors with high prevalence among HIV-1-positive individuals include metabolic abnormalities, such as dyslipidaemia, insulin resistance, hypertension, diabetes, and changes in body fat distribution (lipodystrophy), which may partly be driven by the use of cART, as well as by sustained residual HIV-associated immune activation and inflammation, despite effective cART<sup>49,80</sup>.

In this chapter, we report on mortality and causes of death for adult (18 years and older) HIV-1-positive individuals using updated Stichting HIV Monitoring (SHM) data: 24,245 adults and an additional 439 children (at the time of entry into care) who have since become adults, giving a total of 24,684 adult individuals. 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-positive individuals.

## 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<sup>81</sup>). A CD4 count below 200 cells/mm<sup>3</sup> 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 6 months or longer. In previous Monitoring Reports we used a period of 3 months. In the present Monitoring Report we have extended the period to 6 months because of the large number of CKD episodes that revert shortly after 3 months. 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 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 has increased over time, we also estimated the incidence rates for the periods 2000-2005, 2006-2010, and 2011-2016, while standardising these according to the age distribution of the population during the period 2011-2016 (divided into age classes 18-29, 30-39, 40-49, 50-59, 60-69, and  $\geq 70$  years) using the indirect method<sup>82</sup>. Indirect standardisation compares the incidence rates in the study and reference (2011-2016) 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-positive individuals was defined as the date of HIV-1 diagnosis or January 2000, whichever occurred most recently. Subsequent follow-up time was divided into three-monthly periods. Poisson regression models were used to estimate the independent association between risk factors and each endpoint. Models were adjusted for most recent CD4 cell count (lagged by three months), body mass index, gender, region of birth, most likely HIV-1 transmission route, current age, known time with CD4 count  $< 200$  cells/mm<sup>3</sup>, known time with plasma HIV RNA  $> 1000$  copies/ml while on cART, time on cART, specific antiretroviral drugs used, prior diagnosis of AIDS, presence of chronic active hepatitis B and/or C virus infection, hypertension, smoking, and calendar period.

## Mortality and AIDS

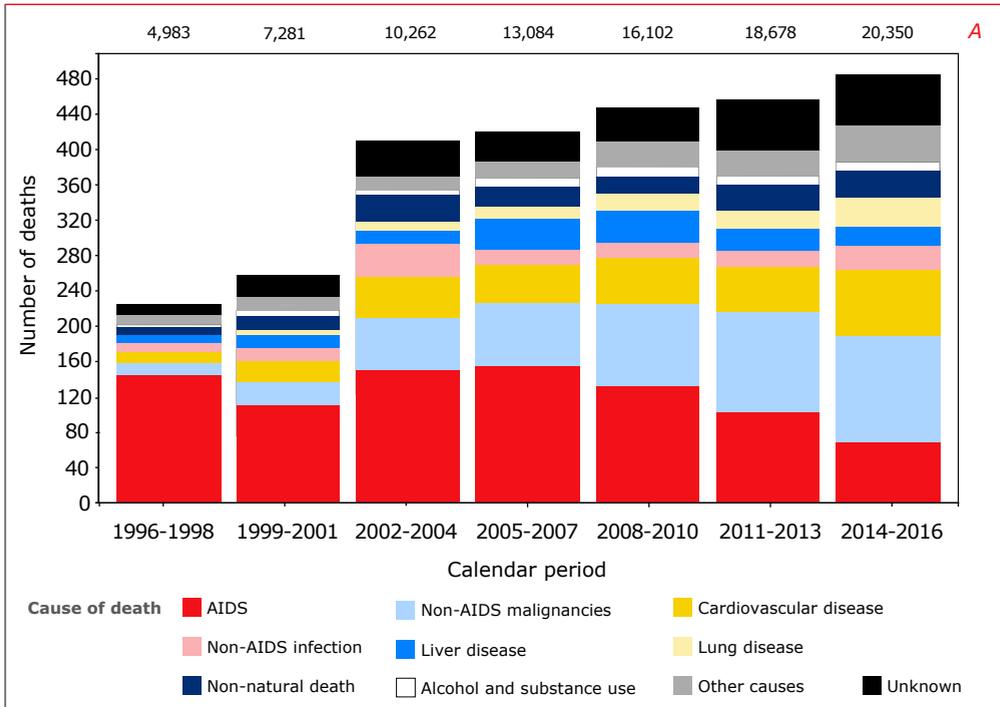
From 1996 onwards, the overall mortality rate in all 24,684 HIV-1-positive adults ever registered in the SHM was 17.9 (95% confidence interval [CI] 13.4-23.5) per 1,000 person years in 1996 and declined over time to 9.8 (95% CI 8.3- 11.5) per 1,000 person years in 2016 (*Appendix Figure 3.1A*; *Appendix Table 3.1*). Despite this improvement over time, the mortality rate in HIV-1-positive adults remains well above that expected for the general population in the Netherlands, namely, 3.9 per 1,000 person years (PY) in 2016, when matched in terms of age and gender of the HIV-positive population. The excess mortality rate can be partly ascribed to individuals who already had AIDS at the time of their HIV diagnosis. When these individuals

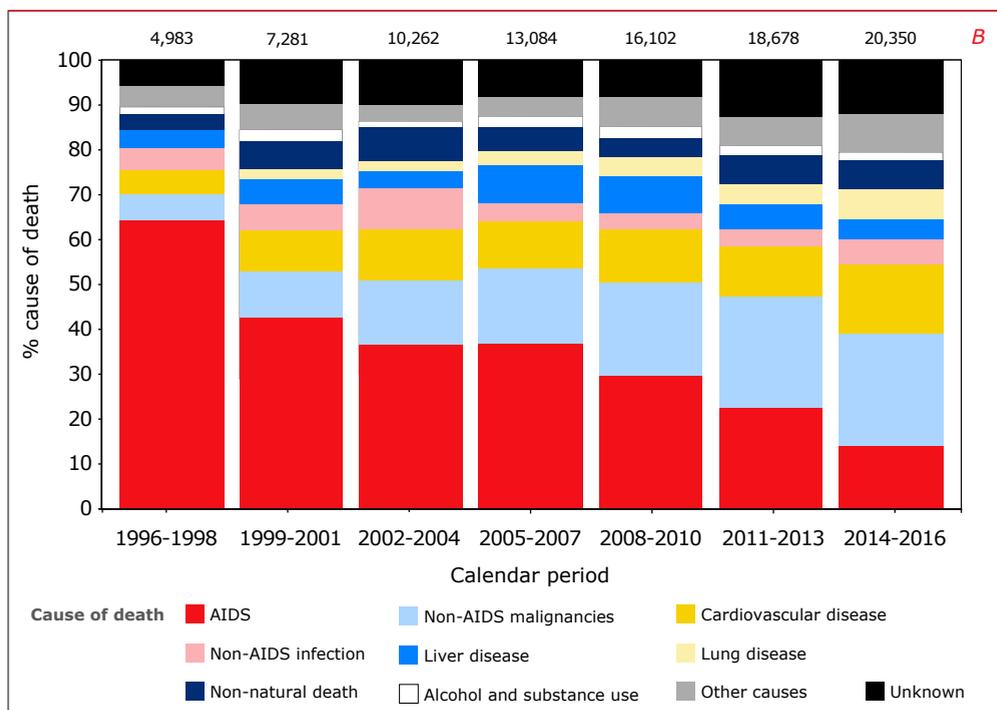
were excluded, the mortality rate was 12.9 (95% CI 12.4-13.4) per 1,000 person years overall (period 1996-2016) and 8.7 (95% CI 7.2-10.3) per 1,000 person years in 2016. In the same group of 24,684 individuals, the incidence of AIDS decreased sharply from 114.9 (95% CI 102.9-127.9) in 1996 to 9.3 (95% CI 7.9-11.0) cases per 1,000 individuals per year in 2016 (*Appendix Figure 3.1B*).

### Cause of death

Observed underlying causes of death are presented in *Appendix Table 3.2*. Although the AIDS-related death rate has decreased significantly since the advent of cART, it still remains substantial and is probably driven largely by the high number of individuals still presenting late for care with already advanced immune deficiency. Thirty-five per cent of all individuals who died of AIDS between 2011 and 2016 had a CD4 cell count < 50 cells/mm<sup>3</sup> when entering care. Individuals who died of AIDS had lower CD4 counts (median 97 cell/mm<sup>3</sup> [interquartile range, IQR, 30-309] when entering care compared to individuals who died of another cause (median 279 cells/mm<sup>3</sup> [IQR 93-480]). Among individuals who entered care with more than 300 CD4 cells/mm<sup>3</sup> and who died of AIDS, the cause of death was relatively more likely to be an AIDS-related malignancy (29.6%) than in individuals who entered care with less than 50 CD4 cells/mm<sup>3</sup> (18.6%). The time between entry into care and death was significantly shorter in individuals who died of AIDS (median 3.4 years [IQR 0.6-9.0]) than in individuals who died of a non-AIDS cause (median 8.5 years [IQR 4.4-14.4],  $p < 0.001$ ). Conversely, the proportion and absolute number of deaths due to non-AIDS-defining conditions have significantly increased over time (*Figures 3.1A and B*), partly as a consequence of the increasing size and average age of the Dutch HIV-positive population.

Figure 3.1: (A) Absolute and (B) relative changes in causes of death in different calendar periods since the introduction of combination antiretroviral therapy (cART) in the Netherlands. The numbers on top of each bar represent the number of individuals that were at risk during that calendar period. Mortality attributed to 'alcohol use' consisted of deaths due to complications of alcohol-related liver cirrhosis.





We used Poisson regression analysis to examine factors associated with death in individuals from the moment of starting cART. 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 an individual's risk of death increased if they were older, belonged to the HIV transmission risk group of people who inject drugs, had a current CD4 cell count less than 500 cells/mm<sup>3</sup> (but even more so when their CD4 cell count was less than 200 cells/mm<sup>3</sup>), had been pre-treated with nucleoside-analogue reverse transcriptase inhibitors (NRTIs) at the start of cART, had a prior AIDS diagnosis, were co-infected with HBV or HCV, were underweight, were current or past smokers, or had spent more time with an HIV RNA level above 1,000 copies/ml while on cART.

Although a lower mortality risk was observed in individuals of non-Dutch origin, this is likely due to the larger proportion of people from sub-Saharan Africa (as well as other non-native groups, except those from the former Dutch colonies

in the Caribbean) being lost to follow up (*Appendix Table 3.4*). In native Dutch individuals and those from the former Dutch colonies, the risk of becoming lost to follow up was not dependent on their CD4 count. On the other hand, people from all other non-Dutch groups were far more likely to become lost to follow up if they had very low CD4 counts. An explanation for this observation could be that these people often return to their families in their country of origin when they experience a severe deterioration in health. As such, it is likely that the high rates of loss to follow up in non-Dutch individuals with very low CD4 counts have led to underestimation of the mortality rate in these groups.

### AIDS-defining events

The incidence of the first occurrence of any AIDS-defining event after entering care was 23.4 events per 1,000 person years of follow up. *Appendix Table 3.5* gives an overview of the AIDS events occurring between 1996 and 2016. The most common AIDS events between 2011 and 2016 were *Pneumocystis jirovecci* pneumonia (21% of all events), oesophageal candidiasis (17%), Kaposi's sarcoma (11%), tuberculosis (pulmonary 8%, extrapulmonary 5%), lymphoma (6%), toxoplasmosis of the brain (5%), AIDS-related wasting (5%), 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 start of cART. The results of these analyses show that individuals were more likely to experience their first AIDS-defining event if they were older, had a current CD4 cell count below 500 cells/mm<sup>3</sup> (but even more so when their CD4 cell count was below 200 or 50 cells/mm<sup>3</sup>), or had more than 1,000 HIV RNA copies/ml for a longer period of time while on cART.

Because the main findings of the analysis of AIDS events after start of cART were heavily influenced by events occurring shortly after the start of cART and/or while HIV-1 viraemia was detectable, we analysed the incidence of CDC-B and AIDS-defining events in the period between 2000 and 2016 in individuals who had started cART at least 1 year previously and had undetectable viraemia (or transient low level viraemia, i.e. 'blips' below 200 copies/mL) at the moment the HIV-related event was diagnosed. Therefore, this analysis focuses on individuals with an optimal response to cART. Events were classified into CD4 strata based on the current CD4 and previously-measured CD4 count, whichever was the lowest. Only 'definitive' or 'probable' diagnoses were considered – 'possible' events or events with incomplete ascertainment data were excluded from the analysis. Between 1 January 2000 and 31 December 2016, 20,891 individuals contributed a total of 148,9 thousand PY of follow up during which 2,996 HIV-related events

were diagnosed, resulting in an incidence rate of 20.1 events per 1,000 PY (1,928 CDC-B events, 12.9 events/1,000 PY; 1,068 CDC-C/AIDS events, 7.2 events/1,000 PY), see *Table 3.1*. As expected, the incidence rates were very high in the CD4 strata below 200 cells/mm<sup>3</sup>. Although the incidence rates declined sharply in the higher CD4 strata, the incidence rates in the 200-349 and 350-499 cells/mm<sup>3</sup> strata remained substantial with 12.2 and 6.0 AIDS-defining illnesses/1000 PY. The incidence rates of AIDS-defining illnesses in the CD4 strata of 500-749 and over 750 cells/mm<sup>3</sup> were 3.5 (3.0-4.0) and 2.1 (1.7-2.7)/1,000 PY, respectively. Note that the incidence in the 750+ stratum is statistically significantly lower than in the 500-749 cells/mm<sup>3</sup> stratum. In these highest CD4 strata the main AIDS-defining events that still occurred were recurrent bacterial pneumonia, Kaposi's sarcoma, oesophageal candidiasis, non-Hodgkin's lymphoma, tuberculosis (pulmonary and extrapulmonary), chronic genital HSV ulcers and AIDS dementia complex (see *Appendix Table 3.8*, which shows the type and number of HIV-related diagnoses by CD4 strata).

*Table 3.1: CDC-B and CDC-C/AIDS events occurring in individuals on cART with undetectable viral load between 2000 and 2016.*

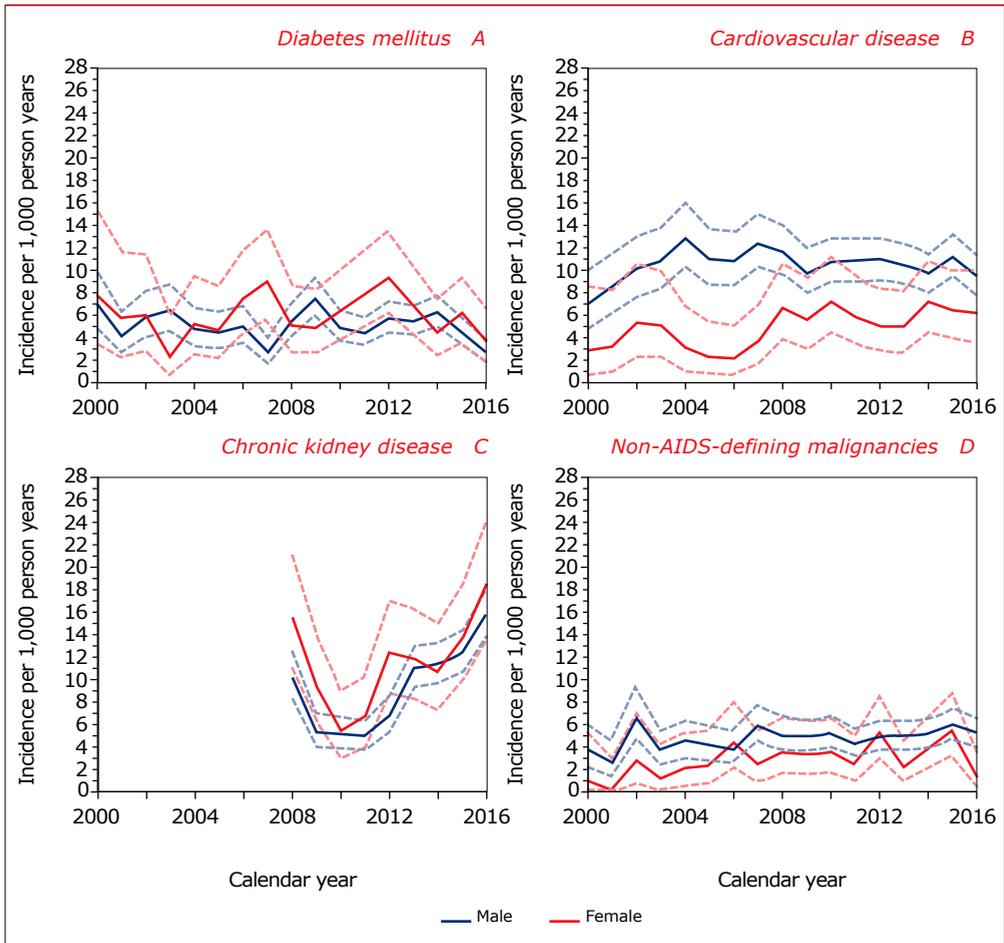
CD4 category (cells/mm <sup>3</sup> )	CDC events (n)	CDC-B events (n)	CDC-C events (n)	Person years follow up (x1,000)	Incidence rate CDC events (per 1,000 PY) (95% CI)	Incidence rate CDC-B events (per 1000 PY) (95% CI)	Incidence rate CDC-C events (per 1,000 PY) (95% CI)
0-49	217	92	125	0.4	551 (480-629)	233 (188-286)	317 (264-378)
50-199	565	335	230	6.9	82.2 (75.6-89.3)	48.8 (43.7-54.3)	33.5 (29.3-38.1)
200-349	678	422	256	20.9	32.4 (30.0-35.0)	20.2 (18.3-22.2)	12.2 (10.8-13.8)
350-499	590	386	204	34.1	17.3 (15.9-18.7)	11.3 (10.2-12.5)	5.98 (5.19-6.86)
500-749	626	447	179	51.8	12.1 (11.2-13.1)	8.64 (7.85-9.47)	3.46 (2.97-4.00)
750+	320	246	74	34.8	9.19 (8.21-10.3)	7.07 (6.21-8.01)	2.13 (1.67-2.67)
<b>Total</b>	<b>2,996</b>	<b>1,928</b>	<b>1,068</b>	<b>148.9</b>	<b>20.1 (19.4-20.9)</b>	<b>12.9 (12.4-13.5)</b>	<b>7.17 (6.75-7.62)</b>

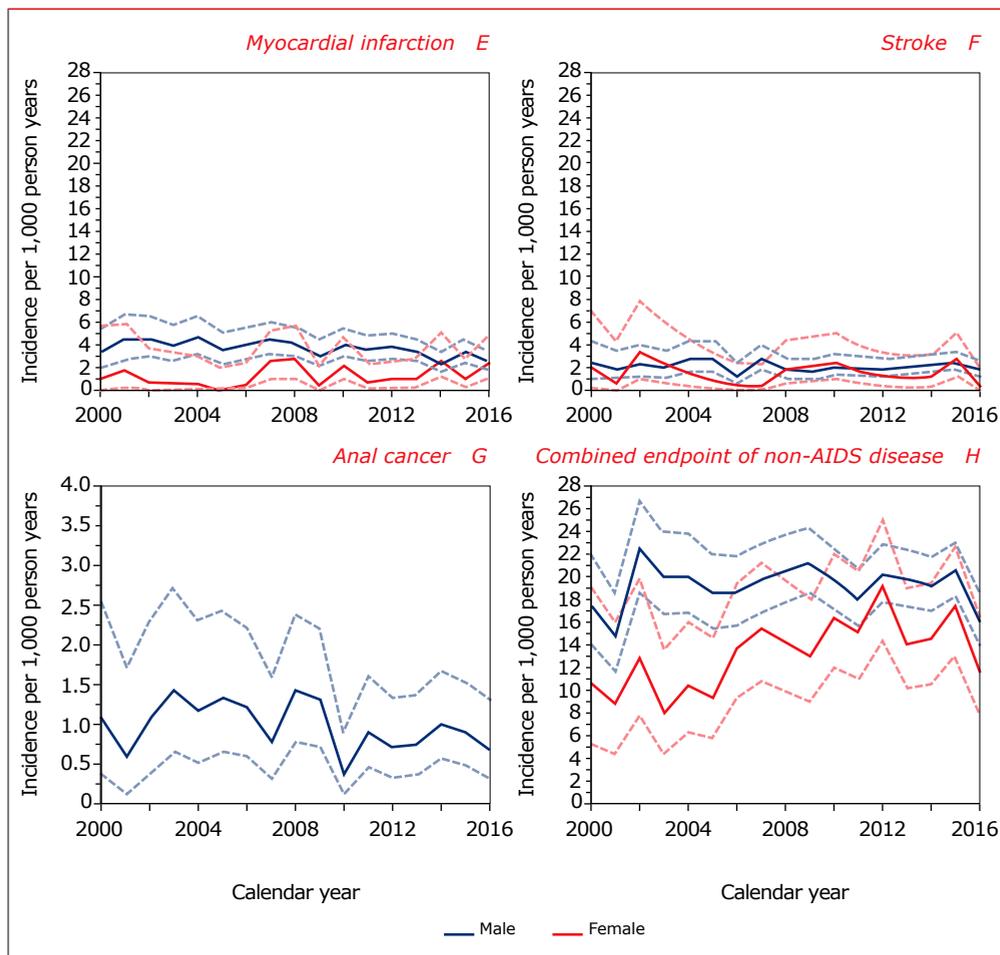
*Legend: CDC=Centre for Disease Control and Prevention; CDC-C=AIDS-defining events; PY=person years of follow up.*

## Non-AIDS-defining events

Of the 24,684 HIV-1-positive adults ever registered with the Dutch national HIV registration and monitoring database, 24,212 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 diabetes mellitus, cardiovascular disease, or non-AIDS malignancies as a combined non-AIDS disease endpoint (*Figure 3.2; Appendix Table 3.6A-H*).

Figure 3.2: Crude incidence rates per 1,000 person years of follow up (solid lines) 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 24,212 individuals aged 18 years or older and in follow up in or after January 2000, a total of 1,079 (831 men and 248 women) were diagnosed with diabetes from 2000 onwards. The crude incidence of diabetes remained stable over time (*Figure 3.2A*) and, in 2016, was 2.7 (95% CI 1.9-3.7) per 1,000 PY of follow up in men and 3.6 (95% CI 1.7-6.6) per 1,000 PY in women. In both men and women, the incidence increased with older age (*Appendix Table 3.6A*). In men, the age-standardised incidence ratio declined over time and was significantly lower in 2011-2016 than in 2000-2005 and 2006-2010. In women, the age standardised incidence in 2000-2005 and 2006-2010 was not significantly different from that in 2011-2016 (*Table 3.2*).

Demographic and clinical factors independently associated with increased risk of new-onset diabetes mellitus were male gender, non-Dutch origin, older age, having acquired HIV heterosexually or through injecting drug use, having a BMI greater than 25 kg/m<sup>2</sup> or a BMI below 18 kg/m<sup>2</sup>, having hypertension, having a latest CD4 cell count below 200 cells/mm<sup>3</sup>, being pre-treated with NRTIs at start cART, and a prior AIDS diagnosis (*Appendix Table 3.7*). Moreover, the risk of new onset diabetes in the period 2000-2005 was significantly higher than in the period 2011-2016. Finally, a longer time on zidovudine or didanosine was also significantly associated with an increased risk.

**Table 3.2: Crude incidence of diabetes mellitus per 1,000 years of follow up during 2000-2005, 2006-2010 and 2011-2016 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)	1.41 (1.21-1.61)	5.0 (3.7-6.6)	0.84 (0.60-1.08)
2006-2010	5.2 (4.6-5.9)	1.21 (1.06-1.36)	6.5 (5.2-8.0)	1.06 (0.83-1.28)
2011-2016	4.9 (4.4-5.4)	1.00 (reference)	6.5 (5.3-7.8)	1.00 (reference)

\*Standardised according to the observed age distribution between 2011-2016.

Legend: CI=confidence intervals; PY=person years.

### Cardiovascular disease

From January 2000 onwards, 1,058 individuals (942 men and 116 women) had a fatal or non-fatal cardiovascular event (563 myocardial infarction, 386 stroke, 79 coronary artery bypass graft, 365 coronary angioplasty or stenting, and 7 carotid endarterectomy). The crude incidence over time remained stable and was lower in women than in men (*Figure 3.2B*). The incidence in both men and women increased with older age (*Appendix Table 3.6B*). 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 2011-2016 (*Table 3.3*).

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 <350 cells/mm<sup>3</sup>, having a prior AIDS diagnosis, being pre-treated with NRTIs at start of cART, use of abacavir (either currently or in the last 6 months), cumulative use of indinavir, current and past smoking, and presence of hypertension. Cardiovascular risk was also higher during 2000-2005 and 2006-2010 than during 2011-2016, independent of other variables included in the analysis

(Appendix Table 3.7). The strong positive association between use of abacavir and CVD was independent of renal function. When eGFR estimated using the Cockcroft-Gault method (available from 2007 onwards) was included into the model, the abacavir effect was only slightly attenuated from an incidence risk ratio (IRR) of 1.51 to one of 1.43,  $p < 0.001$ . Having an eGFR below 90 ml/min was independently associated with a higher risk for CVD; at 60-90 ml/min, the IRR was 1.21 (95% CI 1.02-1.44),  $p = 0.032$ ; at 30-60 ml/min the IRR was 1.74 (1.30-2.31),  $p < 0.001$ ; at 15-30 ml/min, the IRR was 5.53 (3.25-9.41)  $p < 0.001$ ; and at 0-15 ml/min the IRR was 4.13 (1.82-9.38),  $p < 0.001$ .

From January 2000 onwards, 141 men and 11 women experienced a fatal or non-fatal secondary cardiovascular event (96 myocardial infarction [MI], 61 stroke). The crude incidence per 1,000 years of follow up over the whole period between 2000 and 2016 in men and women with a prior cardiovascular event was 28.8 (95% CI 24.2-33.9) and 17.7 (95% CI 8.9-31.8), respectively. The crude rate and age-standardised incidence ratio (SIR; indirect method) of secondary MI and stroke per 1,000 years of follow up did not change significantly during 2000-2005 (crude rate: 35.1 events per 1,000 years of follow up; SIR: 1.36, 95% CI 0.90-1.80) and 2006-2010 (crude rate: 27.3 events per 1,000 years of follow up; SIR: 1.06, 95% CI 0.74-1.38) compared to the reference period 2011-2016 (crude rate: 25.1 events per 1,000 years of follow up).

**Table 3.3: Crude incidence of cardiovascular disease per 1,000 years of follow up between 2000-2005, 2006-2010, and 2011-2016 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	10.3 (9.3-11.4)	1.44 (1.29-1.59)	3.7 (2.6-5.1)	0.99 (0.66-1.32)
2006-2010	11.1 (10.2-12.1)	1.29 (1.18-1.40)	5.4 (4.2-6.8)	1.16 (0.88-1.43)
2011-2016	10.5 (9.7-11.2)	1.00 (reference)	6.0 (4.9-7.3)	1.00 (reference)

\*Standardised according to the observed age distribution between 2011-2016.

Legend: CI=confidence intervals; PY=person years.

### Trends in cardiovascular risk factors

The percentage of men with a cholesterol level of 6.2 mmol/l or higher has decreased over time from 26% of those with an available cholesterol measurement in 2000 (regardless of whether statins were used) to 12% in 2016 (*Figure 3.3*). In women, this figure decreased from 19% in 2000 to a minimum of 11% in 2007 and has since increased somewhat to 16.4% in 2016.

*Figure 3.4* shows that the distribution of body mass index (BMI) of both men and women in the HIV-1-positive population has increased over time. In 2016, the percentage of overweight (25-30 kg/m<sup>2</sup>) and obese ( $\geq 30$  kg/m<sup>2</sup>) men with an available BMI measurement was 32% and 8%, respectively. In women, these percentages were 31% and 26%, respectively. Using mixed-effects modelling, we investigated whether the increase in BMI over time could be ascribed to changes in the demographic characteristics and ageing of the HIV-positive population. This revealed that the increase in BMI over time was at least partially driven by changes over time in population 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 in women.

*Figure 3.5A* shows that, in 2016, 49% of those treated with antihypertensives still had grade 1 hypertension or higher. The figures above the bars show that, over time, an increasing number of individuals are using antihypertensives. In 2016, 2,455 (25%) untreated individuals had grade 1-3 hypertension (*Figure 3.5B*). For 2,195 of these 2,455 individuals, a 5-year cardiovascular disease (CVD) risk could be calculated with the recalibrated D:A:D study algorithm<sup>83</sup>. Of the 2,195 individuals, 5.6% 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<sup>19</sup>. *Figure 3.6* gives an overview of the cART-treated population's estimated risk of developing CVD over time. From 2004 until 2016, the percentage of individuals at high (5-10%) or very high ( $\geq 10\%$ ) risk increased only slightly from 16% and 8%, respectively, in 2004 to 18% and 11%, respectively, in 2016. 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. The numbers on top of each bar represent the number of individuals contributing data during that calendar year.

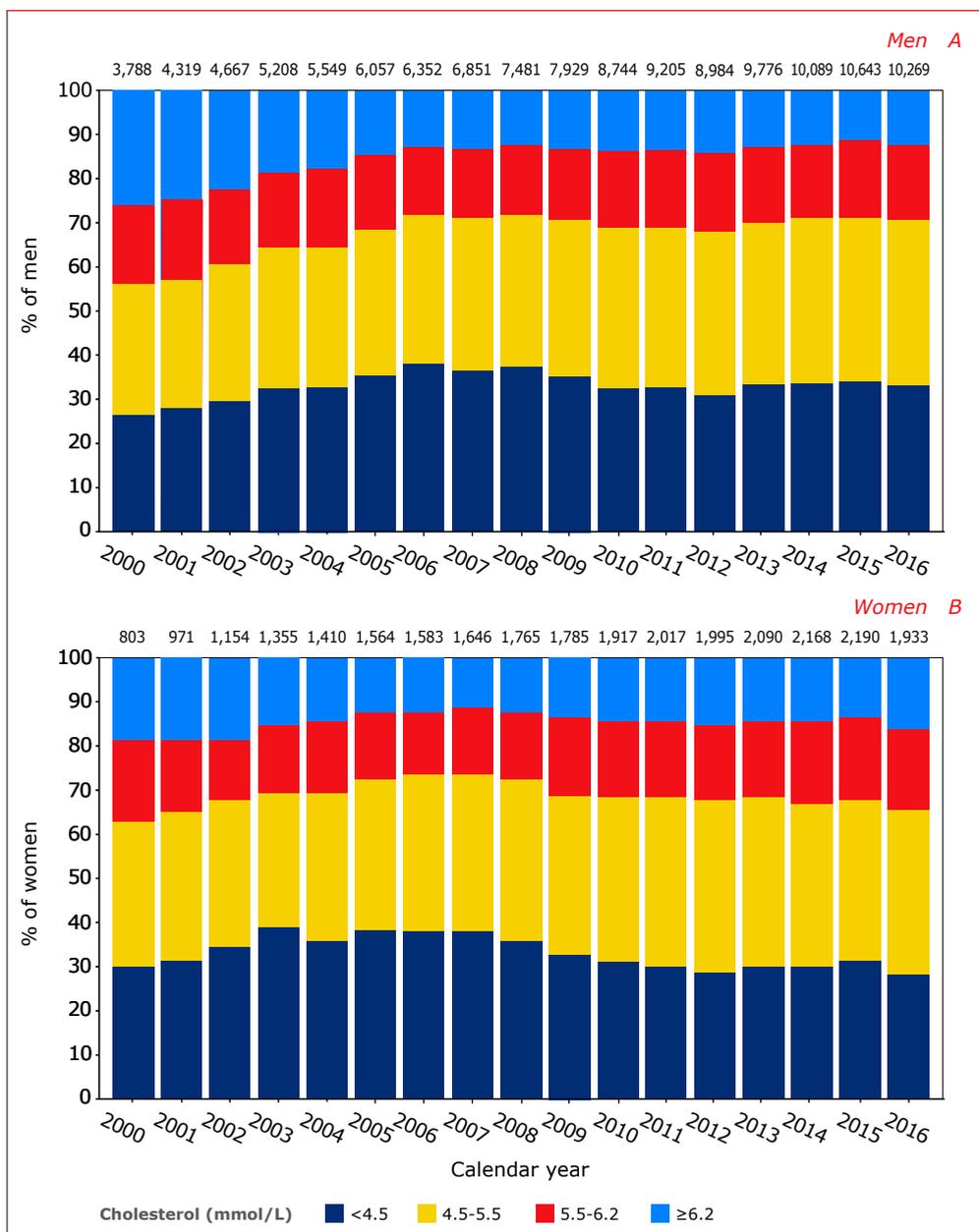
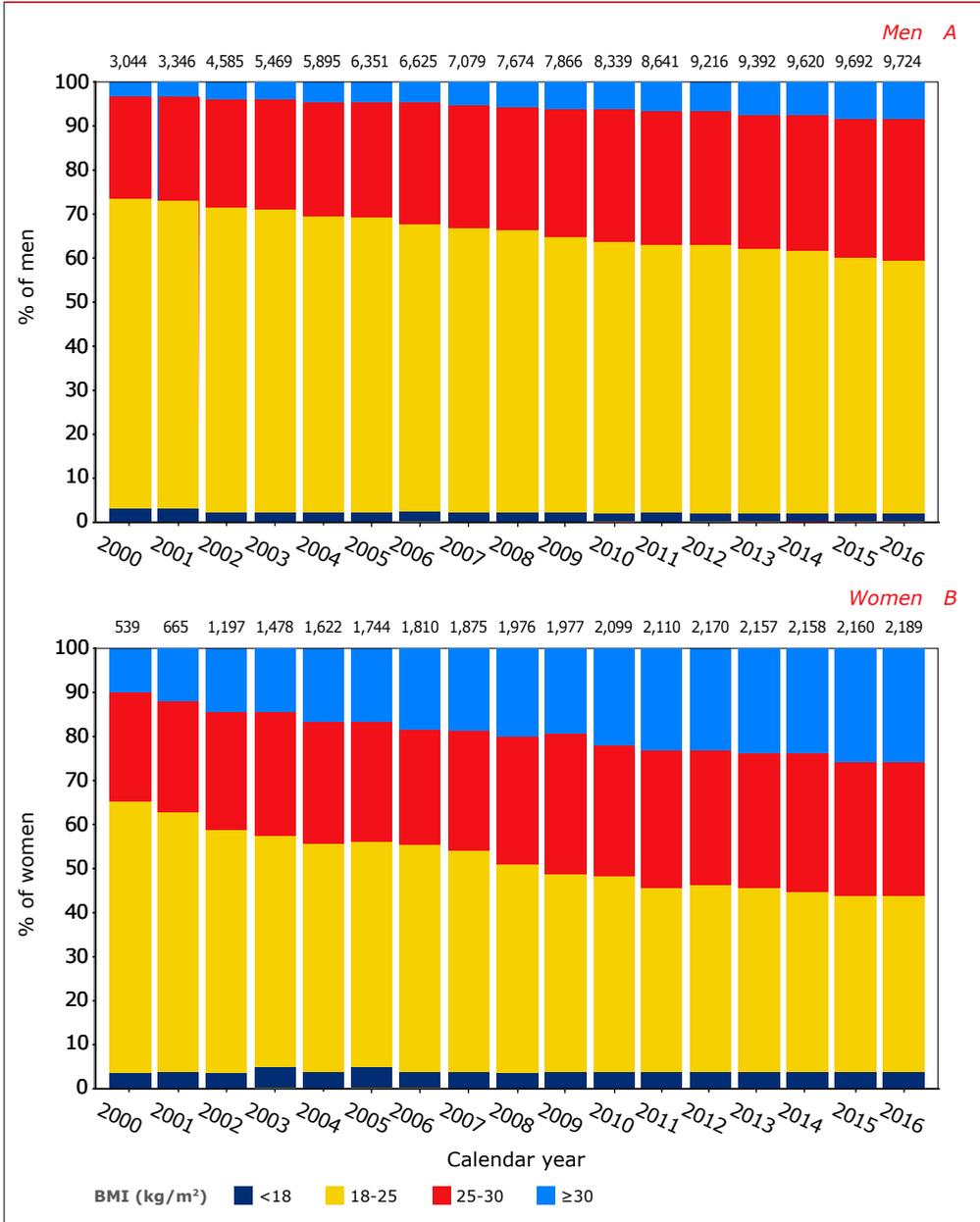
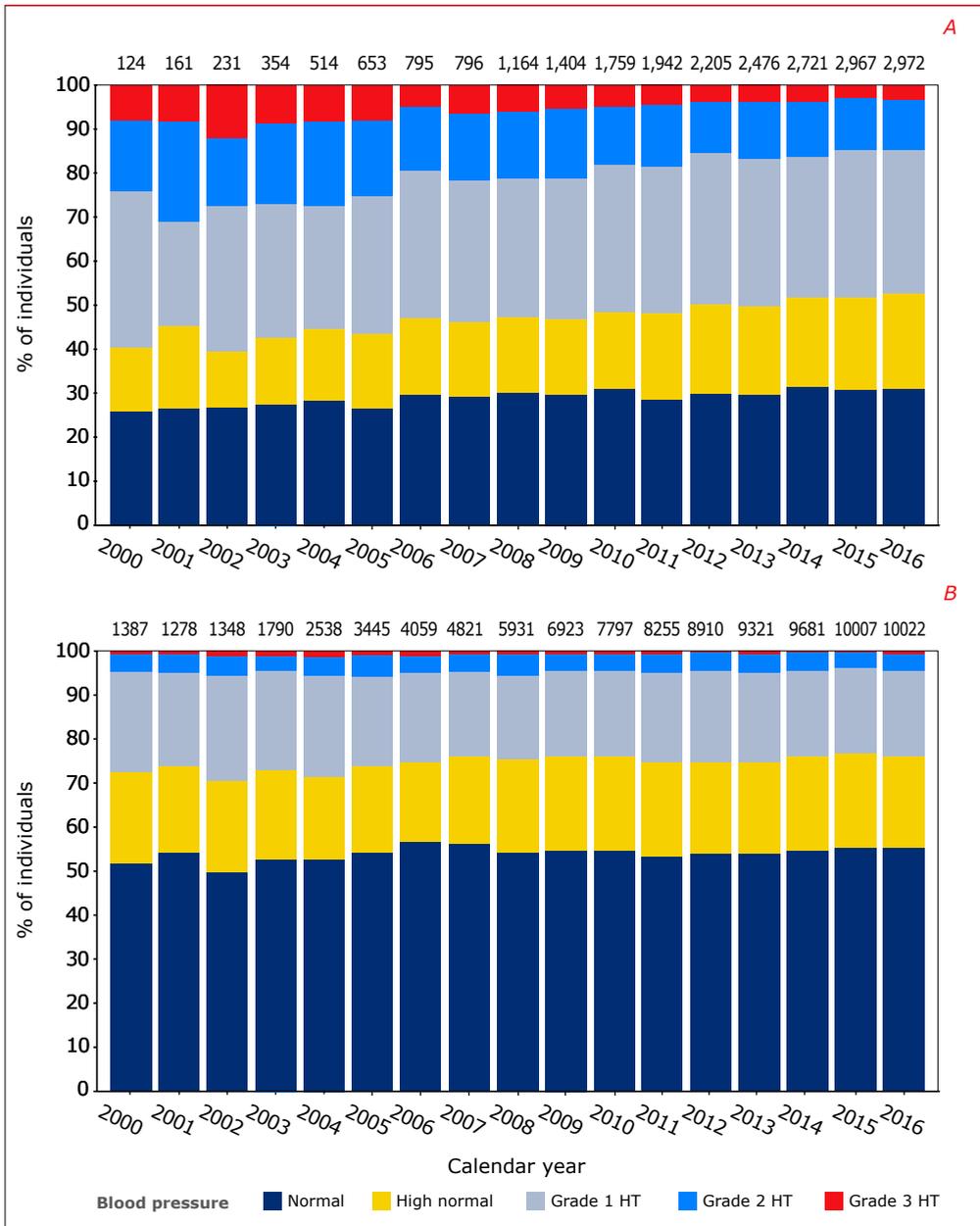


Figure 3.4: Distribution of the body mass index (BMI) at the end of each calendar year in (A) men and (B) women as a percentage of the total number of men and women with a known BMI in each year. For each individual, the last available weight measurement in each year was selected. The numbers on top of each bar represent the number of individuals contributing data during that calendar year.



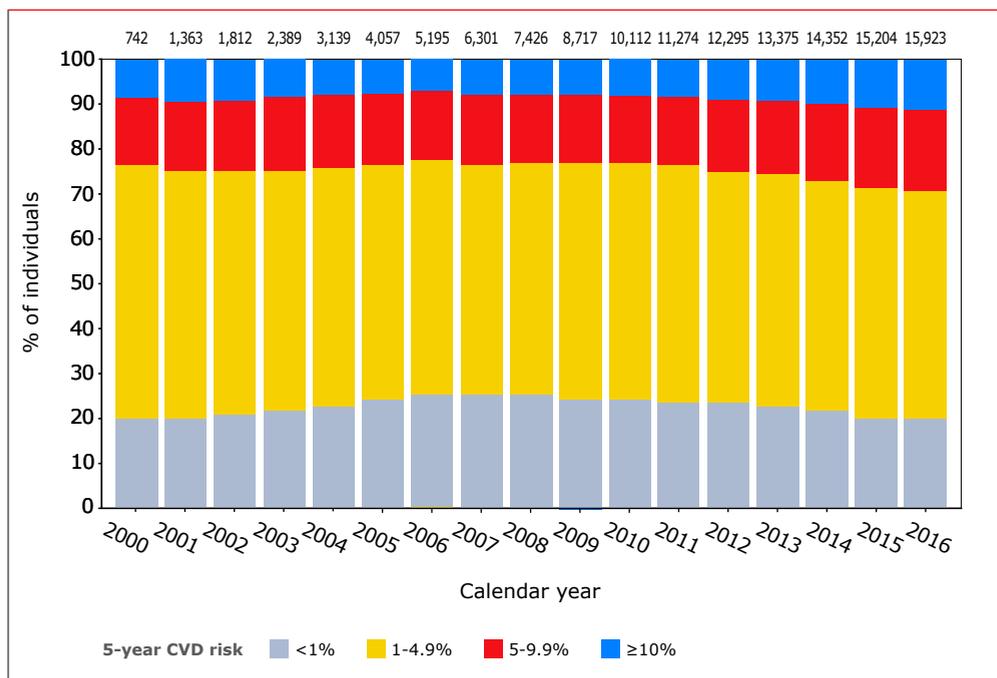
Legend: BMI=body mass index.

*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 of the European Society of Cardiology<sup>84</sup>). 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. The numbers on top of each bar represent the number of individuals contributing data during that calendar year.*



Legend: BP=blood pressure; HT=hypertension.

**Figure 3.6:** Estimated five-year risk of coronary heart disease at the end of each calendar year according to the algorithm from the D:A:D study<sup>83</sup>. 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. 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 smaller than the number of individuals in active follow up at the end of each calendar year, and older individuals are overrepresented. The numbers on top of each bar represent the number of individuals contributing data during that calendar year.



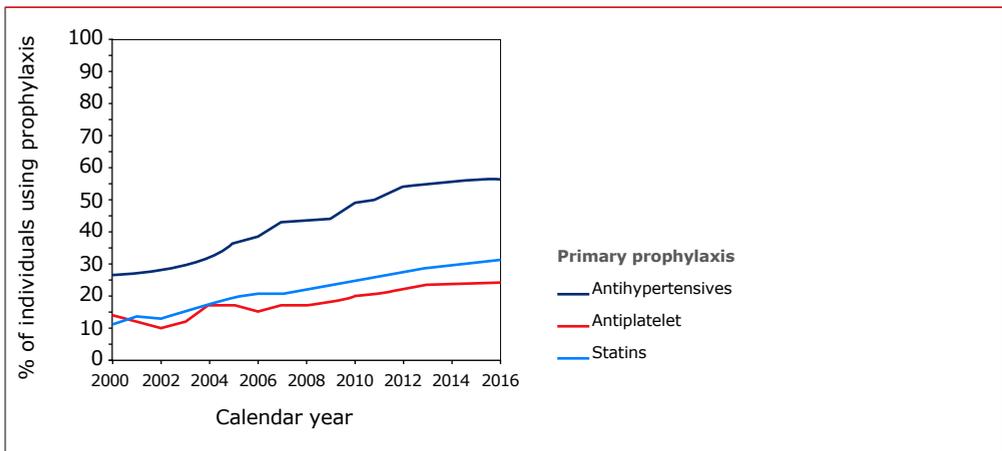
## Use of primary or secondary prophylaxis for myocardial infarction or stroke

### Primary prophylaxis

According to EACS guidelines, statin therapy should be offered to individuals with type 2 diabetes or a 5-year CVD risk  $\geq 5\%$ ; 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  $\geq 140$  mmHg or diastolic blood pressure

$\geq 90$  mmHg and a 5-year CVD risk  $\geq 10\%$ ; and acetylsalicylic acid should be offered to individuals aged 50 years or more with a 5-year CVD risk  $\geq 10\%$ <sup>85</sup>. 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. The percentage of individuals for whom primary prophylaxis using statins and the above-mentioned antihypertensive agents (referred to collectively hereafter as antihypertensives) is recommended has increased over time, although these percentages seem to have levelled off since 2012. Although the percentage of individuals at high risk and aged 50 years or older who use acetylsalicylic acid/clopidogrel as primary prevention increased slowly up to 2012, the overall proportion remains minimal and has remained stable during the last 4 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, antiplatelet therapy, or antihypertensives as primary prophylaxis for myocardial infarction or stroke.

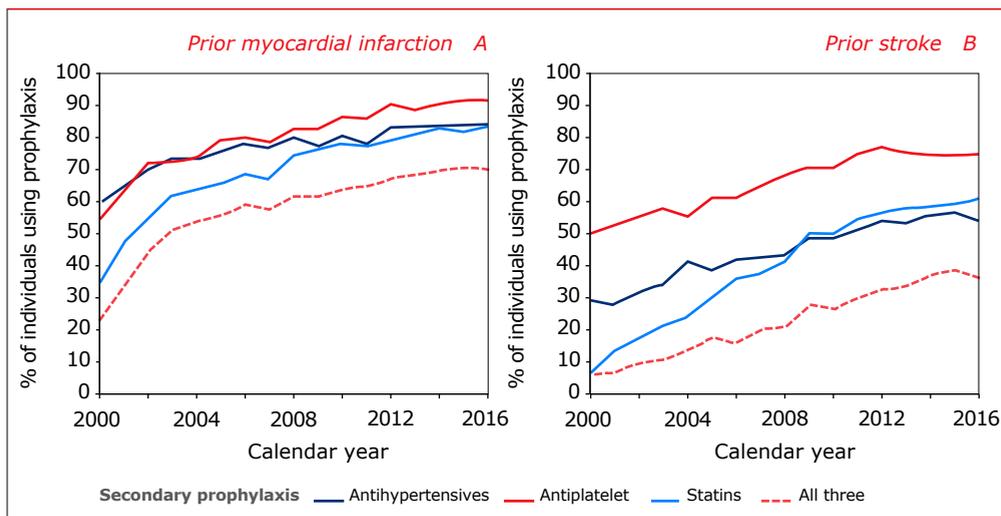


### Secondary prophylaxis for myocardial infarction or stroke

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<sup>86,87</sup>. Figure 3.8A shows that the percentages of individuals using statins, acetylsalicylic acid/clopidogrel, or antihypertensives after a myocardial infarction increased between 2000 and 2016: in 2016, 83% of individuals with a prior myocardial infarction used statins, 84% used antihypertensives, and 92% used acetylsalicylic acid/clopidogrel. Although the use of statins and antihypertensives after an ischaemic stroke also

increased over time, in 2016 these medications were used less frequently after stroke than after a myocardial infarction (61% for statins, 75% for acetylsalicylic acid/clopidogrel, and 54% for antihypertensives) (Figure 3.8B).

Figure 3.8: Percentage of individuals with (A) a myocardial infarction and (B) ischaemic stroke using statin therapy, antiplatelet therapy, or antihypertensives.



### Chronic kidney disease

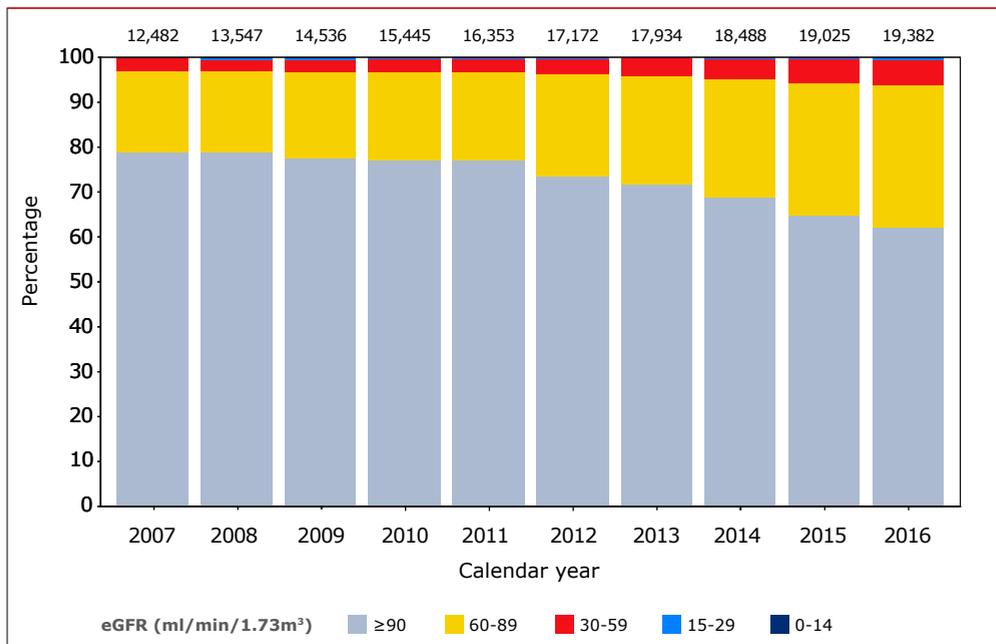
Glomerular filtration rate (GFR) is a marker of renal function and is commonly estimated by one of three formulae, namely, the Cockcroft-Gault, the Modification of Diet in Renal Disease (MDRD), or Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations<sup>88</sup>. As all three equations 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 individuals with advanced HIV disease who commence cART. Of these equations, both the Cockcroft-Gault and the CKD-EPI equations have been validated in HIV-positive individuals<sup>88,89</sup>. 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, in ml/min/1.73m<sup>2</sup> ( $\geq 90$ , 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 individuals with normal kidney function decreased over time from 79% in 2007 to 62% in 2016. This decrease was observed in both men and women (Figure 3.10). Typically, eGFR decreases with increased age, as shown in Figure 3.11, and therefore, the decrease

in the proportion of individuals with normal function over time is likely to partly reflect the increasing age of individuals in care.

In individuals with an eGFR  $>60\text{ml}/\text{min}/1.73\text{m}^2$  at inclusion in the analyses and without previously confirmed CKD, the crude incidence of CKD, defined as eGFR  $<60\text{ml}/\text{min}/1.73\text{m}^2$  confirmed by a second test at least 26 weeks later, varied over time (*Figure 3.2C*). 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 7.2 cases per 1,000 PY in the period 2008-2010 to 11.0 in 2011-2016, and in women the incidence went from 10.0 to 14.1 cases per 1,000 PY during the same periods (*Table 3.4*). The standardised incidence ratio in men, but not in women, increased significantly over time (*Table 3.4*).

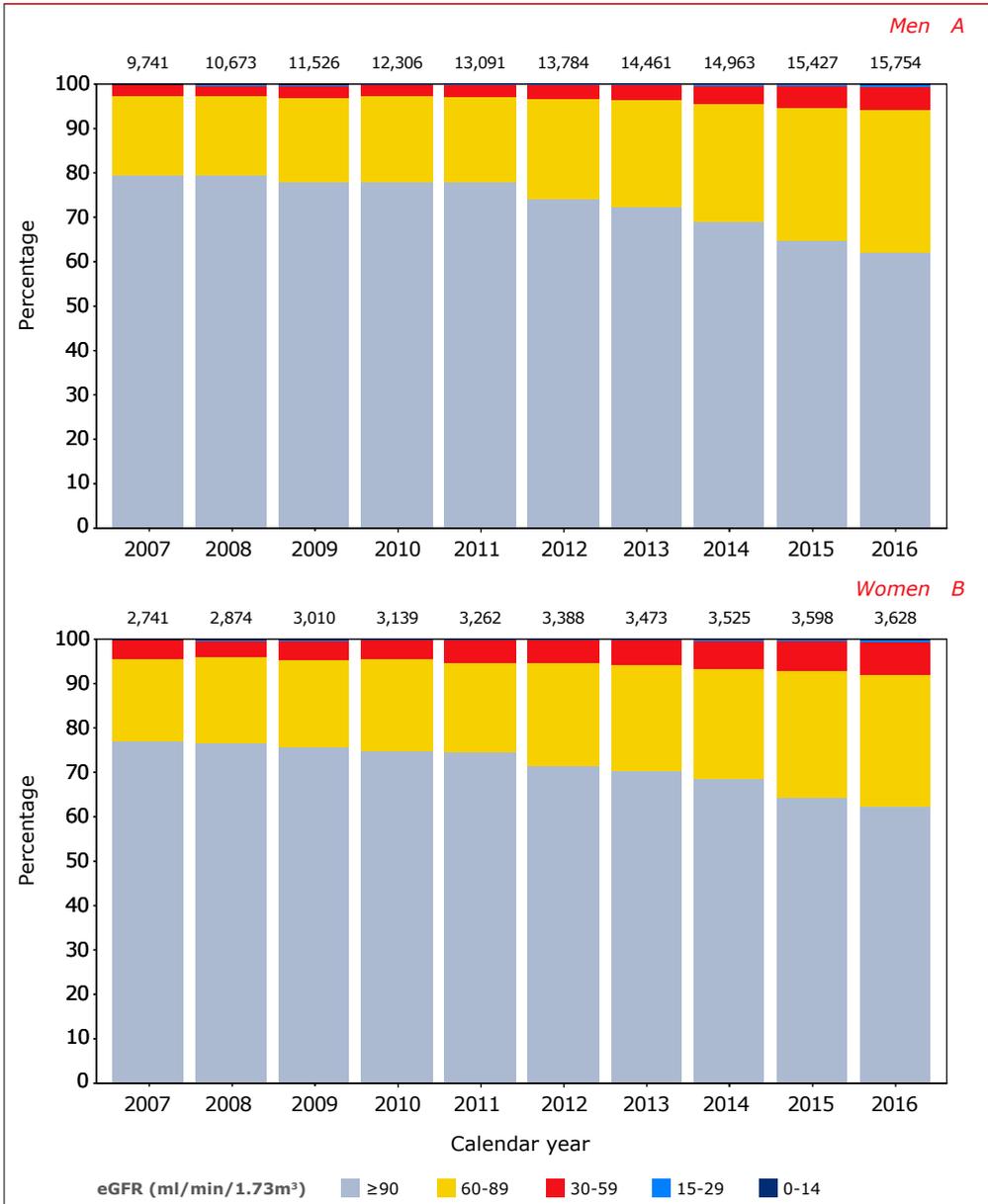
Risk factors for CKD included female gender, non-Dutch origin, low current CD4 cell count ( $<350\text{ cells}/\text{mm}^3$ ), belonging to the HIV transmission risk group of people who inject drugs, older age, lower body mass index, diabetes mellitus, cardiovascular disease, being pre-treated with monotherapy and dual therapy with nucleoside analogues before the start of cART, and HBV co-infection (*Appendix Table 3.7*). In terms of cART, duration of exposure to tenofovir disoproxil fumarate (TDF) was inversely associated with CKD. This is probably because TDF is discontinued in individuals who develop CKD, after which renal function recovers. Moreover, when current use of cobicistat and current use of dolutegravir were added to the model, the increased risk of CKD in the calendar period 2011-2016 compared to that in 2008-2010 disappeared. This suggests that the increase in CKD seen in recent years is largely due to increases in serum creatinine caused by dolutegravir-induced and cobicistat-induced reversible inhibition of two transporters that mediate tubular secretion of creatinine without affecting the glomerular filtration rate, namely organic cation transporter 2 (OCT2) and multidrug and toxin extrusion transporter (MATE1).

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 individual, the last measurement in each year was selected. The numbers on top of each bar represent the number of individuals contributing data during that calendar year.



Legend: eGFR=estimated glomerular filtration rate; eGFR  $\geq 90$  ml/min/1.73m<sup>2</sup>: normal kidney function; 60–89 ml/min/1.73m<sup>2</sup>: mildly reduced; 30–59 ml/min/1.73m<sup>2</sup>: moderately reduced; 15–29 ml/min/1.73m<sup>2</sup>: severely reduced; <15 ml/min/1.73m<sup>2</sup>: 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 individual, the last available measurement in each year was selected. The numbers on top of each bar represent the number of individuals contributing data during that calendar year.



Legend: eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m<sup>2</sup>: normal kidney function; 60-89 ml/min/1.73m<sup>2</sup>: mildly reduced; 30-59 ml/min/1.73m<sup>2</sup>: moderately reduced; 15-29 ml/min/1.73m<sup>2</sup>: severely reduced; <15 ml/min/1.73m<sup>2</sup>: very severely reduced kidney function.

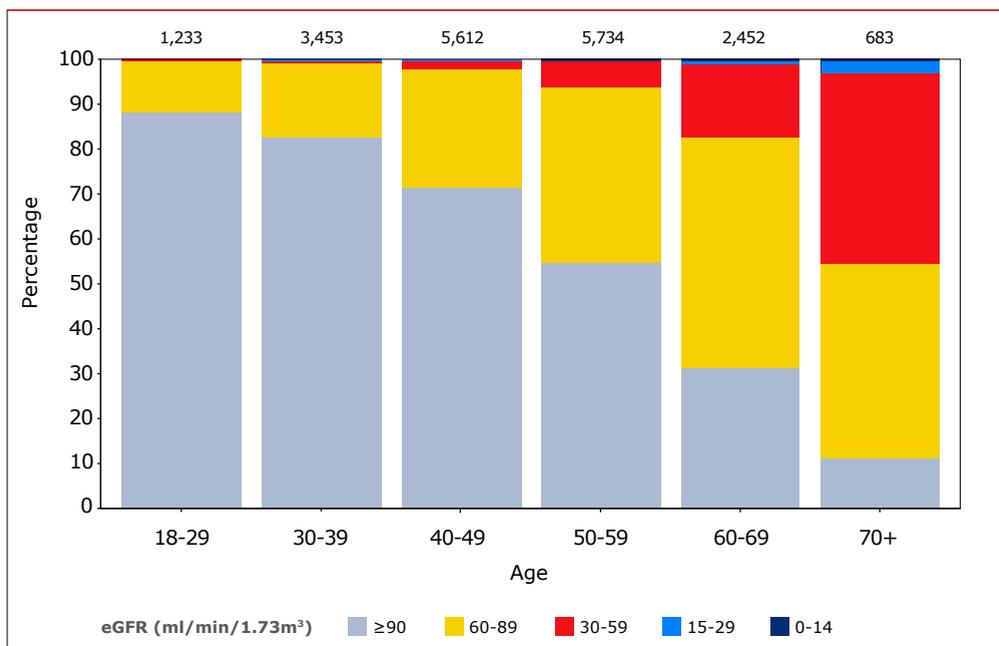
**Table 3.4:** Crude chronic kidney disease incidence per 1,000 person years of follow up between 2008–2010 and between 2011–2016, and age-standardised incidence ratio with 95% confidence intervals.

Calendar year	Male		Female	
	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)	Crude incidence (95% CI)	Standardised incidence ratio* (95% CI)
2008–2010	7.2 (5.9–8.6)	0.74 (0.61–0.87)	10.0 (7.2–13.4)	0.90 (0.63–1.16)
2011–2016	11.0 (10.1–12.0)	1.00 (reference)	14.1 (12.0–16.4)	1.00 (reference)

\*Standardised according to the observed age distribution between 2011–2016.

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

**Figure 3.11:** Distribution of categories of estimated glomerular filtration rate (eGFR) in 2016 for different age categories. For each individual, the last available measurement in 2016 was selected. The numbers on top of each bar represent the number of individuals contributing data to that age category.



Legend: eGFR=estimated glomerular filtration rate; eGFR ≥90 ml/min/1.73m<sup>2</sup>: normal kidney function; 60–89 ml/min/1.73m<sup>2</sup>: mildly reduced; 30–59 ml/min/1.73m<sup>2</sup>: moderately reduced; 15–29 ml/min/1.73m<sup>2</sup>: severely reduced; <14 ml/min/1.73m<sup>2</sup>: very severely reduced kidney function.

### Non-AIDS-defining malignancies

Between 2000 and 2016, 1,209 diagnoses of non-AIDS-defining malignancy and an additional 878 non-melanoma skin cancers in 1,620 unique individuals were recorded in SHM's database. *Table 3.5* shows the most common types of non-AIDS-defining cancer: lung cancer (19%), invasive anal cancer (14%), intestinal cancer (excluding liver, 11%), Hodgkin's lymphoma (8%), head and neck cancers (8%), and prostate cancer (7%). *Figures 3.12A* and *B* show the relative and absolute changes in types of non-AIDS cancers over time. The proportion of individuals with intestinal, prostate and renal cancer has increased over time, possibly reflecting the increasing age of the study population. This is illustrated in *Figure 3.13*, which shows the distribution of non-AIDS malignancies with increasing age at cancer diagnosis.

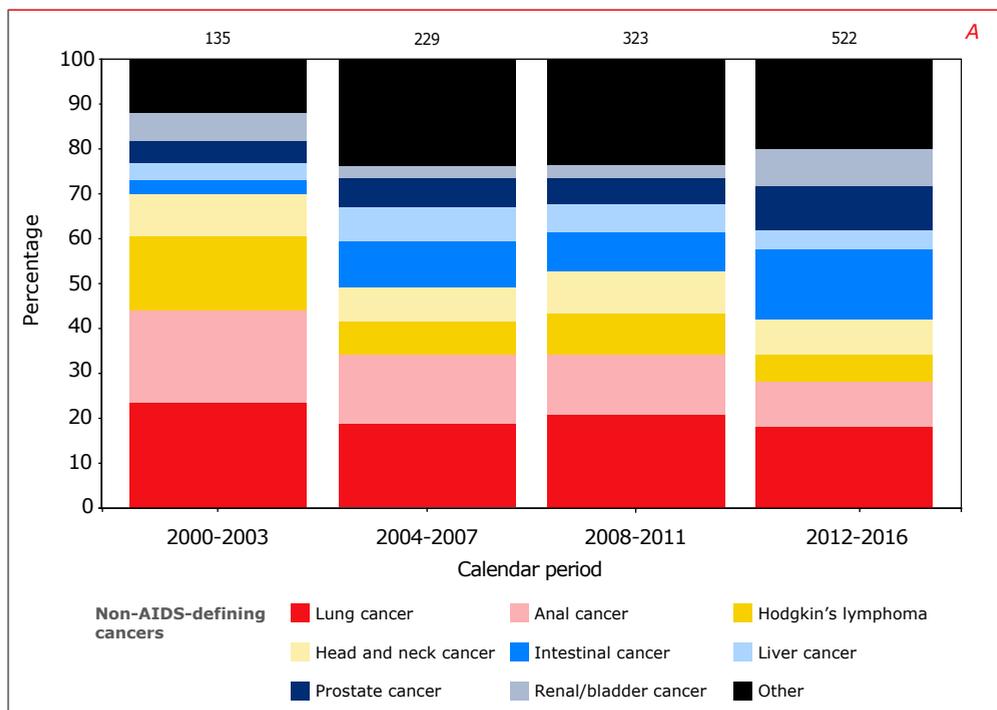
The crude incidence of non-AIDS-defining malignancies in men increased slightly from 5.7 cases per 1,000 person years in 2000-2005 to 6.4 cases per 1,000 person years in 2011-2016, and in women from 2.2 in 2000-2005 to 3.7 cases per 1,000 person years in 2011-2016 (*Figure 3.2D*; *Appendix Table 3.6D*). However, when taking into account the changes in the age distribution of the HIV-positive population, the age-standardised incidence in men was actually lower in the period 2011-2016 than in 2000-2005 and 2006-2010 (*Table 3.6*). This lower standardised incidence in men may be due to changes over time in risk factors such as smoking and a higher proportion of individuals living with high CD4 cell counts. In women, the age-standardised incidence was lower in the period 2011-2016 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, having acquired HIV-1 through injecting drugs or contact with blood or blood products, lower current CD4 cell count (CD4 below 350 cells/mm<sup>3</sup>), low body mass index, prior AIDS, chronic HBV co-infection, and current and past smoker (*Appendix Table 3.7*).

In the period from 1 January 2000 to 31 December 2016, the 5-year survival rate after a first diagnosis of non-AIDS-defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 44.5%, compared to 70.3% for CVD, 80.0% for DM, and 82.2% for CKD (*Appendix Figure 3.2*). In the same period, the 5-year survival rate of adults newly entering care in one of the Dutch HIV treatment centres was 95.4%, and 82.3% for those newly entering care with an AIDS diagnosis. The 5-year survival rates following the most common non-AIDS-defining malignancies are shown in *Table 3.5* and *Appendix Figure 3.3*.

In total, 3 HIV-positive women and 163 HIV-positive men were diagnosed with anal cancer. Among HIV-positive men, the incidence of anal cancer slowly decreased over time from 1.1 cases per 1,000 PY in 2000 to 0.7 cases per 1,000 PY in 2016 (Figure 3.2G). 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<sup>90</sup>. 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-positive individuals in the Netherlands showed a significantly higher incidence of anal cancer in MSM compared to heterosexual men<sup>91</sup>. 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=17) to observe a decreasing trend in anal cancer in this group.

Figure 3.12: (A) Relative changes in, and (B) absolute number of, non-AIDS-defining malignancies between 2000 and 2016 in HIV-1-positive individuals in the Netherlands. The numbers on top of each bar represent (A) the number of non-AIDS defining cancer diagnoses, and (B) the number of persons at risk during that calendar period shown.



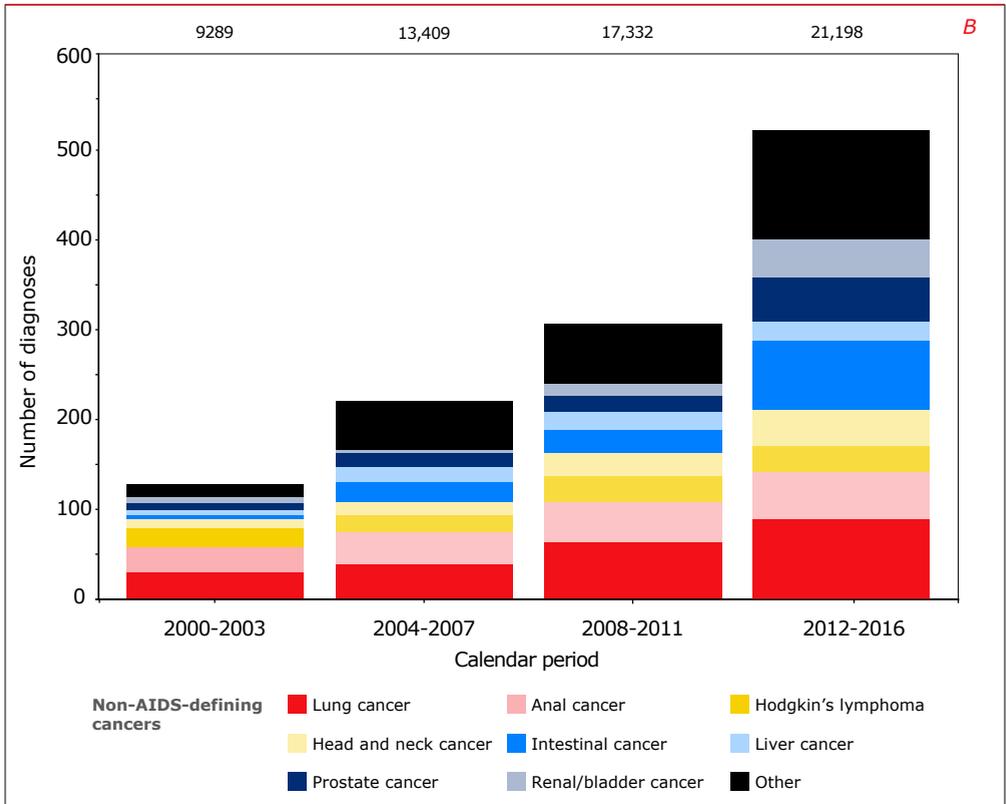
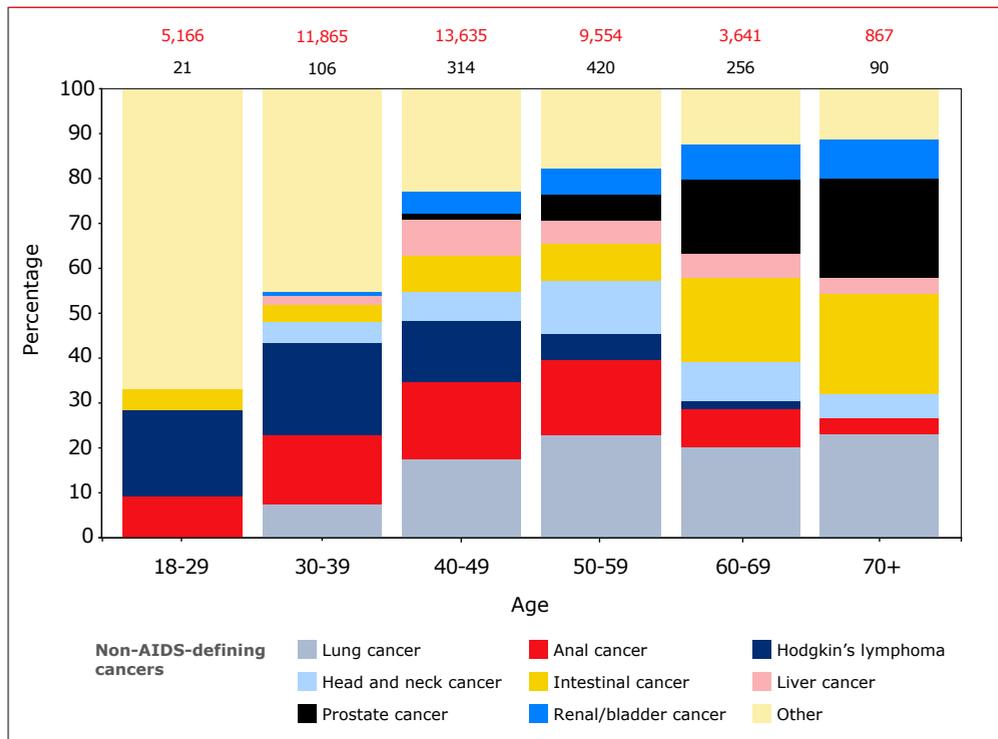


Figure 3.13: Relative changes in non-AIDS-defining malignancies with increasing age in HIV-1 positive individuals in the Netherlands. The red numbers on top of each bar represent the number of individuals at risk in that age category between 2000 and 2016; the black numbers represent the number of diagnoses in each age category between 2000 and 2016.



**Table 3.5: Most common non-AIDS-defining malignancies diagnosed between 2000–2016.**

non-AIDS malignancy	Number of malignancies	%	5-year survival
Lung cancer	235	19.4	10.2
Anal cancer	166	13.7	64.5
Intestinal cancer	137	11.3	34.1
Head and neck cancer	101	8.4	51.3
Hodgkin`s lymphoma	97	8.0	72.0
Prostate cancer	89	7.4	76.8
Renal/bladder cancer	69	5.7	60.9
Other	69	5.7	44.0
Liver cancer	65	5.4	9.4
Castleman's disease	48	4.0	75.7
Leukaemia	40	3.3	45.0
Breast cancer	39	3.2	83.7
Testicular cancer	23	1.9	90.9
Vulvar cancer	17	1.4	71.9
CNS cancer	14	1.2	30.6

*Legend: CNS=central nervous system.*

**Table 3.6: Crude non-AIDS-defining malignancy incidence per 1,000 years of follow up between 2000–2005, 2006–2010, and 2011–2016, 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	5.7 (4.9–6.5)	1.31 (1.13–1.49)	2.2 (1.3–3.3)	0.95 (0.55–1.36)
2006–2010	6.5 (5.8–7.2)	1.25 (1.11–1.38)	3.9 (2.9–5.2)	1.40 (1.02–1.78)
2011–2016	6.4 (5.9–7.0)	1.00 (reference)	3.7 (2.9–4.7)	1.00 (reference)

*\*Standardised according to the observed age distribution between 2011–2016.*

*Legend: CI=confidence intervals; PY= person years of follow up.*

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

In 6,031 therapy-naive individuals who started cART with less than 350 CD4 cells/mm<sup>3</sup> since 1996 and who had 3 years of viral suppression on cART, 1,298 classified as immunological nonresponders (defined as those having less than 350 CD4 cells/mm<sup>3</sup> after 3 years of viral suppression on cART) and 4,733 individuals with a good immunological response (those having a CD4 cell count of 350 cells/mm<sup>3</sup> or higher after 3 years of viral suppression on cART). We analysed the association between immunological response/non-response and the risk of the following endpoints: death, AIDS, non-AIDS-defining malignancy, diabetes mellitus, and cardiovascular disease. We only considered first events and excluded those individuals in whom a particular endpoint had already occurred prior to the start of observation of this analysis (these were mainly prior AIDS events). The observation period for this analysis 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 are ignored in this analysis – individuals remain in their original category of immunological responder/non-responder. The number of events, crude incidence per 1,000 person years of follow up, and age-standardised incidence ratio of these events are reported in *Table 3.7*. 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 and non-AIDS-defining malignancy. After further adjustment for current age, region of origin, gender, and HBV and HCV status, immunological non-response remained significantly associated with death (RR 1.39, 95% CI 1.10-1.77,  $p=0.006$ ) and non-AIDS-defining malignancy (RR 1.40, 95% CI 1.01-1.94,  $p=0.041$ ), but not with AIDS (RR 1.11, 95% CI 0.70-1.77,  $p=0.65$ ), diabetes mellitus (RR 0.84, 95% CI 0.59-1.19,  $p=0.32$ ), or cardiovascular disease (RR 1.16, 95% CI 0.86-1.57,  $p=0.32$ ). However, as the number of endpoints is small, these results should be interpreted with caution.

**Table 3.7:** 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 individuals who started cART with a CD4 cell count below 350 cells/mm<sup>3</sup> and after 3 years of virologically successful cART were either immunological responders (CD4 cell count  $\geq$  350 cells/mm<sup>3</sup>) or non-responders (CD4 cell count < 350 cells/mm<sup>3</sup>).

Outcome	Crude rate			Standardised rate*	
	Patient years	Number of endpoints	Rate/1,000 PY (95% CI)	SIR (95% CI)	p-value
<b>Death</b>					
Responder (CD4 $\geq$ 350)	31,402	195	6.21 (5.37-7.15)	1.00 (reference)	.
Non-responder (CD4 <350)	9,681	109	11.26 (9.24-13.58)	1.35 (1.10-1.60)	0.007
<b>AIDS</b>					
Responder (CD4 $\geq$ 350)	23,520	86	3.66 (2.92-4.52)	1.00 (reference)	.
Non-responder (CD4 <350)	5,274	23	4.36 (2.76-6.54)	1.10 (0.65-1.55)	0.667
<b>Non-AIDS-defining malignancy</b>					
Responder (CD4 $\geq$ 350)	30,850	105	3.40 (2.78-4.12)	1.00 (reference)	.
Non-responder (CD4 <350)	9,440	58	6.14 (4.67-7.94)	1.40 (1.04-1.76)	0.029
<b>Diabetes mellitus</b>					
Responder (CD4 $\geq$ 350)	29,959	137	4.57 (3.84-5.41)	1.00 (reference)	.
Non-responder (CD4 <350)	9,149	42	4.59 (3.31-6.21)	0.88 (0.61-1.14)	0.356
<b>Cardiovascular disease</b>					
Responder (CD4 $\geq$ 350)	30,889	141	4.56 (3.84-5.38)	1.00 (reference)	.
Non-responder (CD4 <350)	9,371	64	6.83 (5.26-8.72)	1.15 (0.87-1.43)	0.294

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

Legend: SIR=standardised incidence ratio; 95% CI= 95% confidence interval; PY= person years.

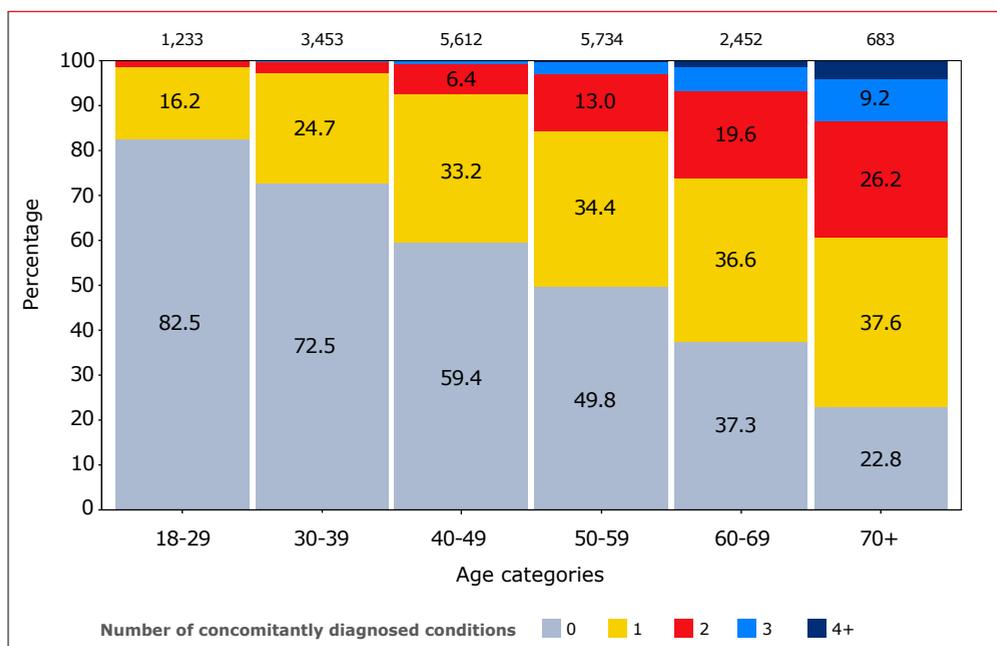
## Multimorbidity

We investigated changes over time in the prevalence of non-HIV/AIDS multimorbidity. The following comorbidities and conditions were scored: (1) cardiovascular disease (either myocardial infarction, coronary artery bypass grafting, coronary angioplasty or stenting, and carotid endarterectomy); (2) stroke; (3) non-AIDS defining malignancies, excluding non-melanoma skin cancers and pre-malignant lesions found at cervical/anal screening; (4) chronic kidney disease (eGFR below 30 ml/min/1.73 m<sup>2</sup>); (5) diabetes mellitus; (6) hypertension, defined as the use of antihypertensive drugs and/or a measured grade 2 (or higher) hypertension with systolic pressure  $\geq$ 160 mmHg and/or diastolic pressure  $\geq$ 100 mmHg; (7) obesity (BMI over 30). Note that more stringent definitions of CKD and hypertension have been applied here than in the analyses presented earlier in this chapter. Recurrences and second events of CVD, stroke, and non-AIDS-defining malignancies were not considered. CKD, hypertension and obesity

could be reversible. HIV infection itself and AIDS diagnoses did not contribute to the multimorbidity score.

Figure 3.14 shows the distribution of the number of concomitantly diagnosed conditions in various age categories of the adult population in 2016. The number of concomitant conditions was slightly higher in women than in men for all age categories (Appendix Figure 3.4). Moreover, although the average number of concomitant conditions has steadily increased over the past 10 years because of the increasing average age of the cohort, the prevalence of multimorbidity by age category has remained stable over the same period (Appendix Figure 3.5).

Figure 3.14: Prevalence of non-HIV/AIDS multimorbidity in the adult population in 2016. The numbers on top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



## Summary and conclusions

### AIDS, mortality and causes of death

AIDS-related deaths have decreased dramatically since cART became available in the Netherlands in 1996, consistent with studies from Spain<sup>92</sup>, Denmark<sup>93</sup>, several other European countries<sup>94</sup>, and the USA<sup>95</sup>. The limited, but decreasing, number of individuals who still die of AIDS each year mainly consists of those presenting late for care with already advanced immunodeficiency. Nonetheless, overall, the 5-year survival after a first AIDS-defining condition was far better than after a diagnosis of cardiovascular disease (CVD) or non-AIDS malignancies. Death is increasingly likely to be the result of a non-AIDS cause, with CVD and non-AIDS malignancies being the most common. This not only reflects the increased risk non-AIDS morbidity in individuals with more advanced HIV infection, but also the continuously increasing age of the population of individuals in care. As a result, on average, mortality rates among people living with HIV remain higher than in the general population, although they do approach, or may even drop below, general population rates in individuals who achieve CD4 counts above 500 cells/mm<sup>3</sup> on treatment<sup>96,97</sup>.

### Diabetes and cardiovascular disease

Whereas the crude incidence of diabetes mellitus and CVD in men and women was found to have remained relatively stable, the age-standardised incidence for both diseases declined over time in men. The decline in age-standardised incidence in men may suggest improved awareness, prevention (including switching from drugs associated with an increased risk of diabetes mellitus<sup>98</sup> and myocardial infarction<sup>99,100</sup> to those that, to date, have not been associated with such risks), and increased attention to managing traditional risk factors for these conditions. 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 mellitus and CVD (including age, hypertension, smoking and obesity), similar to those previously reported in other studies<sup>98,101,102</sup>. Several of these risk factors have been reported to be more prevalent among people living with HIV<sup>78</sup>.

### Cardiovascular risk factors

Despite the increasing age of the HIV-positive population, the proportion at high or very high cardiovascular risk increased only slightly over the period 2000-2016. 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 that have been demonstrated to be associated with increased cardiovascular risk, particularly in individuals with high underlying risk<sup>103</sup> (*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 have suggested that weight gain after starting cART is associated with lower mortality for normal-weight individuals, but found no clear benefit for overweight or obese individuals<sup>104</sup>. However, another study found that weight gain after starting cART was 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<sup>105</sup>. 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-positive population and to study the impact of interventions, such as the use of statins and antihypertensive therapy, in modifying disease risk.

### Renal insufficiency

Since 2008, there has been a steady increase in the incidence of new-onset chronic kidney disease (CKD). 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 individuals with advanced immunodeficiency. In addition, other studies have reported hepatitis B and C virus co-infection<sup>106,107</sup> and the use of tenofovir disoproxil fumarate, atazanavir/ritonavir, and lopinavir/ritonavir to be additional independent predictors of chronic renal impairment<sup>108</sup>. Renal impairment in the HIV-positive population is associated with an increased risk for cardiovascular disease<sup>109</sup>. The increase in CKD in recent years appears to be at least partially caused by the increased use of dolutegravir and cobicistat, both of which cause reversible inhibition of tubular excretion of creatinine, without causing a true decrease in glomerular filtration.

### 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 also observed a decline in age-standardised incidence of

non-AIDS-defining malignancies in men. In addition, our analyses show that individuals diagnosed with non-AIDS-defining malignancies were more likely to be older. This is in line with data from other cohorts, including the Swiss HIV cohort, that have also reported an increased incidence of non-AIDS-defining malignancies with increasing age<sup>110,111,112,113</sup>. Our analyses also showed that individuals diagnosed with non-AIDS-defining malignancies were more likely to be current or past smokers and more likely to have lower CD4 counts (the effect was significant with CD4 cell counts below 350 cells/mm<sup>3</sup>) and a prior AIDS diagnosis. Other studies reported that the effect of immunodeficiency may be stronger for infection-related non-AIDS-defining malignancies<sup>198</sup>. The 5-year survival rate after a first diagnosis of non-AIDS defining malignancy (excluding non-melanoma skin cancers and invasive anal cancers) was 44.5%.

Our analyses found no association between duration of cART and the incidence of non-AIDS-defining malignancies. On the other hand, a recent paper from the D:A:D study looking at the association between non-AIDS-defining malignancies and cumulative cART use in a large study population found an overall increase in the risk of non-AIDS-defining malignancies with longer exposure to a PI-based cART regimen. This association was observed particularly for anal cancer<sup>114</sup>. 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 individuals dying of AIDS in the Netherlands has markedly declined throughout the cART era, this needs to be improved further by identifying 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<sup>11,12,115</sup>. 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 reducing the incidence of such comorbidities.

The relatively poor 5-year survival rates following the diagnosis of several of the studied non-AIDS-defining comorbidities compared to survival after newly entering care with an AIDS diagnosis underlines the importance of primary prevention, early diagnosis and aggressive pursuit of secondary prevention and treatment of non-AIDS comorbidities in the HIV-positive population. Studies such as the ongoing AGE<sub>IV</sub> 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 pathophysiological mechanisms<sup>68,116</sup>. 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-positive individuals compared to those who are HIV-negative, thereby further guiding policy for prevention and management.

It is important to note that the risk of many, if not each, of the comorbidities 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<sup>117</sup>.

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.

Finally, awareness on the part of both physicians and people living with HIV concerning the role of modifiable, lifestyle-related risk factors, particularly in older individuals or those 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 people living with HIV.

## 4. Viral hepatitis

Colette Smit, Joop Arends, Peter Reiss, 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 percent of the total Dutch population has evidence of ever having been exposed to HCV and that the same percentage has ever been exposed to HBV<sup>118,119</sup>. In contrast, HCV and HBV co-infections are far more prevalent in HIV-positive individuals due to shared routes of transmission with HIV<sup>120</sup>.

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)<sup>121,122</sup>. HBV infection can also directly lead to HCC without cirrhosis. Progression to severe liver disease takes, on average, 20 to 30 years in HCV or HBV mono-infected individuals<sup>123,124</sup>. Although liver fibrosis progression was faster in HIV-coinfected persons prior to the availability of combination antiretroviral therapy (cART), the rate of such progression in those with optimally managed HIV has become increasingly similar to that in HCV or HBV mono-infected individuals<sup>125</sup>.

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 died 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 cART, liver disease has become an increasingly frequent cause of morbidity and mortality in persons living with HIV<sup>126</sup>.

From 2012 onwards, an extensive retrospective collection of data on liver disease and hepatitis has been established by SHM in conjunction with the Dutch association of HIV-treating physicians (*Nederlandse Vereniging van HIV Behandelaren, NVHB*). These data span the entire spectrum of both HBV and HCV infection. This chapter reports on the demographic and clinical characteristics, progression to severe chronic liver disease and mortality, as well as responses to treatment in the population with HIV and HCV and/or HBV co-infection.

## HCV

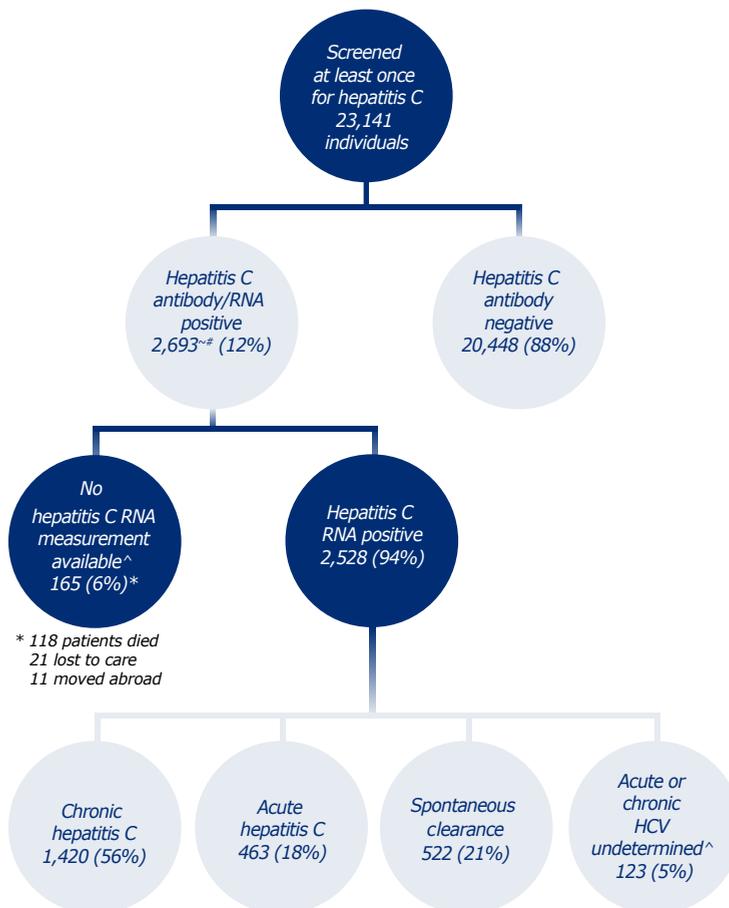
### Demographic and clinical characteristics

In total, 2,693 (12%) of the 23,141 HIV-1-positive adults ( $\geq 18$  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. This confirms the far greater prevalence of HCV in the HIV-positive population than estimated for the general population in the Netherlands (*Figure 4.1*). In 165 of the 2,693 individuals (6%), HCV RNA data were not documented. Of these 165 individuals, 118 had died, 21 were lost to care and 11 had moved abroad. Of the remaining 2,528 patients with positive HCV RNA test results, 1,420 (56%) 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 463 (18%) were diagnosed with acute HCV infection (documented anti-HCV IgG seroconversion or HCV RNA conversion within 12 months). Another 522 (21%) individuals 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 123 individuals of the 2,528 individuals 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 individuals was excluded from further analysis.

The analyses described in the remainder of this section on HCV are therefore limited to those people who could be definitively classified as having either chronic ( $n=1,420$ ) or acute ( $n=463$ ) HCV infection. Most of these individuals with chronic or acute HCV infection were male (84% and 98%, respectively). Most individuals originated from the Netherlands (chronic 888/1,420 [61%], acute 366/463 [79%]) (*Table 4.1*). Fifty-nine percent of the individuals ever registered and infected with HIV through injecting drug use (IDU) or former IDU had chronic HCV infection (427 of the total 723 [former] IDU), while 5% of men who have sex with men (MSM) had chronic HCV infection (686 of the total of 14,076 MSM) and 3% of MSM had experienced an acute HCV infection (436 of the total of 14,076 MSM). For 1,290 of the 1,420 individuals (91%) with a chronic HCV infection, the HCV genotype was determined and documented in the clinical records. The majority of these people (62%) were infected with HCV genotype 1 ( $n=800$ ); of those with genotype 1, 62% were infected with genotype 1a ( $n=503$ ) and 13% with genotype 1b ( $n=98$ ). Five percent were infected with HCV genotype 2 ( $n=63$ ), 15% were infected with genotype 3 ( $n=188$ ), and 16% with genotype 4 ( $n=212$ ). Two percent of the people

were either infected with genotype 5 or 6 or had an undeterminable genotype. In 428 of the 463 individuals (92%) with an acute HCV infection, an HCV genotype was available. In most of the cases, people with an acute HCV infection were infected with either genotype 1 (67%) (n=288) or genotype 4 (21%, n=90). Of the 288 infected with genotype 1, 230 (80%) were infected with genotype 1a and 12 (4%) with genotype 1b; for the remaining 46 individuals with genotype 1, no differentiation between genotype 1a or 1b was available.

**Figure 4.1:** Flowchart of HIV-positive individuals tested at least once for hepatitis C virus (HCV).



**Legend:** ~Including patients who are HCV RNA positive but no known HCV antibody data.

#Including documented seroconversion.

^Excluded from further analyses.

**Table 4.1: Demographic characteristics of HIV/hepatitis C virus (HCV) co-infected individuals registered in the SHM database, 1998–2017.**

	Total	Chronic HCV	Acute HCV	Spontaneous clearance
Total number of individuals screened for HCV	23,141	1,420	463	522
Male gender, n (%)	18,955 (82)	1,187 (84)	456 (98)	406 (78)
Region, n (%)				
Netherlands	13,252 (57)	868 (61)	366 (79)	267 (51)
Europe	1,534 (7)	214 (15)	32 (7)	75 (14)
Sub-Saharan Africa	3,215 (14)	46 (3)	7 (2)	56 (11)
Caribbean/South America	2,685 (12)	89 (6)	27 (6)	62 (12)
South-East Asia	793 (3)	46 (3)	10 (2)	16 (3)
Other	1,662 (7)	157 (11)	21 (5)	46 (9)
HIV transmission route, n (%)				
Men who have sex with men	14,076 (61)	686 (48)	436 (94)	249 (48)
Heterosexual				
Current/former injecting drug users	6,869 (30)	150 (11)	16 (3)	96 (18)
Other	723 (3)	427 (30)	5 (1)	111 (22)
cART, n (%)	1,473 (6)	157 (11)	6 (1)	66 (13)
cART, n (%)	21,881 (95)	1,362 (96)	458 (99)	496 (95)
HCV genotype (GT), n (%*)				
Total determined		1,290	428	
GT 1		800 (62*)	288 (67*)	
1a		503	230	
1b		98	12	
1c, 1a/b or not further specified		199	46	
GT 2		63 (5*)	24 (6*)	
GT 3		188 (15*)	11 (3*)	
GT 4		212 (16*)	90 (21*)	
Other		27 (2*)	15 (4*)	
Not determined		130	35	
Deaths, n (%)	2,372 (10)	278 (20)	19 (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.

## Changes over time

### Testing for HCV over time

Screening for HCV infection among HIV-positive individuals in care increased over calendar time. In 1998, 39% of the HIV-positive individuals 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 individuals with a known HCV status has been observed. In 2012, only 5% of the people in care had not been screened for HCV co-infection, and this total declined further to 0.4% in 2016 (*Figure 4.2*).

### Prevalence of chronic HCV co-infected individuals per calendar year

The overall prevalence of ever being diagnosed with a chronic HCV co-infection (defined as the proportion of individuals who tested positive for HCV RNA for at least six months) among HIV-positive individuals in care decreased from 12.5% in 1998 to 5.8% in 2016, but was not equally distributed among HIV transmission categories. The highest prevalence was found among individuals infected with HIV by IDU, and this number varied between 64% and 70% (*Figure 4.3A*).

### Prevalence of individuals with detectable HCV RNA

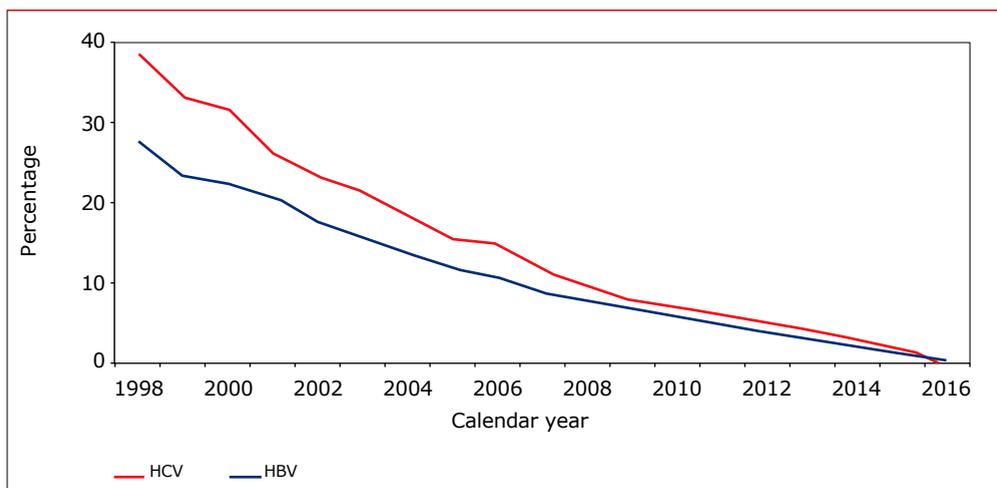
*Figure 4.3B* shows the proportion of individuals with an active HCV infection (defined as a time-updated positive HCV RNA test result) per calendar year of follow up, regardless of whether the diagnosis was chronic or acute infection or re-infection. Individuals were included in follow-up time if they were in care in a specific calendar year and the HCV RNA positivity was based on the last available HCV RNA test result before the end of that calendar year. The overall proportion of individuals with detectable HCV RNA varied between 4.0% in 1998 and 6.2% in 2007, but dropped to 1.8% in 2016. In MSM, the highest proportion of HCV RNA positivity was observed in 2008, when 4.6% of the men had a positive HCV RNA test result; in 2016 positive results in this group sharply decreased to 1.4%.

### Incidence of acute HCV infection over time

The incidence of the first diagnosis of acute HCV infection showed important differences between HIV transmission categories. The vast majority of acute HCV infections occurred in MSM (436/463 [94%]). For IDU or former IDU, the overall incidence was low (2.4/1,000 person years [PY], 95% confidence interval [CI] 0.8-5.5), 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 individuals heterosexually infected with HIV, the overall incidence of acute HCV was 0.2/1000 PY (0.13-0.38). *Figure 4.4* shows the incidence of acute HCV infection among MSM over time. The overall

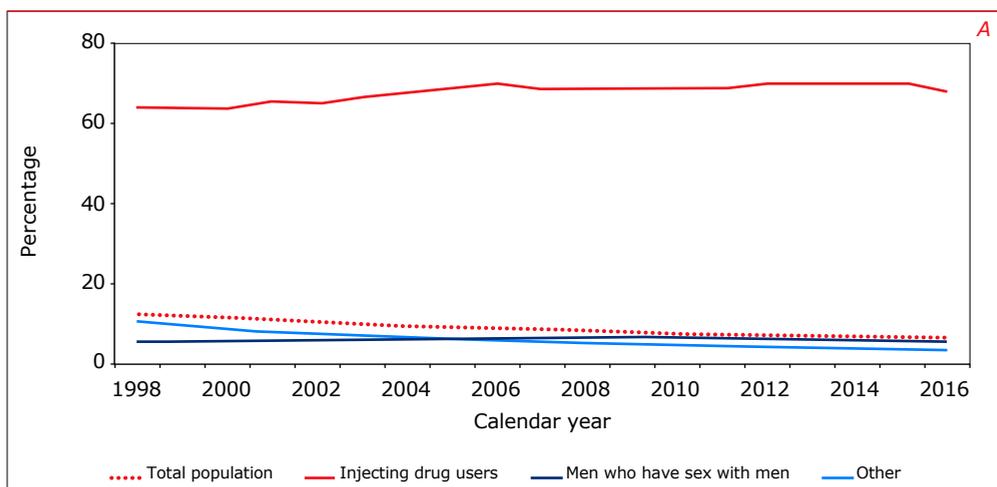
rate of acute HCV infection in this group was 3.4 per 1,000 PY of follow up (95% CI 3.2-3.7). This incidence increased from zero diagnoses per 1,000 PY in 1998 to 4.8 diagnoses per 1,000 PY in 2015, with a peak in 2007 and 2008 of 6.8 and 7.2 acute HCV infections per 1,000 PY, respectively. In 2016, the incidence of first diagnosis of acute HCV infection was 2.0 per 1,000 PY.

Figure 4.2: Percentage of individuals 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 (A) chronic hepatitis C co-infection and (B) detectable HCV RNA per calendar year.



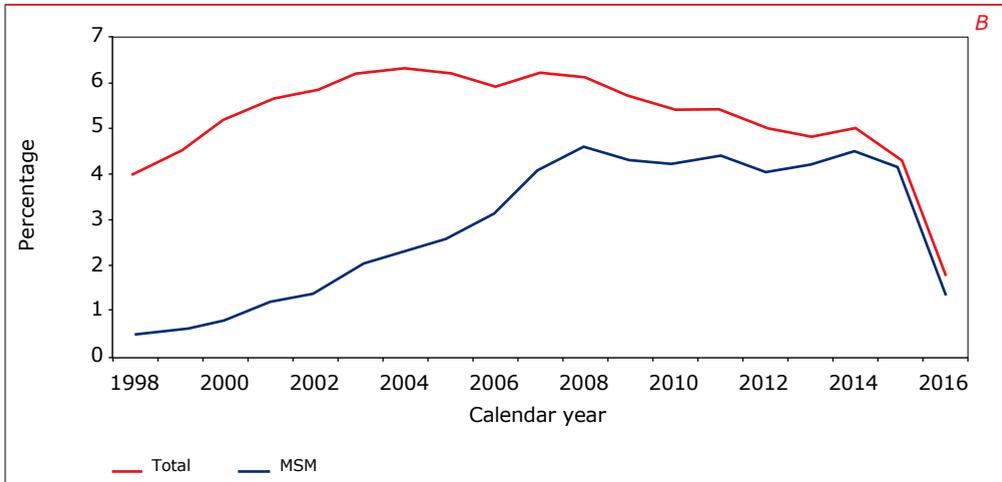
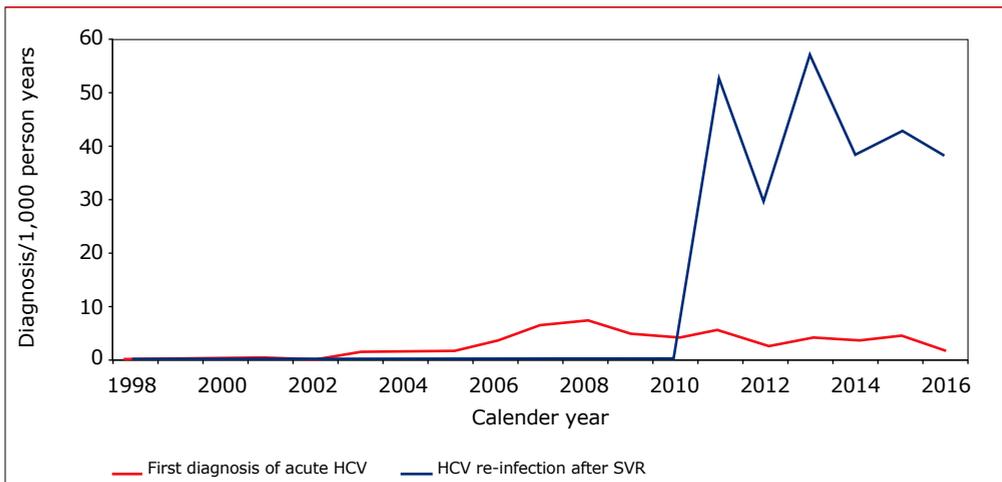


Figure 4.4: Incidence of acute hepatitis C infection among men who have sex with men, per calendar year.



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

### Treatment for HCV infection

The primary aim of treatment for HCV is to achieve a sustained virological response (SVR)<sup>19</sup>. 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 NS<sub>3</sub>/4a protease inhibitors (PI)

boceprevir and telaprevir, two direct-acting antivirals (DAAs) active against HCV genotype 1, became available in the Netherlands<sup>127,128</sup>. 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, sofosbuvir was reimbursed only for HCV-infected individuals with severe liver fibrosis or cirrhosis (metavir score F3-F4 or Fibroscan® stiffness  $\geq 9.5$ ), 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 was made available for all HCV-infected patients regardless of their fibrosis status, followed shortly by the introduction of additional novel DAAs like new HCV NS3/4A protease inhibitors (PI) (simeprevir, paritaprevir and grazoprevir), NS5A inhibitors (daclatasvir, ledipasvir, ombitasvir and elbasvir) and an NS5B polymerase inhibitor (dasabuvir). Table 4.2 gives an overview of all DAA-containing HCV treatment combinations currently available in the Netherlands<sup>129</sup>.

*Table 4.2: Overview of treatment regimens available as of 31 December 2016, including direct-acting antivirals (DAAs) active against hepatitis C virus (HCV) in the Netherlands.*

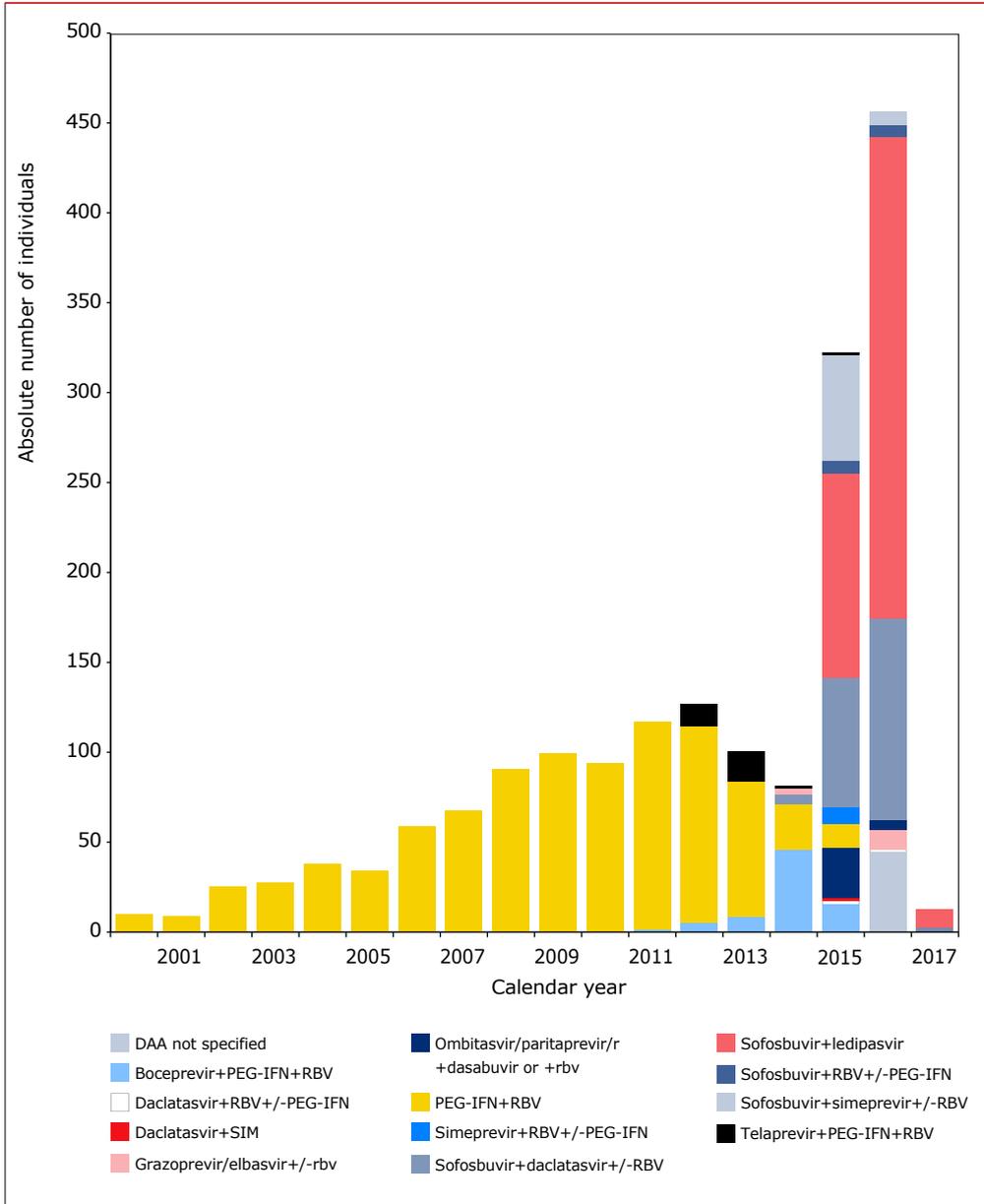
DAA/HCV treatment combination*	Available since	HCV genotypes covered	Treatment duration
Sofosbuvir+RBV+PEG-IFN	2014	All	12 weeks
Sofosbuvir+RBV	2014	2+3	12-24 weeks
Simeprevir+RBV+ PEG-IFN	2014	1+4	24-48 weeks
Simeprevir+sofosbuvir +/- RBV	2014	1+4	12-24 weeks
Daclatasvir+sofosbuvir +/- RBV	2015	1,2,3,4	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
Elbasvir/grazoprevir	2016	1,4	12 weeks

\*Boceprevir and telaprevir were only temporarily available and therefore not included in this table.

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

Figure 4.5 shows the absolute number of individuals who have started HCV treatment per calendar year. In total, 1,412 individuals have received HCV treatment; of those, 294 have received HCV treatment more than once, including individuals who were unsuccessfully treated and those who became re-infected with HCV after previously successful treatment.

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



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

**Treatment with IFN alpha/PEG-IFN alpha plus ribavirin and boceprevir or telaprevir**

The number of individuals per year starting IFN alpha/PEG-IFN alpha plus ribavirin (RBV) treatment increased from 11 in 2000 to 117 in 2011, followed by a decrease to 15 in 2015 (*Figure 4.5*). The number of individuals treated with boceprevir or telaprevir was 18 in 2012, 26 in 2013, 48 in 2014 and 16 in 2015. In 2016 none of these PEG-IFN-containing regimens were being used as a result of the availability of more novel DAAs. The outcome of individuals treated with such former regimens was described in detail in the SHM monitoring report of 2016<sup>7</sup> and is not included in the current report.

**Treatment with novel DAAs**

In total, 766 HIV co-infected individuals have been treated with a regimen containing sofosbuvir, simeprevir, daclatasvir, ledipasvir, ombitasvir, paritaprevir, dasabuvir or elbasvir/grazoprevir in a variety of combinations. Of these 766 patients, 9 started their treatment in 2014, 293 in 2015, and the remaining 469 started in either 2016 or the first 4 months of 2017 (*Table 4.3*). The most frequently-used regimens were 1) sofosbuvir plus ledipasvir +/- RBV (n=391), which was prescribed in 266 patients infected with genotype 1 and in 91 patients infected with genotype 4, and 2) sofosbuvir plus daclatasvir +/- RBV (n=192), which was prescribed in 111 patients infected with genotype 1 and in 21 infected with genotype 3. Ten patients died after receiving treatment with DAAs; 2 of the 10 deaths were due to liver disease, 2 to cardiovascular disease, 2 to non-natural causes, 1 to non-AIDS infection, 1 to lung disease, and for 2 patients the cause of death was unknown.

**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 1 May 2017.**

Regimen	n	HCV genotype (GT)	Severe chronic liver disease (see definition)	Treatment completed and SVR12* data available	SVR12* (n/total no. individuals with available HCV RNA test results)
Sofosbuvir+ledipasvir+/-RBV	391		111	349/391	339/349 (97%)
GT 1		269			
GT 2		5			
GT 3		6			
GT 4		91			
GT 6		1			
unknown		19			
Sofosbuvir+daclatasvir+/-RBV	192		90	167/192	162/167 (97%)
GT 1		113			
GT 2		7			
GT 3		38			
GT 4		22			
unknown		12			
Sofosbuvir+simeprevir +/-RBV	67		53	64/67	62/64 (97%)
GT 1		52			
GT 3		1			
GT 4		14			
Sofosbuvir++RBV+/- PEG-IFN	17		8	13/17	12/13 (92%)
GT 1		2			
GT 2		10			
GT 3		2			
GT 4		2			
Unknown		1			
Paritaprevir/r/ombitasvir +/- dasabuvir or RBV	33		9	33/33	31/33 (94%)
GT 1		17			
GT 4		5			
Other		1			
unknown		10			

Regimen	n	HCV genotype (GT)	Severe chronic liver disease (see definition)	Treatment completed and SVR12* data available	SVR12* (n/total no. individuals with available HCV RNA test results)
Simeprevir+PEG-IFN+RBV	10		2	10/10	10/10 (100%)
GT 1		4			
GT 4		5			
unknown		1			
Daclatasvir+RBV +/- PEG-IFN	4		2	4/4	4/4 (100%)
GT 1		2			
GT 4		2			
Simeprevir+daclatasvir	1		1	1/1	1/1 (100%)
GT 1		1			
Grazoprevir/elbasvir	11		4	7/11	7/7 (100%)
GT 1		7			
GT 4		3			
unknown		1			
DAA, regimen not specified	45		12	35/45	34/35 (97%)
GT 1		25			
GT 2		4			
GT 3		2			
GT 4		10			
unknown		4			
<b>Total</b>	<b>771</b>		<b>290</b>	<b>683/771 (89%)</b>	<b>662/683 (97%)</b>

\*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 2017, 766 individuals were known to have started a DAA regimen, and 5 individuals had been treated twice with a DAA regimen. Reasons for receiving DAA treatment twice were: re-infection (n=1), no SVR achieved during the first episode of DAA treatment (n=3), and patient's decision to discontinue the first episode of DAA treatment (n=1). HCV RNA data were collected up to 1 May 2017. At that point, 647 individuals had completed treatment with one of these regimens, and sufficient time had elapsed since discontinuation of treatment to enable calculation of the SVR12 rate (Table 4.3). In total, 628 out of these 647

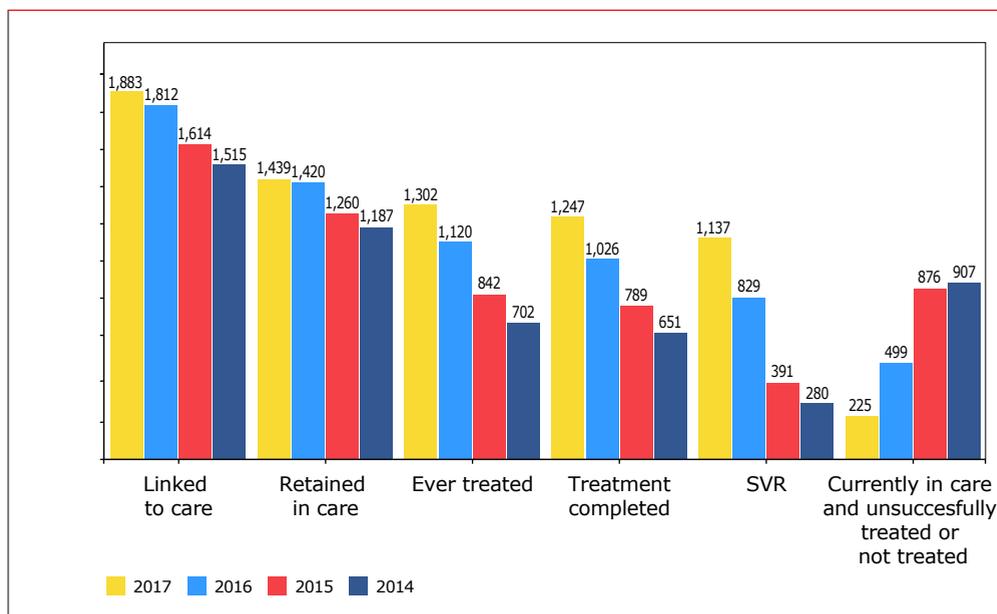
individuals achieved an SVR<sub>12</sub> (97%), with the same rate for both treatment-naive and pre-treated individuals. The SVR rate was 98% in people with chronic liver disease. Twenty-one individuals failed to achieve an SVR, and failure occurred among all genotypes. Although this group was not specifically different from the group that achieved an SVR, the small number of individuals in this group limits conclusions regarding failure to achieve an SVR.

#### **Continuum of care for those with diagnosed HCV co-infection**

*Figure 4.6* shows the continuum of care for individuals with an HCV co-infection, based on the number known to be in care as of 1 May 2017, with data from the reports from 2014 (data cut-off 1 June 2014), 2015 (data cut-off 15 September 2015) and 2016 (data cut-off 1 May 2016) shown for comparison. Out of a total of 1,883 individuals linked to HIV care and diagnosed with HCV, 1,439 individuals (76%) were retained in care, and of these 1,439, 1,302 (90%) had ever received treatment for HCV. Of the 1,302 individuals treated for HCV, 1,247 (96%) had completed HCV treatment and had data available to calculate their HCV treatment response. Overall, 1,137 of the 1,247 (91%) individuals who completed treatment had achieved an SVR. As a result, 302 of the 1,439 individuals (21%) who were alive and in care as of 1 May 2017 in one of the Dutch HIV treatment centres remained untreated (n=137), not successfully treated (n=85), were still being treated or had insufficient time after treatment discontinuation to allow SVR calculation (n=80). All 80 individuals 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 extrapolated the observed DAA SVR rate of 97% and assumed that 97% of these 80 individuals (n=77) will eventually be successfully treated. This resulted in an estimated number of  $302-77=225$  individuals who remain untreated or unsuccessfully treated.

Compared with 2016, the continuum of care for 2017 shows that an additional 182 individuals have received HCV treatment, resulting in an increase in HCV/HIV co-infected people ever having been treated for HCV from 59% in 2014 and 67% in 2015 to 90% in 2016. Furthermore, since last year's report, an additional 308 patients have documented evidence of cure. Finally, despite the increase in the total number of individuals retained in care with an acute or chronic HCV infection to 71, the total number of individuals who remain in need of HCV treatment has decreased from 499 in last year's report to 225 currently.

Figure 4.6: Hepatitis C continuum of care.



Legend: SVR=sustained virological response.

### HCV reinfection

Re-infection with HCV following successful treatment has been reported mainly in HIV-infected MSM<sup>130,131</sup>, with high rates of re-infections among MSM in the Netherlands, Germany<sup>132</sup> and the United Kingdom<sup>133</sup>.

To identify possible HCV re-infection among HCV co-infected individuals, we selected the 1,199 individuals who had initially achieved an SVR after ever having received any type of HCV treatment. For these 1,199 individuals, the incidence of HCV reinfection was reported between 2010 and 2016. Follow-up time was calculated from the SVR date, or if a SVR was achieved before 2010, follow up time was from 1 January 2010, until the earliest occurrence of date of HCV re-infection, date of death, or date of last contact. Of these 1,199 individuals, 139 (12%) had documented detectable HCV RNA levels after having an earlier documented SVR. This strongly suggests HCV re-infection. Moreover, for 45 of these 139 individuals (32%), an HCV genotype switch was reported, providing additional evidence of HCV re-infection.

The majority of individuals who again became HCV RNA-positive after successful treatment for HCV (based on SVR) were MSM (125/139, 88%). A further six were injecting drug users (6/139, 4%). For the remaining eight individuals, the HCV transmission route is unknown. However, documented HIV transmission routes were heterosexual contact (n=2), blood-blood contact (n=3) and three through an unknown route of HIV transmission. Out of the 139 individuals with a re-infection, 85 were re-treated; of those, 64 were re-treated with a DAA-containing regimen. In total, 77 out of these 85 individuals achieved an SVR. Among the 64 individuals that had been re-treated with a DAA-containing regimen, 59 achieved an SVR, 2 individuals failed to achieve an SVR and for 3 individuals the SVR was not yet available.

The incidence of HCV reinfection was 34 re-infections per 1,000 PY (95%: 28-41) for the total population and 44 infections per 1,000 PY (95%: 35-55) for MSM. *Figure 4.4* shows the incidence of HCV re-infection after achieving an SVR among MSM over time. This incidence increased from 0 to 58 infections per 1,000 PY between in 2010 and 2013 and then declined between 2014 and 2016. The majority of individuals with a re-infection documented between 2014 and 2016 were MSM (92%) or injecting drug users (6%).

## HBV

Forty-four percent of the 23,268<sup>c</sup> HIV-positive individuals ever registered in the SHM database and ever screened for hepatitis B core antibody (anti-HBc) tested positive during screening and thus had been exposed to HBV. In total, 13,032 (56%) HIV-positive individuals tested negative for anti-HBc. Of those individuals, 5,222 (22%) were anti-hepatitis B surface antigen-positive (anti-HBs+), indicating that they had been successfully vaccinated against HBV (*Figure 4.7*). These proportions were 26% for MSM, 16% for heterosexuals and far lower (6%) for IDU and former IDU. For 957 individuals (4%) who had not been tested for anti-HBs, the HIV-treating physician had noted HBV vaccination in the medical record; 731 of these individuals were MSM. Therefore, overall, approximately 30% of the HIV-positive individuals 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 44% exposed minus 22% with serological evidence of successful vaccination minus 4% former successful vaccination otherwise documented=30%).

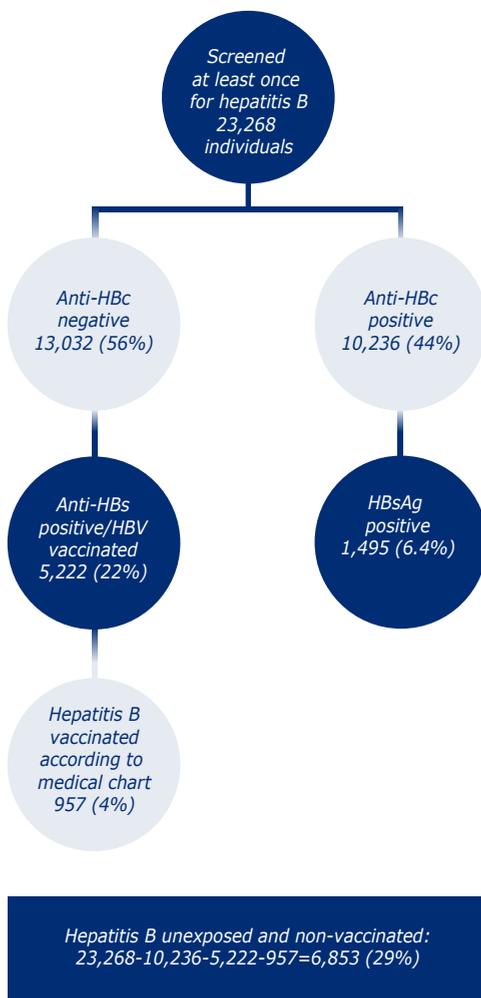
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<sup>c</sup> The total number of patients screened for HBV differs from the total number of patients screened for HCV, as not all patients screened for HBV are also screened for HCV.

Furthermore, 18% of MSM remained at risk (100% minus 46% exposed minus 31% serological evidence of successful vaccination minus 5% former successful vaccination otherwise documented=18%). MSM, in particular, should be offered HBV vaccination, although they may be protected from HBV infection by the use of tenofovir (TDF) or tenofovir alafenamide (TAF) as part of their cART regimen, as suggested by findings reported by an international study and by one of the Dutch HIV treatment centres<sup>134,135</sup>. Of the individuals who are still at risk for acquiring HBV, 61% are currently being treated with a cART regimen that includes TDF or TAF.

HBV co-infection (defined as two or more consecutive positive test results for HBsAg over a period of at least six consecutive months) was found in 1,495 of the 23,268 (6.4%) HIV-positive individuals ever screened for HBV, which, similar to HCV co-infection, is considerably higher than the rate of HBV infection in the general Dutch population. Individuals co-infected with HBV were predominantly male (1,288/1,495, 86%), in line with those co-infected with HCV (*Table 4.4*). However, compared to individuals 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.

Figure 4.7: Flowchart of HIV-positive individuals tested at least once for hepatitis B.



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

**Table 4.4:** Demographic characteristics of HIV-positive individuals with an active chronic hepatitis B virus (HBV) co-infection registered in the SHM database, 1998–2017

	Total, n (%)	Hepatitis B surface antigen (HBsAg) positive, n (%)
Total number of individuals screened for HBV	23,268	1,495 (6,4)
Male gender	18,939 (81)	1,288 (86)
Region		
Netherlands	13,273 (57)	742 (50)
Europe	1,527 (7)	89 (6)
Sub-Saharan Africa	3,322 (14)	336 (22)
Caribbean/South America	2,695 (12)	158 (11)
South-East Asia	801 (3)	66 (4)
Other	1,650 (7)	104 (7)
HIV transmission group		
Men who have sex with men	13,987 (60)	887 (59)
Heterosexual	7,062 (30)	430 (29)
Injecting drug use	723 (3)	69 (5)
Other	1,496 (6)	109 (7)
cART	21,972 (94)	1,414 (94)
Deaths	2,508 (10)	256 (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-positive individuals in care has improved over calendar time. In 1998, 28% of the individuals 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-positive individuals with an unknown HBV status, with only 0.36% of all HIV-positive individuals in care having an unknown HBV status in 2016 (Figure 4.2).

### Prevalence

The overall prevalence of chronic HBV co-infection among HIV-positive individuals in care decreased from 9.8% in 1998 to 5.8% in 2016. The highest prevalence was found in MSM: in 1998, 11% of MSM had chronic HBV co-infection, and this figure decreased to 5.9% in 2016 (Figure 4.8). This decreasing prevalence of chronic HBV co-infection could be the result of increasing HBV vaccination rates among individuals (Figure 4.9), together with the preventive effect of treatment with a cART regimen that includes tenofovir/TAF.

Figure 4.8: Prevalence of chronic active hepatitis B co-infection per calendar year.

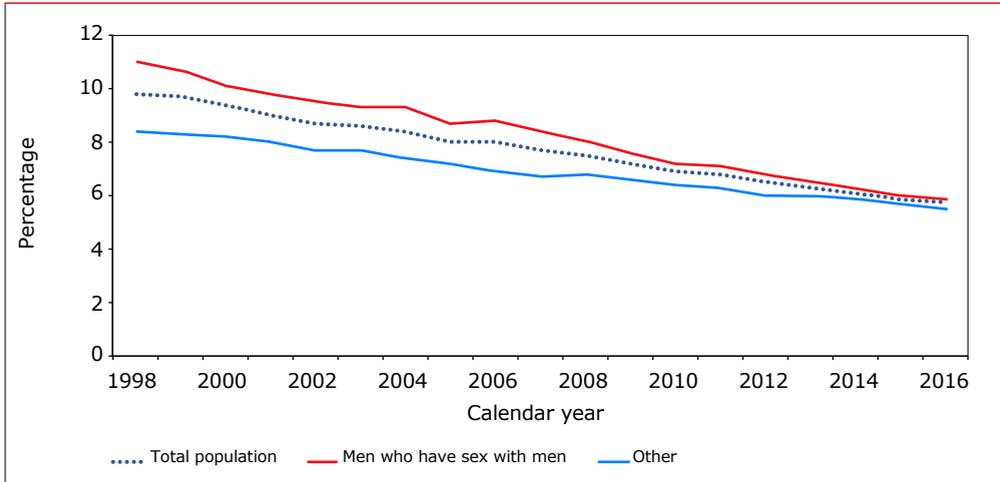
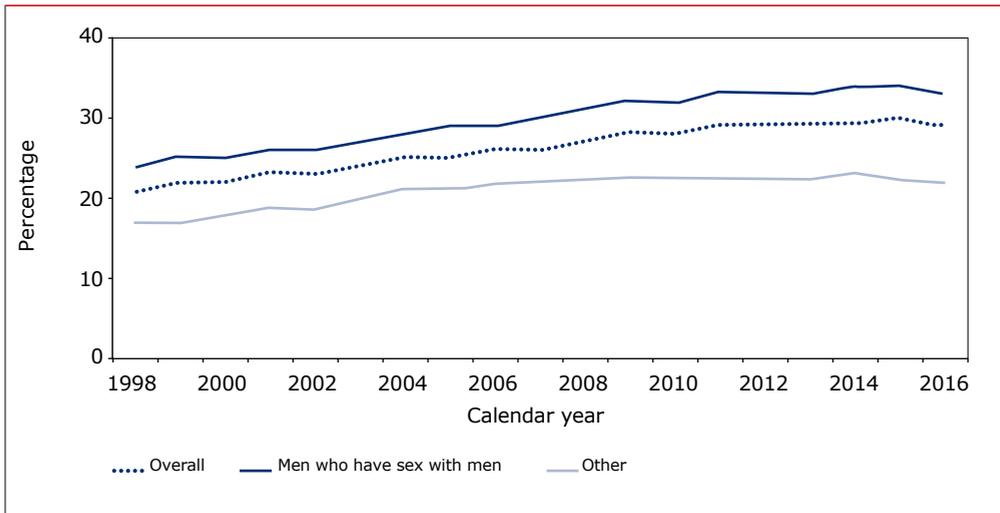


Figure 4.9: Prevalence of individuals vaccinated against hepatitis B per calendar year.



### Treatment for chronic HBV infection

Chronic HBV infection is defined by the presence of hepatitis B surface antigen (HBsAg+). The aim of treatment is to reduce virus replication, reflected in decreased HBV DNA levels, which may result in HBsAg negativity in a subgroup of individuals. 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. Moreover, persistent lowering of HBV DNA levels to less than 20 IU/ml has been shown to delay progression of liver fibrosis to cirrhosis<sup>136</sup>. 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 individuals who are also e-antigen positive (HBeAg+), a similar seroconversion from HBeAg positivity to HBeAg negativity can occur, with subsequent development of anti-hepatitis B e-antigen (anti-HBe) antibodies. This so-called e-seroconversion is an important secondary treatment parameter, since studies have shown that it results in a clinically important lowering of HBV DNA, thereby lowering the risk of progression of liver fibrosis. Several antiviral agents used for treatment of HIV, such as lamivudine, emtricitabine and particularly tenofovir/ TAF, are also active against HBV.

Of the 1,495 individuals with HIV in the SHM database who were co-infected with chronic HBV, 1,411 (94%) had ever received a cART regimen that included one or more agents with activity against both HIV and HBV. Reasons for the remaining 84 individuals not having received anti-HBV treatment included: death before being able to start treatment (n=21), recent entry into care (n=8), loss to follow up (n=42) and lack of sufficient information (n=13).

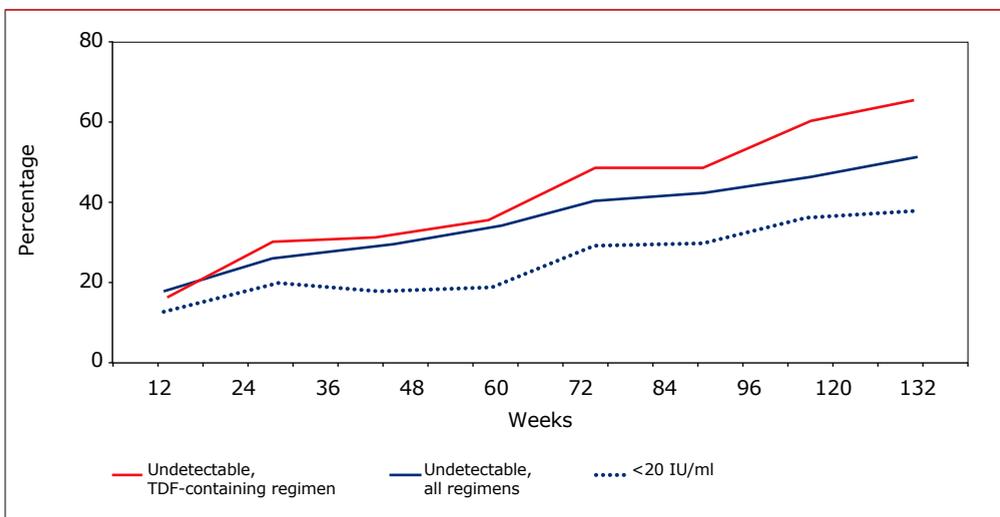
Most individuals (n=751/1,414, 53%) initially received lamivudine against HBV. Of the patients treated for HBV with lamivudine, 295 (39%) switched to a regimen containing tenofovir plus lamivudine after a median of 1.7 years (IQR 0.5-4.1), and 220 (29%) to a regimen containing tenofovir plus emtricitabine after a median of 1.3 years (IQR 0.4-3.7) of prior exposure to lamivudine monotherapy for HBV. For 653 of 1,414 patients (46%), their initial cART regimen included tenofovir and one additional agent with activity against HBV; for 114 of these 653 patients (17%), the additional agent was lamivudine, and for 539 patients (83%) the additional agent was emtricitabine; another 7 patients started with a tenofovir alafenamide-containing regimen.

In most HBV mono-infected individuals, a persistently HBeAg-negative chronic HBV infection with undetectable HBV DNA confers a favourable long-term outcome, with low risk of cirrhosis and HCC<sup>137</sup>. We therefore examined the HBV DNA levels in the population of individuals co-infected with HIV and HBV. *Figure 4.10* shows the proportion of individuals who had an undetectable HBV DNA level less than 20 IU/ml as a percentage of the total number of individuals with an HBV DNA measurement. For HBV DNA measurements with a 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 individuals 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 individuals with an undetectable HBV DNA level was 34% 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 individuals with an HBV DNA level less than 20 IU/ml was 20% one year after the start of treatment, 31% after two years, and 39% after three years. In terms of individuals who were using a tenofovir-containing cART regimen, 66% of individuals with HBV DNA follow-up data had an undetectable HBV DNA level after three years of receiving treatment (Figure 4.11).

Among the 1,414 individuals whose cART regimen ever included one or more agents with activity against HBV, 526 of the 1,040 individuals with an available test result (51%) had a documented positive test result for HBeAg. Of these 526 individuals, 367 (70%) were re-tested, with 188 (51%) converting from HBeAg positivity to HBeAg negativity and 106 (29%) developing HBe antibodies. In total, 275 (28%) out of the 999 individuals who were HBsAg positive at time of treatment initiation became HBsAg negative. In addition, 79 individuals became anti-HBs positive.

Figure 4.10: Percentage of individuals 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, regardless of HBeAg status.



Legend: TDF=tenofovir.

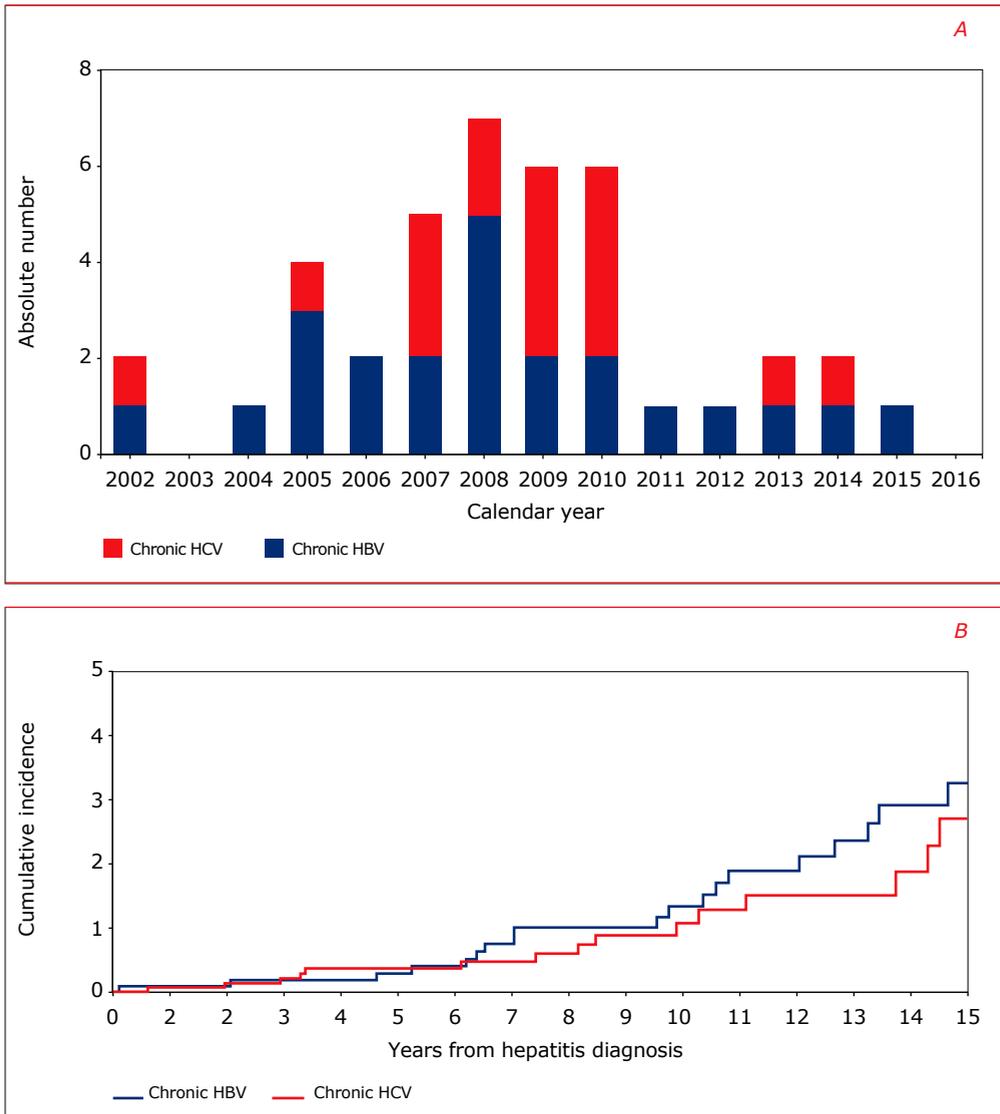
## Morbidity and mortality in HCV and/or HBV co-infected individuals

### Liver-related morbidity

Additional data on pathology reports from liver biopsy, transient elastography, or a combination of both, were available for 1,569 of the 1,883 individuals with chronic or acute HCV co-infection and for 1,116 of the 1,495 individuals with an HBV co-infection. Review of these additional data showed that severe chronic liver disease according to our definition (Box 4.1) was considered to be present (presumptive and definitive categories combined) in 667 of the 1,569 patients (43%) with HCV co-infection, and in 386 of the 1,116 (35%) patients with HBV co-infection. Definitive severe chronic liver disease was documented for 161 patients with an HCV co-infection and 67 with an HBV co-infection.

Figure 4.11A shows the annual number of new HCC diagnoses. This number of HCC diagnoses declined from 2010 onwards. HCC was diagnosed in 19 out of 1,420 individuals (1.3%) with a chronic HCV co-infection, of whom 14 were born in the Netherlands. HCC was found in 25 individuals (1.7%) with a chronic HBV co-infection, 14 of whom were born in the Netherlands, 7 in sub-Saharan Africa, and 1 each in South America, Asia, the United States, and Australia. Figure 4.11B 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 individuals with an HCV co-infection and those with an HBV co-infection. Ten years after a known diagnosis of viral hepatitis, HCC had developed in 1.0% (95% CI 0.5-2.1%) of individuals with HCV co-infection and in 1.3% (95% CI 0.7-2.4%) 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 4.11:** (A) Absolute number of reported hepatocellular carcinoma (HCC) cases over time and (B) cumulative incidence of HiHCC among individuals co-infected 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 2017.



## Mortality

### All-cause mortality

The overall rate of death from any cause was 16% for the 1,883 individuals with an HCV infection and 17% for the 1,495 individuals with an HBV infection (Table 4.5). The cumulative incidence of death from any cause was higher among individuals who were diagnosed with HCV or HBV before 2000 than among those who were diagnosed in later calendar years (Figure 4.12). 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 individuals with HIV and HCV co-infection diagnosed before 2000 compared to HIV mono-infected individuals. For individuals with an HCV co-infection diagnosed after 2000, the adjusted overall risk of death was non-significantly higher than in HIV mono-infected individuals.

**Table 4.5: Morbidity and mortality in HIV-positive individuals 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	1,883	1,495
Severe chronic liver disease <sup>#</sup>	667 (35)	386 (26)
HCC	19 (1.0)	25 (1.7)
Liver transplantation	2 (0.1)	1 (0.07)
Deaths from any cause <sup>*</sup>	297 (16)	256 (17)
Liver-related deaths	67 (3.6)	47 (3.1)

<sup>\*</sup>Including liver-related death

<sup>#</sup>Including presumptive and definitive liver disease

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

In addition, the overall risk of death was significantly higher for individuals with a chronic HBV co-infection diagnosed before 2000, after adjustment for differences in demographic and clinical characteristics, than for HIV mono-infected individuals. For individuals with an HBV co-infection diagnosed after 2000, the adjusted overall risk of death was non-significantly higher than in HIV mono-infected individuals (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-positive individuals with hepatitis co-infection compared with HIV mono-infected individuals. 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 2017.

	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 (1.51-2.32)		15.7 (8.24-30.1)	
HIV/chronic HCV, ≥2000	1.13 (0.90-1.42)		8.45 (4.88-14.93)	
HIV/chronic HBV, <2000	1.91 (1.60- 2.29)		26.4 (15.4-44.3)	
HIV/chronic HBV, ≥2000	1.22 (0.98-1.51)		4.29 (1.98-9.27)	

\*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.

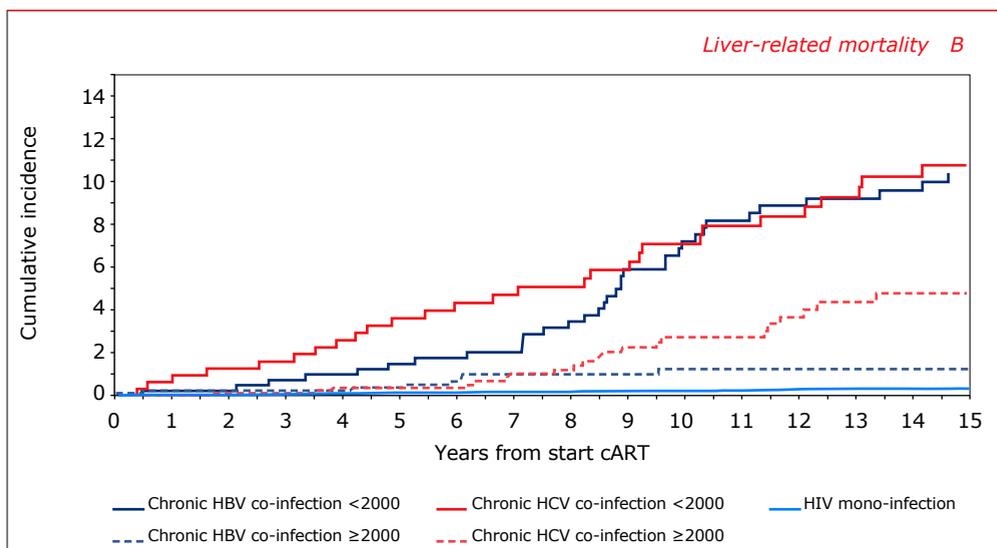
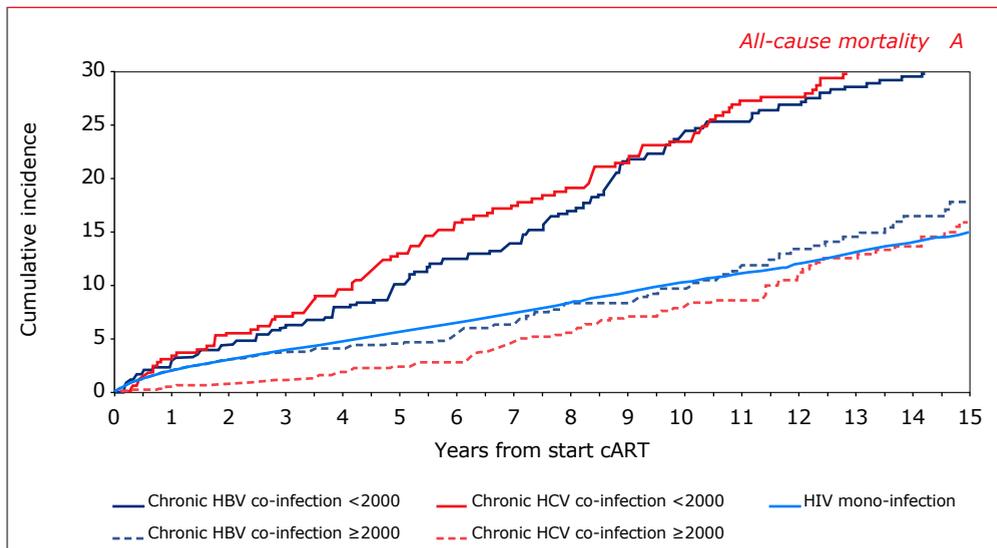
Legend: HBV=hepatitis B virus; HCV=hepatitis C virus; CI=confidence interval.

### Liver-related mortality

In total, 114 individuals co-infected with hepatitis died of a liver-related cause (Table 4.5). Ten years after cART initiation, 7% (95% CI 4-11) of chronically HCV co-infected individuals diagnosed with HCV before 2000 had died of a liver-related cause. This proportion was lower, (3%, 95% CI 2-5) among individuals with an HCV diagnosis after 2000. Among those with HBV co-infection, 7% of individuals diagnosed before 2000 died of a liver-related cause (95% CI 5-11), which dropped to 1% (95% CI 0.6-3) in those diagnosed after 2000 (Figure 4.12).

After adjustment for demographic and clinical characteristics, HBV co-infected individuals and HCV co-infected individuals diagnosed both before and after 2000 remained more likely to have a liver-related cause of death than HIV mono-infected individuals (Table 4.6). However, the adjusted risk of death from a liver-related cause strongly decreased in HBV co-infected individuals from a hazard ratio (HR) of 26.4 (95% CI 15.4-44.3) in individuals diagnosed with HBV before 2000 to an HR of 4.29 (95% CI 1.98-9.27) in individuals diagnosed from 2000 onwards. In HCV co-infected individuals, the adjusted risk of death from a liver-related cause decreased from an HR of 15.7 (95% CI 8.24-30.1) in individuals diagnosed with HCV before 2000 to an HR of 8.45 (95% CI 4.88-14.9) in individuals diagnosed with HCV from 2000 onwards.

Figure 4.12: (A) Cumulative incidence of 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 2017.



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

## Conclusion

Screening for HCV and HBV co-infection in the HIV-positive population in the Netherlands continues to improve over time. Although approximately 39% of the individuals in care in 1998 had not been screened for HBV or HCV co-infection, by 2016 screening had become universal. Six percent of HIV-positive individuals 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.

Our data clearly show that, with the advent of novel DAAs from 2014 onwards, PEG-IFN-containing regimens have largely been replaced in clinical practice by a variety of novel DAAs. The number of HIV-positive individuals treated for HCV has rapidly increased. More than 750 individuals have received or are currently receiving treatment with novel DAAs. Overall, 97% of all individuals 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 the former IFN alpha/PEG-IFN alpha-containing regimens. This high cure rate has resulted in a lower number of HCV co-infected individuals remaining in need of HCV treatment, despite an increase in the total number of individuals currently in care compared with the numbers reported last year<sup>7</sup>. Overall, a rapid reduction in the prevalence of an active HCV infection has been achieved, with prevalence in MSM declining to less than 1.5% in 2016. 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, which is possibly reflected in a lower number of acute HCV infections in the past year. However, in line with earlier reports<sup>130,133</sup>, HCV re-infection after successful treatment has been observed. Although the rate of re-infection has declined in the most recent years, there is still ongoing transmission of HCV.

Six percent of the HIV-positive individuals ever in care had chronic HBV co-infection. The prevalence of HBV has decreased over time as a result of increased HBV vaccination rates, together with the HBV-prophylactic effect of tenofovir/TAF in cART-treated individuals. Nonetheless, an estimated 30% of all HIV-positive individuals and 18% of MSM either have not been exposed to HBV or have not been successfully vaccinated and may remain at risk of acquiring HBV. However, 61% of those individuals still at risk of acquiring HBV infection use a cART regimen that includes tenofovir/TAF and may therefore be at a substantially lower risk due to sustained chemoprophylaxis. The remaining 39% of the individuals remain unprotected against HBV, which represents an estimated 13% of the total population of HIV-positive individuals.

In general, HIV-positive individuals co-infected with HCV or HBV are at increased risk of progression to severe liver disease<sup>121,122</sup>. In our study population, 35% of the chronically HCV co-infected individuals had evidence of severe chronic liver disease. In both HCV and HBV co-infected individuals, we observed an increase in the proportion of individuals with hepatocellular carcinoma in relation to the duration of hepatitis infection. However, the absolute number of HCC diagnoses has been decreasing since 2010, which can likely be attributed to the use of effective antiviral treatment for HBV and HCV co-infections. Overall, individuals with chronic HCV or HBV co-infection remain at increased risk of having a liver-related cause of death. This risk has, however, become significantly lower for individuals with chronic HBV diagnosed after 2000, likely as a result of increasingly effective treatment through the use of tenofovir-containing cART, and for those with chronic HCV diagnosed after 2000.

## Recommendations

Continued efforts must be made to ensure that all individuals with HIV are adequately assessed for the presence of HBV and HCV co-infection or HCV re-infection. In particular, there should be ongoing efforts to increase HBV vaccination rates among HIV-positive individuals at increased risk of becoming infected with HBV, particularly those who are not receiving an antiretroviral regimen containing TDF or TAF. In the long term, provision of highly effective DAA regimens for all known HCV co-infected HIV-positive individuals 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 individuals 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 re-infection 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.

**Box 4.1: 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<sup>199</sup>.

**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.

**SVR<sub>24</sub>**

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.

**SVR<sub>12</sub>**

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 transient elastography report documenting severe liver fibrosis or cirrhosis (metavir score F3-F4 or transient elastography stiffness  $\geq 8$ kPa).

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## 5. Distinct populations: Children living with HIV-1 in the Netherlands

Colette Smit, Tom Wolfs, 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 26 adult HIV treatment centres. As with adult individuals, diagnosis, treatment and follow up of these children is monitored by Stichting HIV Monitoring (SHM). Overall, demographic and clinical data have been collected by SHM for 590 children aged up to 18 years at the time of their HIV-1 diagnosis, representing an increase of 26 children compared with last year's report.

Combination antiretroviral therapy (cART) has dramatically decreased morbidity and mortality in HIV-1-positive children worldwide<sup>138,139,140</sup>. In particular, early initiation of cART in HIV-1-positive children has been proven to benefit the survival of these children<sup>141,142,143,144,145</sup>. Until 2010, the World Health Organization (WHO) recommended starting cART in all HIV-positive children less than 2 years of age, regardless of their CD4 T-cell count or clinical status<sup>146</sup>. However, as of June 2013, this recommendation was extended to include all HIV-positive children less than 5 years old<sup>147</sup>. More recently, evidence from studies showing a clinical benefit of early cART initiation led to a 2015 revision of the WHO guidelines on when to start cART, with the guidelines now recommending initiation of cART in everyone living with HIV at any CD4 cell count, including all children<sup>148</sup>.

Here we report the demographics, clinical characteristics, and long-term virological and immunological response to treatment in the 590 HIV-1-positive 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 acquired HIV-1 through sexual transmission are predominantly under clinical observation in an adult HIV treatment centre (*Table 5.1*). All HIV-1 positive individuals 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 the 590 HIV-1-positive children ever registered with SHM.

Characteristics	Vertically-acquired HIV-1 infection*	Non-vertically-acquired HIV-1 infection*	Route of transmission unknown*
<b>Total</b>	330 (55)	239 (41)	21 (4)
<b>HIV-1 treatment centre</b>			
Child care	317 (96)	29 (12)	9 (43)
Adult care	13 (4)	210 (88)	12 (57)
<b>Gender</b>			
Male	160 (48)	106 (44)	14 (67)
Female	170 (52)	133 (56)	7 (33)
<b>Country of origin child</b>			
The Netherlands	107 (32)	60 (25)	1(5)
Sub-Saharan Africa	177 (54)	121 (51)	12 (57)
Other	46 (14)	58 (24)	8 (38)
<b>Country of origin mother</b>			
The Netherlands	23 (7)	6 (3)	1(5)
Sub-Saharan Africa	180 (55)	34 (14)	5 (24)
Other/unknown	127 (38)	199 (83)	15 (71)
<b>Age at HIV-1 diagnosis</b>	1.2 (0.3-4.0)	16.8 (16-18)	15.5 (12-17)
<b>CDC** event at HIV-1 diagnosis</b>			
CDC-b	30 (9)	10 (4)	2 (10)
CDC-c	56 (17)	13 (5)	2 (10)
<b>Current age in years</b>	15 (9-20)	31 (25-34)	26 (23-31)
<b>cART-treated</b>	320 (97)	215 (90)	21 (100)
<b>Therapy-naive at cART initiation</b>	278 (84)	174 (73)	20 (95)
<b>CD4 at cART initiation</b>	527 (270-1164)	290 (168-406)	293 (40-350)
<b>VL (log copies/ml) at cART initiation</b>	5.2 (4.5-5.8)	4.4 (3.7-5.1)	4.9 (4.7-5.3)

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

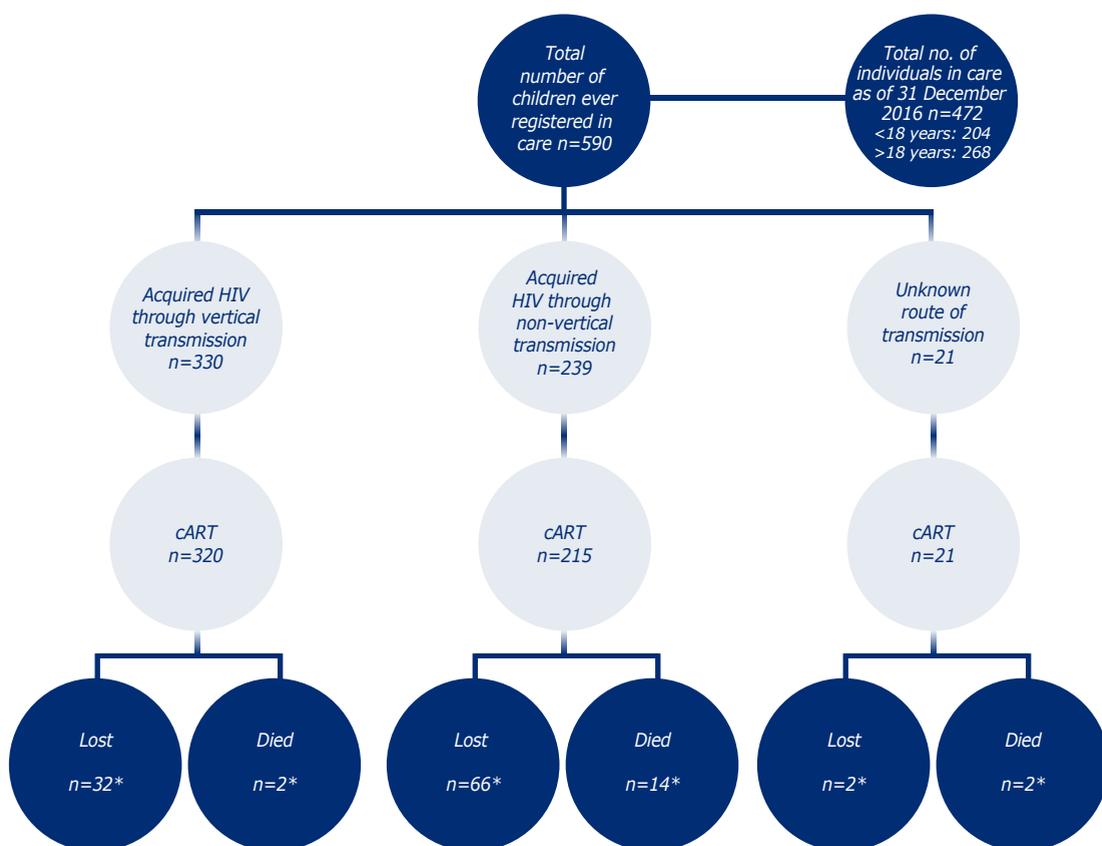
\*\*Categories as defined by the Centers for Disease Control and Prevention (CDC)

Legend: cART=combination antiretroviral therapy; VL=viral load.

As of 31 December 2016, 590 HIV-1-positive children had ever been registered by SHM since 1998. Of those, 330 had acquired HIV-1 through vertical transmission, and 239 through non-vertical transmission (*Figure 5.1*). For a small group of 21 children, the route of HIV-1 transmission was unknown. *Figure 5.2* shows the number of newly-registered individuals per calendar year and according to the mode of HIV transmission, and, for those who acquired HIV through vertical transmission, whether or not they had been adopted. The majority of children

had acquired HIV through vertical transmission or through sexual contact. Among those 590 children ever registered, 471 were known to be in care as of 31 December 2016, 203 of whom were less than 18 years of age at that date. Ten out of the 26 newly-registered children had acquired HIV-1 through vertical transmission, 7 of these children had been adopted by Dutch parents. A further 12 children had acquired HIV through sexual transmission, and for the remaining 4 children the route of HIV transmission was unknown.

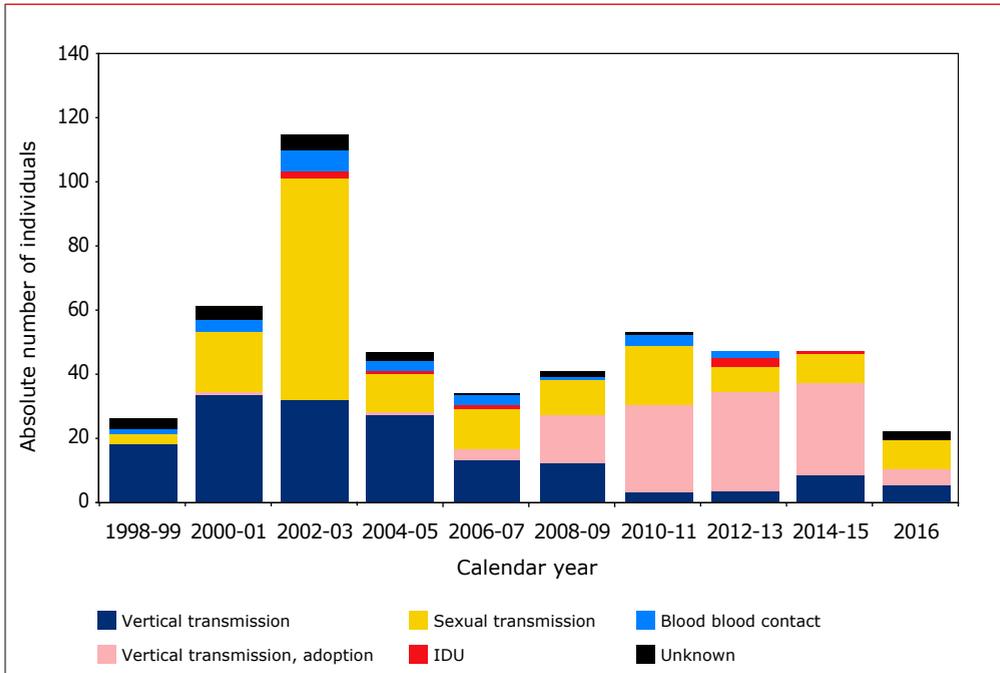
Figure 5.1: Overview of HIV-positive children registered by Stichting HIV Monitoring



\*Of the total number of children who acquired HIV through vertical, non-vertical or an unknown route of transmission.

Legend: cART=combination antiretroviral therapy.

Figure 5.2: Number of HIV-positive children who entered paediatric care, stratified by HIV transmission mode and, for those who had acquired HIV through vertical transmission, by whether they had been adopted or not, 1998–2016.



Note: low numbers in 2016 may be due to a delay in the treatment centre registering the child with SHM.  
Legend: IDU=transmission through injecting drug use.

### Children with vertically-acquired HIV-1

A total of 330 children had acquired HIV-1 through vertical transmission (Table 5.1). From 2008 onwards, the majority of newly-registered children who had acquired HIV-1 through vertical transmission had been adopted by Dutch parents. In the children with vertically-acquired HIV-1, the median age at the first reported HIV-1 positive test result, including self-reported tests in the country of origin, was 1.2 years (interquartile range [IQR] 0.3-4.0 years). Although 31% of the children were born in the Netherlands, only 3% of these children (11 out of 330) had parents who both originated from the Netherlands, while 56% (185 out of 330) had at least one parent who originated from sub-Saharan Africa. Of the 330 children with vertically-acquired HIV-1, 96% received care in a paediatric HIV treatment centre, and 97% of these 320 children had started cART.

### Children with non-vertically-acquired HIV-1

Of the 590 HIV-1 positive children ever registered, 239 had acquired HIV-1 through non-vertical transmission. These 239 children were much older at the time of HIV-1 diagnosis than those who had acquired HIV-1 through vertical transmission, with a median age at diagnosis of 16.8 years (IQR 15.5-17.5). The majority of the 239 children who had acquired HIV-1 through non-vertical transmission received care in an adult HIV treatment centre (210/239, 88%). The main route of HIV-1-transmission was sexual contact. Of the children who acquired HIV-1 through non-vertical transmission, 137 out of 256 (57%) had acquired HIV-1 through heterosexual contact and 45 (19%) had acquired HIV-1 through homosexual contact. In total, 46 (19%) children had acquired HIV-1 through contaminated blood or blood products, although this mode of transmission was no longer reported from 2013 onwards (*Figure 5.2*). Moreover, among newly-registered children born in the Netherlands, HIV transmission by contaminated blood or blood products has not been reported since 2004. In more recent years, children who acquired HIV-1 through non-vertical transmission mostly acquired HIV through sexual contact (*Figure 5.2*). The remaining 11 children acquired HIV through injecting drug use or accidentally through contaminated needles. Fifty-one percent of the children who acquired HIV-1 through non-vertical transmission were born in sub-Saharan Africa. Finally, of the 239 children who acquired HIV-1 through non-vertical transmission, 215 (90%) had started cART (*Table 5.1*).

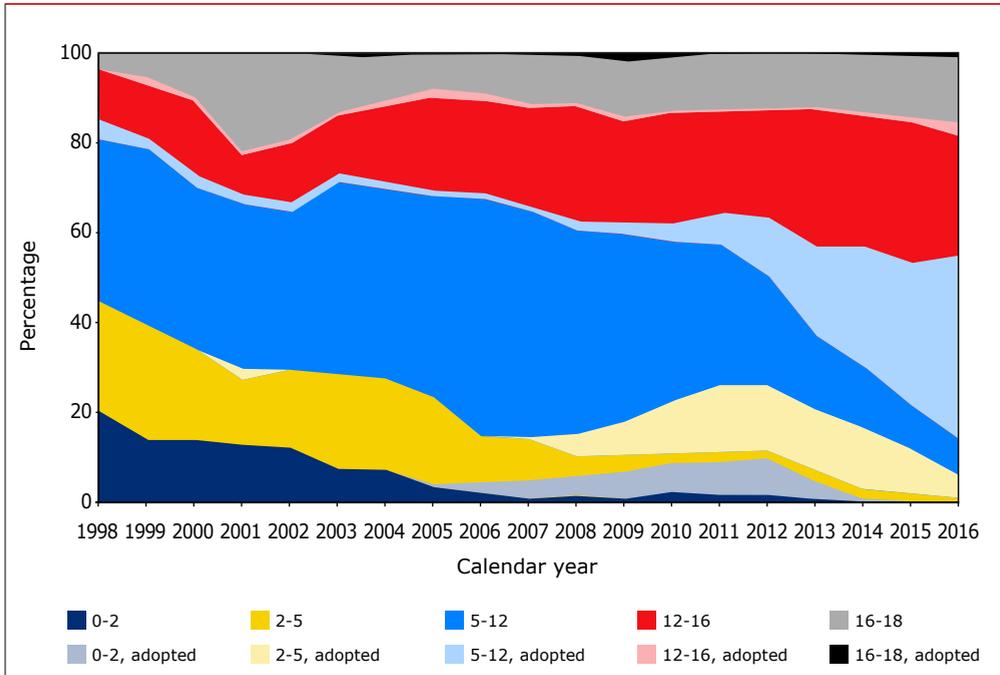
### Unknown route of HIV-1 transmission

For 21 of the 590 HIV-1-positive children, the route of transmission was unknown. Their median age at diagnosis was 15.5 years (IQR 12-17); 9 of these children were in care at a paediatric HIV treatment centre and all 21 had started cART (*Table 5.1*).

### Age distribution

The age distribution of the HIV-1-positive children ever in care over calendar time demonstrates a gradual decrease in the proportion of children below 12 years of age between 1998 and 2008 (*Figure 5.3*). However, from 2008 onwards, the proportion of children aged between 0 and 5 years increased slightly. This small increase is due to an increase in adoption of HIV-positive children in this age group, which is shown by the shaded areas in *Figure 5.3*.

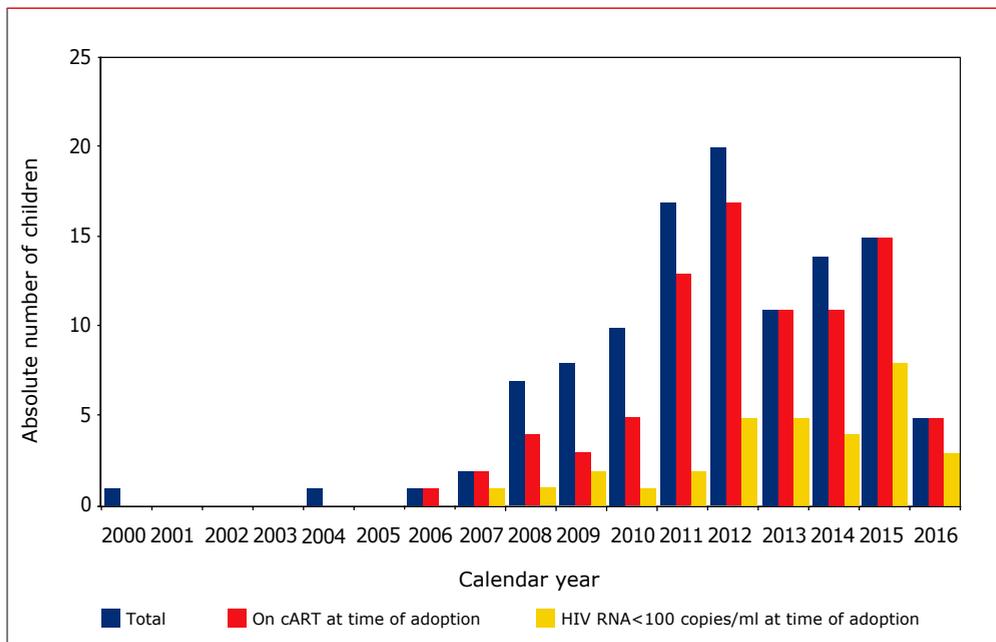
Figure 5.3: Time-dependent age distribution of HIV-1 positive children in care over time. The shaded areas represent the proportion of adopted children.



### Adopted children

In total, 115 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 had been diagnosed with HIV-1 before the age of 2.5 years (82%). The number of children adopted varied between 1 and 20 per calendar year (Figure 5.4). The low number in 2016 may be due to a delay in the treatment centre registering individuals with SHM.

Figure 5.4: Number of HIV-1 positive children who came into paediatric care through adoption, by calendar year.



Legend: cART=combination antiretroviral therapy.

### Children currently in clinical care

Of the 590 HIV-1-positive children ever registered by SHM, 472 (80%) are currently in clinical care (Figure 5.1). Of these 472 children, 204 are currently aged <18 years. Of the 118 individuals who are no longer in clinical care, 18 (15%) have died (3 of whom were younger than 18 years at the time of death), 46 (39%) individuals have moved abroad and 54 (45%) have been lost to care. The median age at date of last contact for the individuals who became lost to care was 21 years (IQR 19-26). Of the 54 individuals lost to care, 50 (93%) were born outside the Netherlands and 43 of the 54 children (85%) had acquired HIV through non-vertical transmission. In total, 32 (59%) children were using a cART regimen at their last clinical visit and the median last measured CD4 cell count was 490 (IQR 320-700). Furthermore, 22 of the 54 children (41%) had a last available HIV RNA level below 100 copies/ml.

## Continuum of care

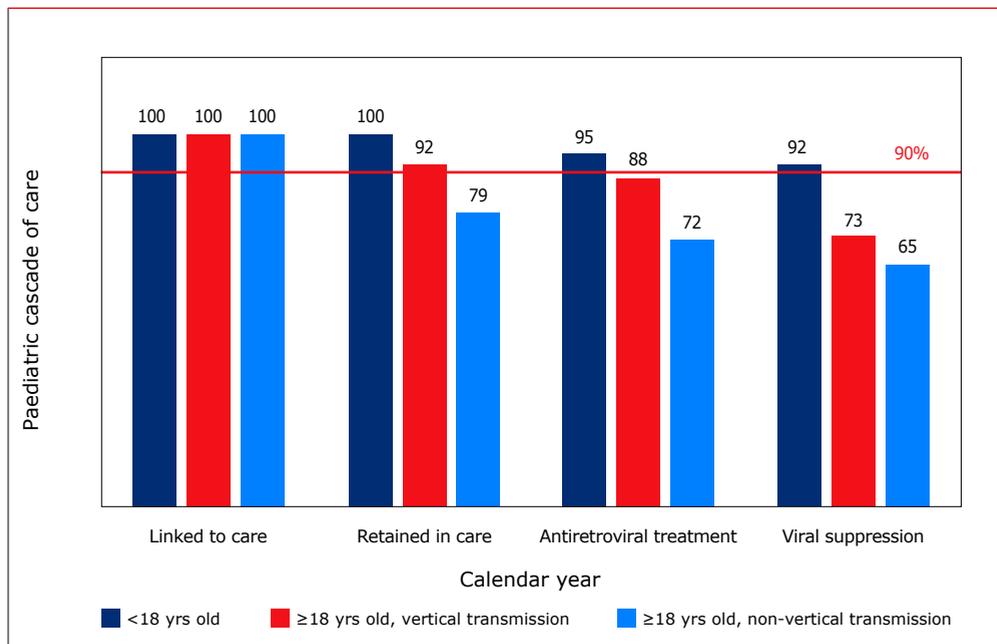
On the basis of the total number of HIV-1-positive children ever registered by SHM, still alive at 31 December 2016 and not reported as having moved abroad, a 'continuum of care' was constructed. This continuum of care depicts engagement in HIV-1 care across a number of key indicators, the last one being the number of children with a most recent HIV RNA measurement below 100 copies/ml (*Figure 5.5*). Individuals were stratified by age on 31 December 2016 and further categorised as current age <18 years; current age  $\geq$ 18 years and vertically-acquired HIV; and current age  $\geq$ 18 years and non-vertically-acquired HIV.

In total, 204 children aged below 18 years on 31 December 2016 were linked to care, registered by SHM, still alive, and not reported as having moved abroad. Of the children linked to care, 100% were retained in care (204/204) and 95% (192/204) were using antiretroviral therapy during their last clinical visit. Overall, 92% of those linked to care and aged less than 18 years had a most recent HIV RNA measurement below 100 copies/ml (188/204).

In addition, 112 individuals who had acquired HIV through vertical transmission and who were over 18 years of age on 31 December 2016 were linked to care. Of these 112 individuals, 92% (103) were still in care as of 31 December 2016 (9 had been lost to follow up), 88% (99/112) were using antiretroviral therapy during their most recent clinical visit, and 73% (82/112) had a most recent HIV RNA measurement below 100 copies/ml.

Another 209 individuals were aged above 18 years on 31 December 2016 and had acquired HIV through non-vertical transmission. Of these 209 individuals, 165 (79%) were still in care as of 31 December 2016 (44 individuals had been lost to follow up), 72% (150/209) were using antiretroviral therapy during their last registered clinical visit and 65% (135/209) had a most recent HIV RNA measurement below 100 copies/ml.

Figure 5.5: Cascade of care by age and route of HIV acquisition, as of 31 December 2016. The numbers on top of the bars indicate the proportion of individuals.



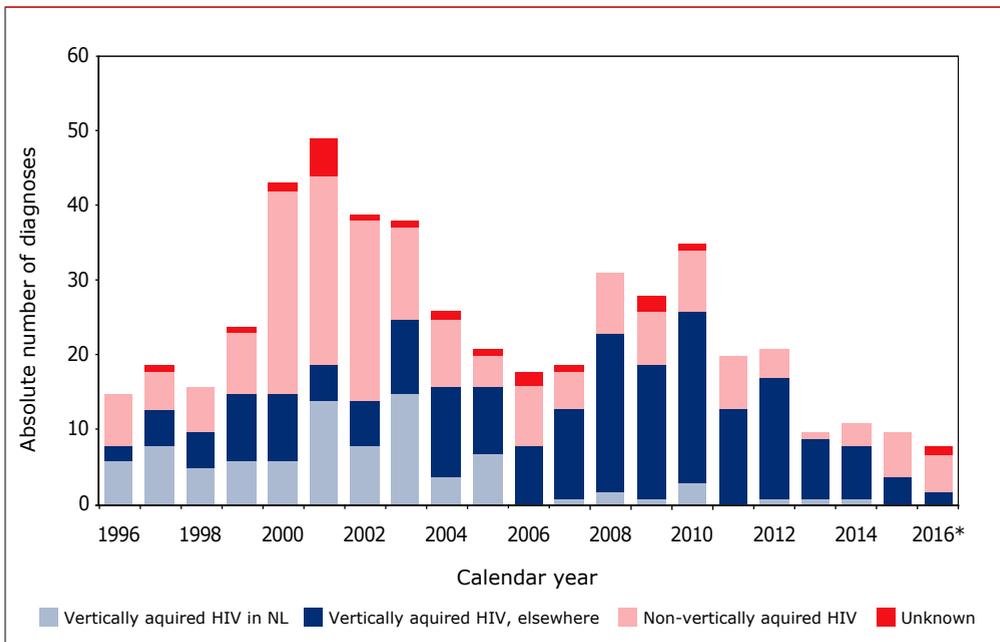
## Registered HIV-1 diagnoses and vertical transmission of HIV-1 in the Netherlands

Figure 5.6 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 children born 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 and no cases in 2015 and 2016. The decline in vertical transmission in the Netherlands is most likely due to HIV-1 screening among pregnant women, which was introduced nationally in 2004<sup>149,150</sup>. 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 1 January 2004. Another six of the 11 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 acquired HIV-1 during their 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.

However, the majority of children with a newly-registered diagnosis of HIV-1 infection through vertical transmission in recent years acquired HIV outside the Netherlands, and this number fluctuates annually (e.g., 21 cases in 2008 and 7 cases in 2014). The number of children who acquired HIV-1 infection by another mode of transmission ranged between 1 and 27 per calendar year.

*Figure 5.6: Number of registered HIV-1 diagnoses among children, according to year of HIV diagnosis, route of transmission, and region of origin.*



*\*Low numbers in 2016 may be due to a delay in registration.*

## Mortality

During follow up, 3 out of 590 children (0.5%) died at less than 18 years of age. Three boys who were born outside the Netherlands died in 1998, 2001 and 2009 at the ages of 12, 17 and 11 years, respectively. The boy who died in 1998 had acquired HIV-1 through vertical transmission. He was diagnosed when he was 9 years old

and experienced severe issues with compliance during 14 months of cART, which had just become available for children in 1997. He died at 12 years of age, following the diagnosis of an AIDS-related event. The 17-year-old boy was diagnosed when he was 16, and his route of HIV-1 transmission was unknown. He had been on cART for two months when he died from toxoplasmosis in 2001, 10 months after HIV-1 diagnosis. Finally, 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 in 2009 of multiple organ failure 1.5 years after the diagnosis and two months after entering care in the Netherlands.

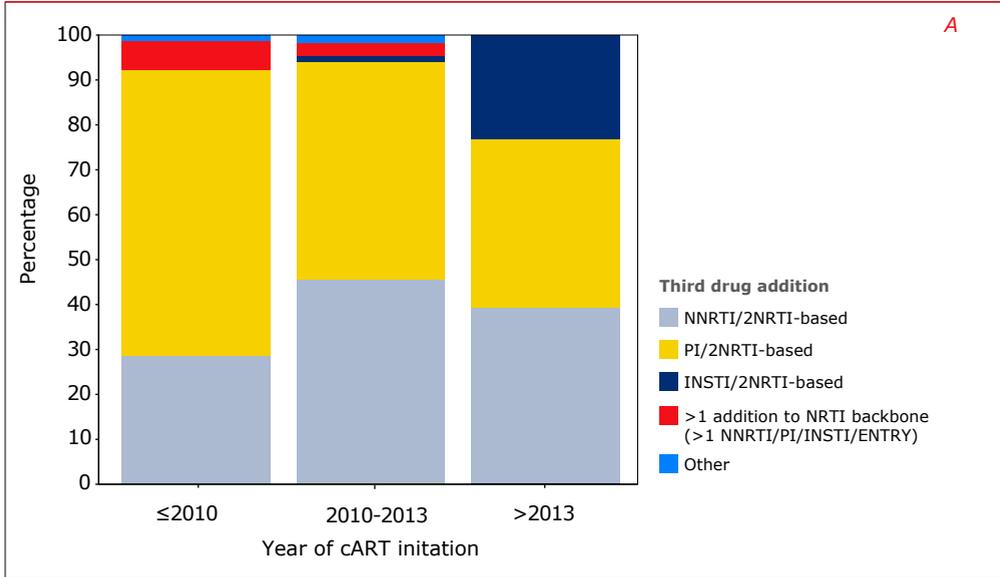
## Treatment

The majority of HIV-1-positive children (556/590) ever registered in the Netherlands have received cART (defined as a combination of at least three antiretroviral agents). Of these 556 children, 472 (85%) were treatment-naïve at the start of cART and 84 (15%) had previously been exposed to monotherapy or dual therapy (i.e., pre-treated). However, the number of pre-treated children starting cART decreased over time to 0 in 2016. Of these pre-treated children, 47% were born in the Netherlands and 25% originated from sub-Saharan Africa. The pre-treated and treatment-naïve children were grouped according to calendar year of starting cART: 396 started a cART regimen before 2010, 96 started between 2010 and 2013, and 64 started cART from 2013 onwards. Among those not treated with cART, 7 children had recently entered care, one child died shortly after entering care, and another 5 children had been in care for less than one year.

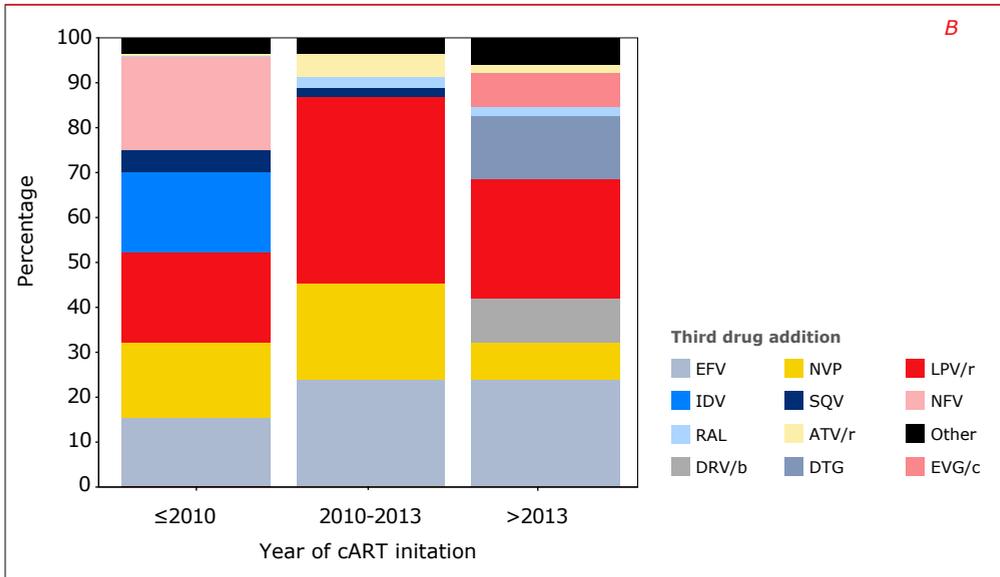
### Initial combination antiretroviral therapy regimen use

Most children (60%) were treated with a first-line cART regimen that included a protease inhibitor (PI) and two or more nucleoside reverse transcriptase inhibitors (NRTIs); 38% of the children received a non-nucleoside reverse transcriptase inhibitor (NNRTI)-based first-line regimen with two or more NRTIs. *Figures 5.7A and B* show the trends over time for the third-drug additions to the NRTI backbone as part of the initial cART regimens. The protease inhibitors nelfinavir and (boosted) indinavir were used when cART was initiated before 2000<sup>151</sup> and have since been replaced by improved regimens that include ritonavir-boosted lopinavir or efavirenz as the most-frequently used NNRTI, in line with current guidelines<sup>152,153,154,155</sup>. With the introduction of dolutegravir and elvitegravir in 2013 and 2014, these integrase inhibitors have also become part of the initial cART regimens.

Figure 5.7: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial cART regimen, stratified by calendar year period, according to (A) antiretroviral class and (B) specific drug.



Legend: ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor.

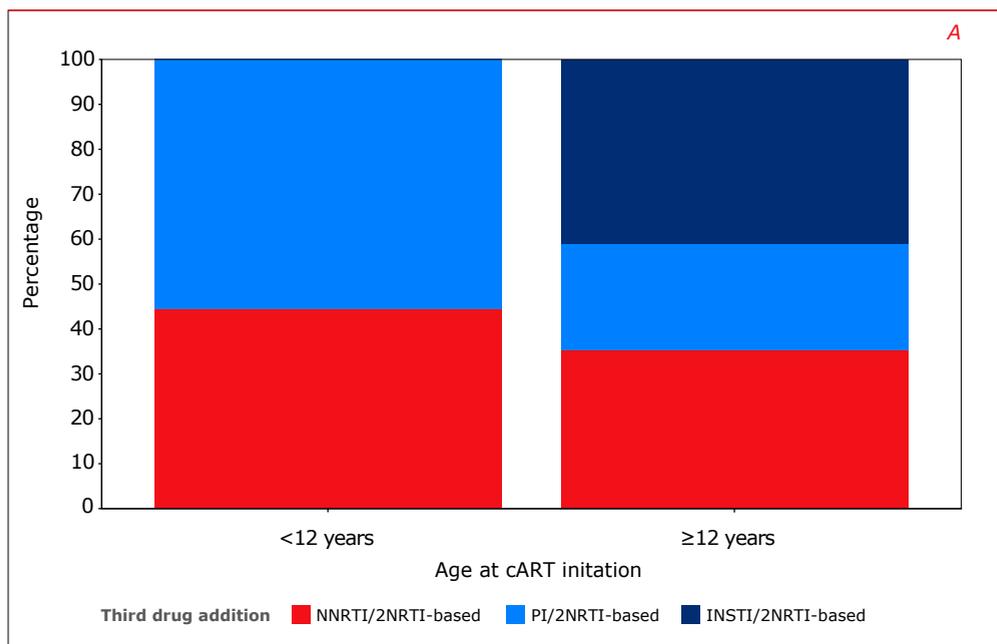


Legend: cART=combination antiretroviral therapy; EFV=efavirenz; NVP=nevirapine; LPV/r=ritonavir-boosted lopinavir; IDV=indinavir; SQV=saquinavir; NRV=nelfinavir; RAL=raltegravir; ATV/r=ritonavir-boosted atazanavir; DTG=dolutegravir; EVG/c=cobicistat-boosted elvitegravir; DRVb=cobicistat/ritonavir-boosted darunavir.

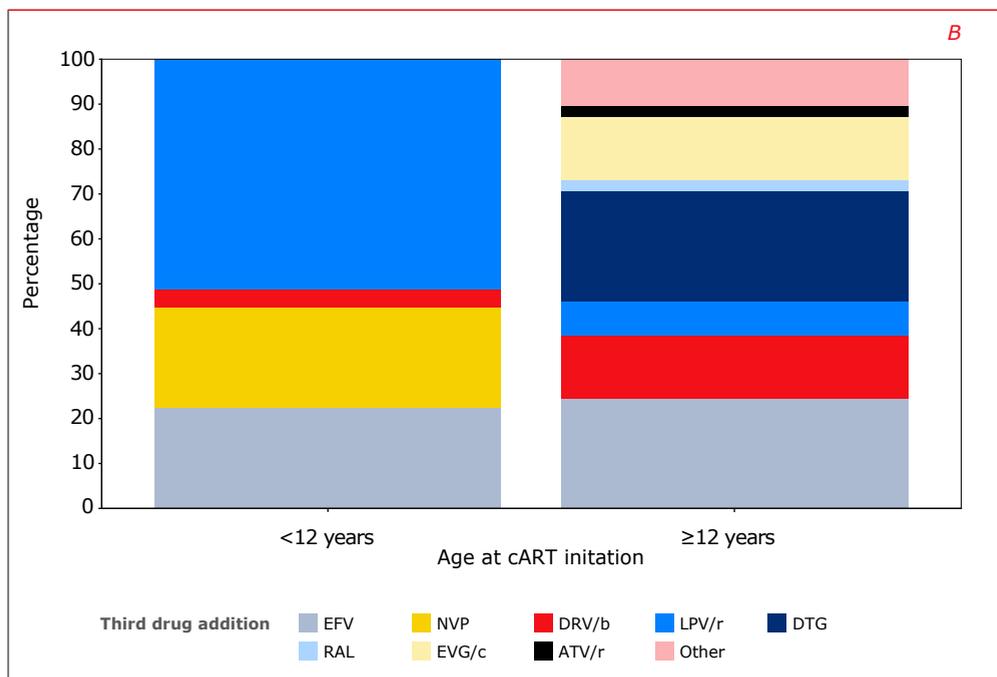
Figures 5.8A and B further specify these third-drug additions to the NRTI backbone according to the age at the start of cART in 2013-2016. Between 2013 and 2016, more than 50% of children aged below 12 years at time of cART initiation used lopinavir and none of the children used an integrase inhibitor. On the other hand, among older children ( $\geq 12$  years), there was more variation in the third-drug additions, including the use of integrase inhibitors (dolutegravir 24% and elvitegravir 14%).

The median time on first-line regimens was 15 months (IQR 3.3-36.2). Discounting weight-related dose changes, 414 children (74%) discontinued their first-line treatment regimen. The most important reasons for changing first-line cART regimens included toxicity (13%), low drug plasma concentrations (9%), simplification (15%), 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.

Figure 5.8: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the initial cART regimen in 2013-2016, stratified by age at cART initiation, according to (A) antiretroviral class and (B) specific drug.



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

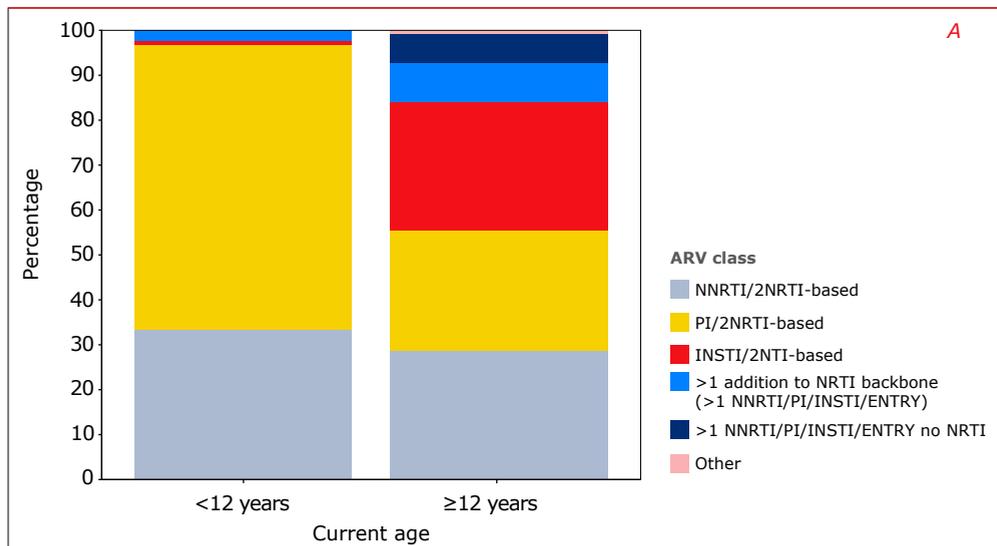


*Legend: cART=combination antiretroviral therapy; EFV= efavirenz; NVP=nevirapine; DRV/b=cobicistat/ritonavir-boosted darunavir; LPV/r=ritonavir-boosted lopinavir; DTG=dolutegravir; RAL=raltegravir; EVG/c=cobicistat-boosted elvitegravir; ATV/r= ritonavir-boosted atazanavir.*

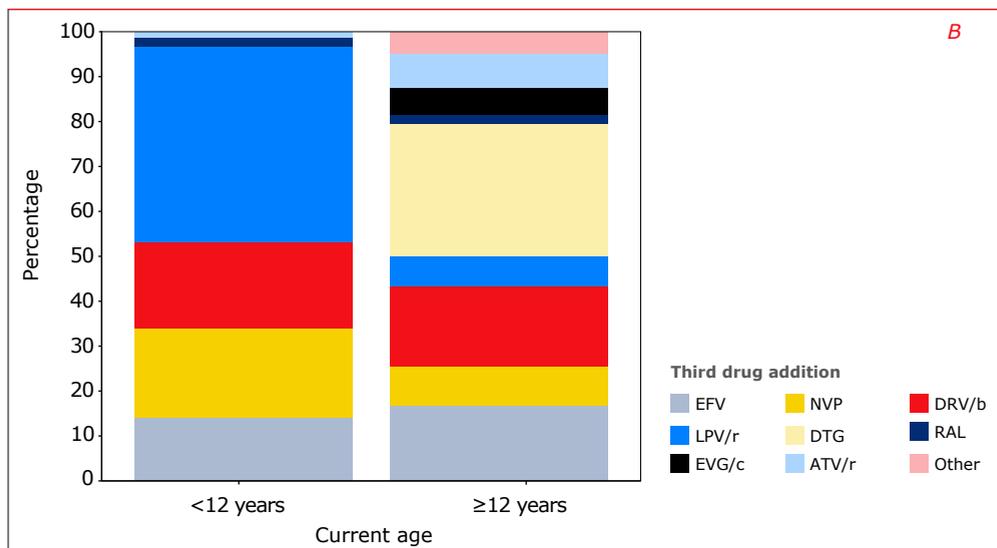
### Combination antiretroviral therapy regimen use as of 31 December 2016

The third-drug additions to the NRTI backbone in the currently used regimens are shown in *Figures 5.9A and B*, stratified by current age (<12 years and  $\geq 12$  years). In younger children (<12 years), a PI-containing regimen is currently used most often (63%), with lopinavir being the most frequently used (44%), followed by nevirapine (20%) and, in contrast to the initial regimens, cobicistat/ritonavir-boosted darunavir (18%). In older children ( $\geq 12$  years), 29% are using an NNRTI-based regimen, 27% are using a PI-based regimen and 28% are using an INSTI-based regimen. In terms of specific drugs, dolutegravir is used by 30% of the individuals aged  $\geq 12$  years, followed by efavirenz and darunavir, which are used by 17% and 18%, respectively, of the older children.

Figure 5.9: Third-drug additions to the nucleoside reverse transcriptase backbone used as part of the current regimen, stratified by current age, according to (A) antiretroviral class and (B) specific drug.



Legend: ENTRY=entry inhibitor; INSTI=integrase inhibitor; NRTI=nucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; PI=protease inhibitor.



Legend: cART=combination antiretroviral therapy; EFV=efavirenz; NVP=nevirapine; DRVb=cobicistat/ritonavir-boosted darunavir; LPV/r=ritonavir-boosted lopinavir; DTG=dolutegravir; RAL=raltegravir; EVG/c=cobicistat-boosted elvitegravir; ATV/r=ritonavir-boosted atazanavir.

## Immunological response

Median CD4 counts at time of cART initiation were higher in children who initiated cART from 2010 onwards than in 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 556 children who initiated cART, stratified by calendar year and age categories according to World Health Organization (WHO) treatment guidelines for different calendar years (to account for the changing guidelines for treatment initiation over time).*

cART initiation	<2010 (median, IQR)	≥2010 and <2013 (median, IQR)	≥2013 (median, IQR)
0-1 year	1,205 (546-1,770)		
1-3 years	1,010 (480-1,520)		
3-5 years	685 (420-970)		
0-2 years		1,903 (631-2,216)	
2-5 years		641 (406-860)	
<5 years			1,240 (819-2,531)
≥5 years	282 (150-420)	340 (275-460)	420 (241-594)

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

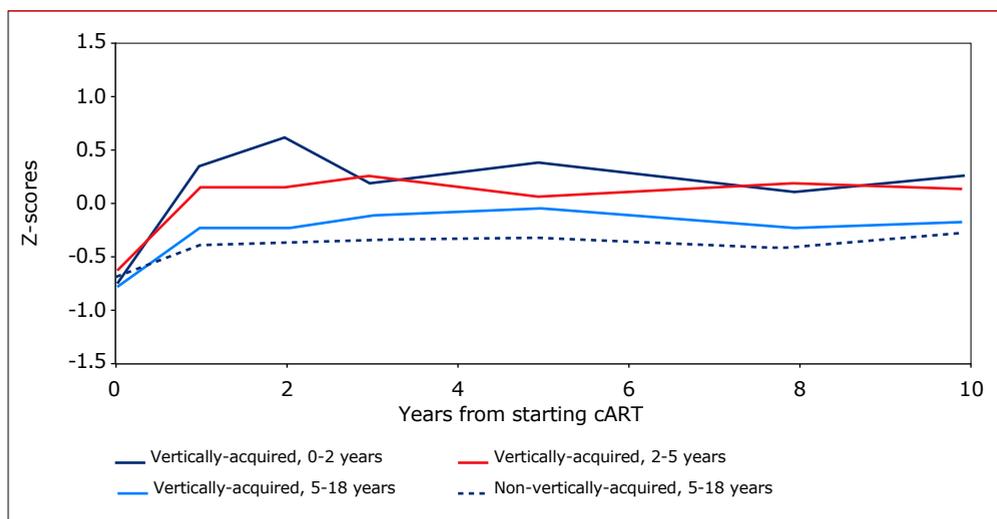
The clinical benefit of cART is strongly related to the degree to which the CD4 cell count recovers<sup>62</sup>. To investigate long-term CD4 cell count changes, we stratified the children who had acquired HIV through vertical transmission according to their age at the time of cART initiation. These categories were as follows: (1) vertically-acquired HIV, 0-1 year; (2) vertically-acquired HIV, 2-5 years; (3) vertically-acquired HIV, 5-18 years; and (4) non-vertically-acquired HIV or unknown mode of HIV-1 transmission, 5-18 years<sup>156</sup>. The number of children with an unknown route of HIV-1 transmission is too small to include as a separate category in the analysis. Because these children had the same age distribution as those who had acquired HIV-1 through non-vertical transmission, they were included in the category of non-vertical transmission. *Appendix Table 5.1* shows the differences in CD4 counts between younger and older HIV-1-positive 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 by expressing the 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<sup>157</sup> 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<sup>154</sup> is 1 standard deviation below the age-specific median of the HIV-1-negative population.

The youngest children (less than 2 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 5.10*). However, this increase was lower in children aged 5-18 years at cART initiation from both the vertically and non-vertically-acquired HIV groups than in children aged less than 2 years of age in the vertically-acquired HIV group.

*Figure 5.10: Changes in z-scores for CD4 T-cell counts among HIV-1 positive children stratified by age at initiation of combination antiretroviral therapy (cART).*



*Legend: cART=combination antiretroviral therapy.*

## Virological response to cART

### Initial virological response to cART

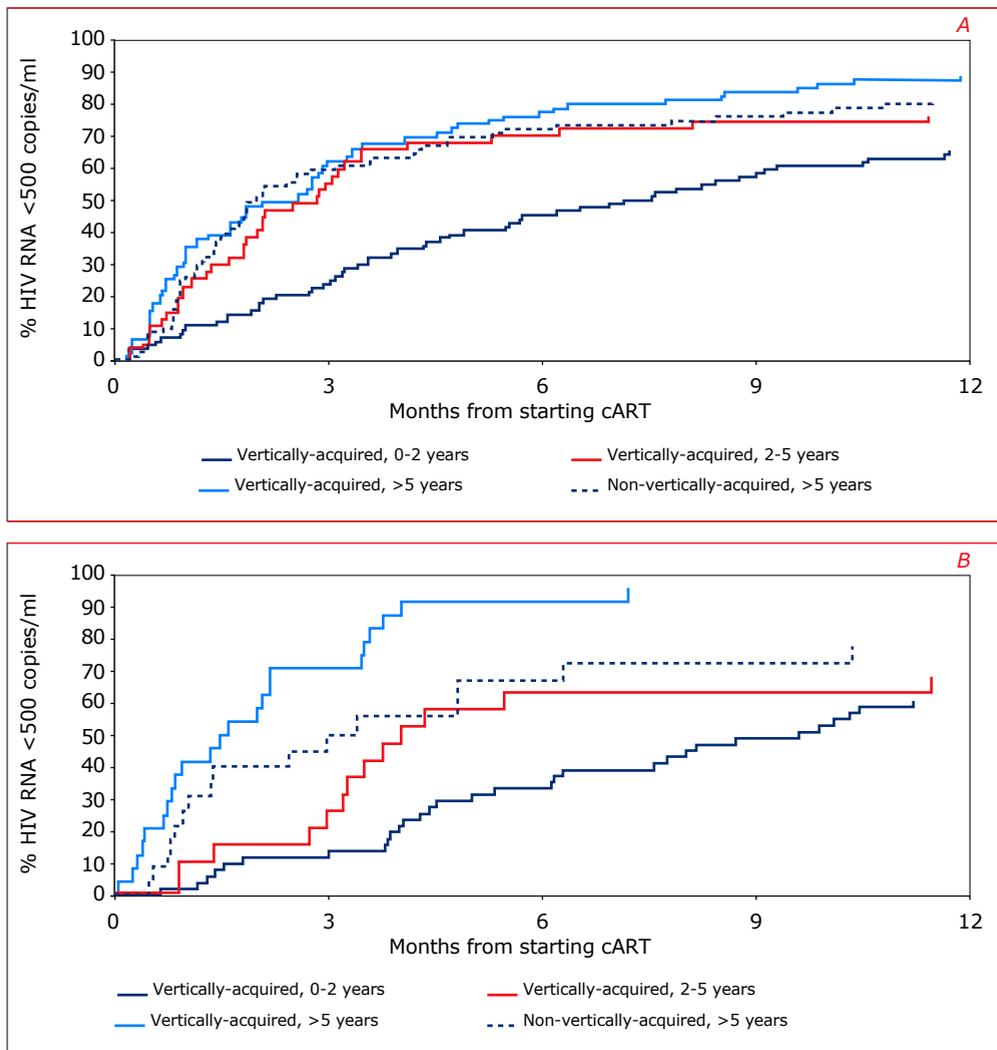
At the time of cART initiation, children less than 2 years of age had significantly higher HIV-1 RNA levels than older children, which is in line with findings from other studies<sup>153</sup> (*Appendix Table 5.1*). We assessed longitudinal virological suppression after the start of cART for children with vertically and non-vertically acquired HIV-1, stratified by age at cART initiation (these are the same groups as those presented in the paragraph on immunological response to cART). 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<sup>153</sup>. Overall, 12 months after starting cART, 75% of all children had a successful virological response.

Among children who initiated cART before 2010, the poorest virological responses were observed in those less than 2 years of age (46% reached an undetectable HIV-1 RNA level 6 months after the start of cART). The best responses were among children aged 5 years or more who had acquired HIV either through vertical transmission (77%) or non-vertical transmission (73%) and among those aged 2 to 4 years (72%) (*Figure 5.11A*).

Viral suppression among children who initiated cART in, or after, 2010 is shown in *Figure 5.11B*. In this group, 35% of the children less than 2 years of age and 63% of children aged between 2 and 4 years achieved an undetectable HIV RNA within 6 months. The highest virological response rates were once again observed among children with vertically-acquired HIV who were aged 5 years or more (91%). This rate was higher than in those children with vertically-acquired HIV and aged 5 years or more who had initiated cART before 2010. No improvement of viral suppression over time was seen in other age groups.

The less favourable initial virological response among the youngest children has previously been described by others<sup>155</sup> and might be explained by difficulties in performing regular dosing adjustments in young children<sup>51</sup>, but also could be due to the higher pre-cART viral loads in younger children<sup>156</sup>.

Figure 5.11: Kaplan-Meier estimates of the percentage of HIV-1 positive 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: (A) initiation of cART between 1998-2010 and (B) initiation of cART between 2010-2016.



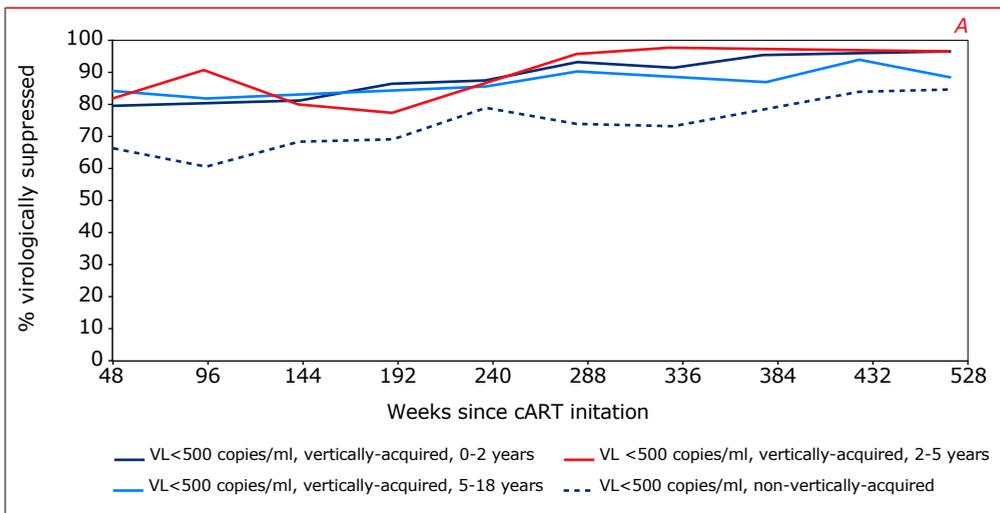
Legend: cART=combination antiretroviral therapy.

### Long term virological suppression

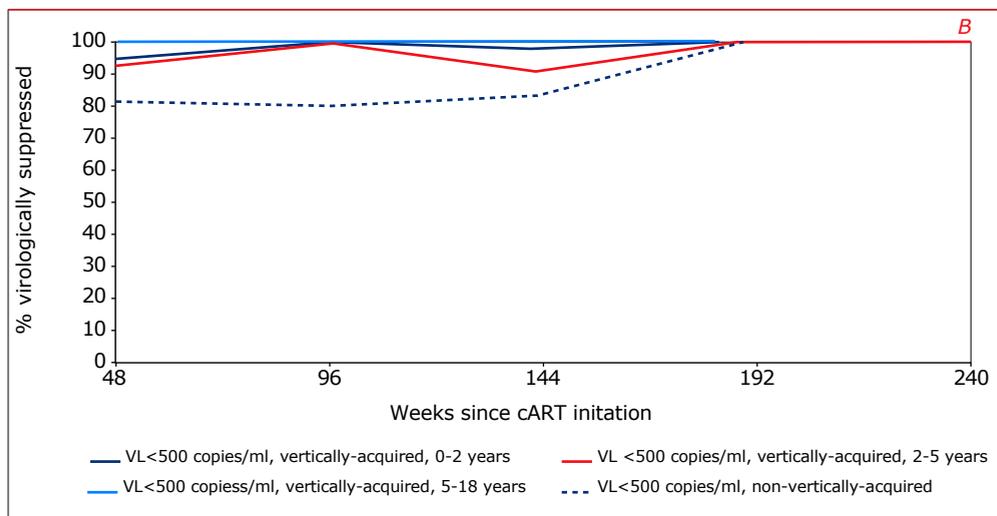
We assessed longitudinal viral suppression rates (i.e., viral load <500 cps/ml) over time on cART at 24-weekly intervals among the 556 children after cART initiation. The viral load measurement after at least 24 months of cART and closest to each 24-weekly time point ( $\pm 12$  weeks) was included in the analysis, irrespective of the viral load of that time point.

Figure 5.12 shows viral suppression rates by calendar period of cART initiation: 1998-2009 and 2010-2016. In those initiating cART between 1998 and 2009, suppression rates after 1 year of cART use were around 80% for the children with vertically-acquired HIV-1 and 66% for the children with non-vertically-acquired HIV-1. These rates increased to 96% after 10 years of cART use in children with vertically-acquired HIV-1 and aged either 0-2 or 2-5 years at the time of cART initiation, but was lower in children with vertically-acquired HIV-1 who were aged over 5 years and in children with non-vertically-acquired HIV-1 (88% and 85%, respectively) (Figure 5.12A). Overall, the long-term viral suppression rates improved over time. Among those who started cART in or after 2010, the viral suppression rates were 100% in all groups after 3.5 years of cART use (Figure 5.12B).

Figure 5.12: Viral suppression since combination antiretroviral therapy initiation, by calendar period of therapy initiation: (A) 1998–2010 and (B) 2010–2016.



Legend: cART=combination antiretroviral therapy.



Legend: cART=combination antiretroviral therapy.

## Adopted children

Of the 590 children, 115 children had been adopted by Dutch parents and their median age was 2.8 years (IQR 1.8-4.7) at the time of entering care in the Netherlands. Of these 115 adopted children, 112 received cART during follow up in clinical care in one of the Dutch HIV treatment centres, nine of whom had been pre-treated with monotherapy or dual therapy before the start of cART. In total, 82 children had been receiving cART before adoption. The proportion of children receiving cART prior to adoption increased over time and reached 100% in 2015 and 2016 (Figure 5.4). Although 82 children had been receiving cART before being adopted, only 32 (28%) of the 115 adopted children had a viral load <100 copies/ml upon entry into care in the Netherlands. Furthermore, although the number of children receiving cART prior to adoption increased, there was no substantial increase in the proportion of children with an undetectable HIV RNA level.

All 115 adopted children are currently alive and in care, and their median current age is 7.8 years (IQR 5.5-10.1). All children who started cART currently remain on treatment, and 111/112 (99%) had an undetectable viral load ( $\leq 100$  copies/ml) at the last known time point.

## Transfer to adult care

As of 31 December 2016, 121 of the 355 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 2000 to 20 in 2011, 15 in 2015 and 11 in 2016. The median age at transfer was 18.9 years (IQR 18.4-19.8).

At the time of transfer to an adult HIV treatment centre, 85 children (70%) had an HIV RNA level  $\leq 100$  copies/ml. The median time in care after transfer was 4.1 years (IQR 1.8-6.1). Of the children who transferred to adult care, nine were subsequently lost to follow up, four have since moved abroad, and one patient died at age 27. The remaining 107 are currently alive and in care. Of these 107 individuals, 102 (95%) are currently on a cART regimen. For three out of the five individuals not on treatment, the reason for not using treatment was known and was either lack of compliance (n=1) or the individual's own decision (n=2).

One year after transfer to adult care, 71% of the young adults had an undetectable HIV RNA level ( $\leq 100$  copies/ml). However, at the most recent clinical visit in 2016, this figure had risen to 86% (92/107). The remaining 14% (15/107) had a detectable viral load (median 5,000, IQR 659-27,000) and a current median CD4 count of 335 cells/mm<sup>3</sup> (IQR 210-460). The majority of these 15 individuals with a detectable viral load were girls (73%) who had acquired HIV through vertical transmission (80%) and who did not originate from the Netherlands. Although they were all currently using cART, 13 out of the 15 individuals had a history of frequent treatment discontinuation; previously-reported reasons for treatment interruption included it being the individual's own decision and lack of compliance. In total, drug resistance results were available for 11 out of these 15 children (39 sequences) at the time of virological failure. To gain insight into current drug susceptibility, we excluded drug resistance results obtained before 2012. Since 2012, drug resistance results were available for 9 out of 15 children (16 sequences). For each child, we used the last available sequence for further analysis. The HIVdb genotypic resistance interpretation algorithm by Stanford University (Version 8.3) was used to infer antiretroviral drug susceptibility scores for each sequence, according to a five-level scheme: susceptible, potential low-level resistance, low-level resistance, intermediate resistance, and high-level resistance<sup>158,33</sup>. The definition of acquired HIV drug resistance used in our analyses is summarised in *Box 2.3 (Chapter 2)*. High-level resistance to at least one antiretroviral drug was detected in 5 out of 9 children. High-level NRTI resistance was detected in 2 out of 9 children, and high-level NNRTI resistance was found in 5 out of 9 children. Dual-class (NNRTI and NRTI) resistance was detected in 2 out of 9 children. However, no high-level PI-resistance was detected.

The virological and social outcomes of HIV-positive adolescents and young adults in the Netherlands before and after transition to adult care have been explored in more detail by Weijnsfeld *et al.*, who confirmed an increased risk of virological failure when aged between 18-19 years, with this risk being concentrated around the time of transition to adult care. In particular, virological failure between 18-19 years of age was significantly associated with low education and lack of autonomy of medication adherence at the time of transitioning to adult care<sup>159</sup>.

## Summary and conclusions

Of the 590 children diagnosed with HIV before the age of 18 years and ever registered with SHM, the majority are still in care and, of those currently in care, 57% have survived into adulthood. There has been a small increase in the proportion of children in care between 0 and 5 years of age. This is due to a substantial proportion of the children newly-registered since 2010 being children who have been adopted by Dutch parents.

The majority of children who acquired HIV through vertical transmission were born outside the Netherlands. Within the Netherlands, vertical transmission of HIV-1 has become extremely rare with no cases reported in 2015 and 2016, reflecting the success of standardised HIV-1 screening in the first trimester of pregnancy<sup>149</sup>. This measure, however, does not completely prevent vertical transmission from occurring and therefore, when women present with possible symptoms of primary HIV infection, professionals should remain alert to the possibility of incident HIV infection later during pregnancy in women who tested HIV-negative during the first trimester. Given the low estimated prevalence (between 0.04 and 0.08%)<sup>150</sup> of primary HIV-1 infection among pregnant women in the Netherlands, standardised repeated screening during pregnancy is not likely to be cost-effective.

The continuum of care shows a high retention in care rate for children currently aged less than 18 years. However, in young people currently aged 18 years and older and with non-vertically-acquired HIV-1, the lost to follow up rate is high. Moreover, compared to children currently aged less than 18 years, a substantially lower proportion of young people aged  $\geq 18$  years currently have suppressed HIV RNA levels.

We observed low mortality rates in HIV-1-positive children in care in the Netherlands. The majority of HIV-1-positive children ever in care in the Netherlands have received cART. Over time, the initial cART regimens have changed and,

in recent years, mostly include lopinavir and efavirenz, as well as the integrase inhibitors dolutegravir and elvitegravir in children aged 12 years or above.

Age at cART initiation appears to importantly affect both immunological response and viral suppression. In particular, long-term immunological outcomes after initiating cART were poorer in children aged >12 years if they had started cART when they were five years of age or older. The overall viral suppression rate of the HIV-positive children receiving cART is high and continues to improve over time. Nonetheless, as with immunological response, long-term virological suppression was lower in children who were aged over 5 years at the time of cART initiation. Regardless of this lower response among children who were older at the start of cART, all individuals who initiated cART in or after 2010 had an HIV RNA level < 500 copies/ml after 3.5 years of cART use.

A substantial proportion (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 young people are on cART. However, the high rate of detectable HIV-1 viral load in these children around the time of transitioning to adult care is of concern. Moreover, although viral suppression rates have substantially improved over time and relatively more young adults are now virally suppressed at their most recent clinical visit after transitioning to adult care, there remains a group of young adults who are not able to achieve HIV RNA suppression despite cART use.

## Recommendations

The provision of care for children living with HIV-1 in the Netherlands has resulted in generally favourable outcomes. An increasing proportion of children are surviving into adulthood and transitioning to adult care. However, special attention is needed for those children transitioning to adult care, as this period seems to be associated with an increased risk of virological failure.

## 6. Distinct populations: Pregnancies in women living with HIV in the Netherlands

Colette Smit, Jeannine Nellen, Liesbeth van Leeuwen

### Introduction

Transmission of HIV from an HIV-positive mother to her child is the most common route of HIV transmission among children aged 0 to 15 years worldwide<sup>160</sup>. 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 45%<sup>161,162</sup>. However, since the introduction of combination antiretroviral therapy (cART) in pregnant women, the risk of MTCT has been dramatically reduced to less than 1%<sup>163,164</sup>.

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<sup>165</sup>. Since then, 319 women who were unaware of their HIV status were diagnosed with HIV during their pregnancy and reported to SHM. By May 2017, a total of 2,355 pregnancies in 1,359 women had been registered among the total 4,525 HIV-positive women monitored by SHM. Overall, 55% of the pregnant women had been diagnosed with HIV before the onset of pregnancy.

### Demographics

#### Maternal characteristics

The characteristics of HIV-positive women with a registered pregnancy are presented in *Table 6.1*. Of the 1,359 women with a documented pregnancy, 1,114 (82%) were of non-Dutch origin and 245 women (18%) originated from the Netherlands. The majority of women of non-Dutch origin were born in sub-Saharan Africa (n=759, 68%) or in the Caribbean/South American region (n=197, 18%). Women of Dutch origin were more often aware of being HIV-positive before they became pregnant than those of non-Dutch origin (73% versus 51%, 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%), although women of Dutch origin were more likely to have acquired HIV by another route (including injecting drug use, needle accidents, blood or blood products or an unknown route of transmission) than women of

non-Dutch origin ( $p < 0.0001$ ). In particular, injecting drug use was reported as the route of transmission in 12 out of the 28 women of Dutch origin with another route of HIV transmission (5%). However, all transmissions by injecting drug use occurred before 2003; since then, no further HIV transmission by injecting drug use has been observed. Two pregnant women originating from sub-Saharan Africa were known to have themselves acquired HIV by MTCT and both gave birth to an HIV-negative child.

Thirty-five mothers were documented as having died during follow up, with a median time between the onset of pregnancy and death of 8.5 years (IQR 3.1-11.7). Two out of 35 mothers died within two months of parturition: the cause of death was acidosis and rhabdomyolysis associated with sepsis in one woman and unknown in the other. Fifteen of the 35 deaths were AIDS-related and 4 deaths were caused by non-AIDS-related infections.

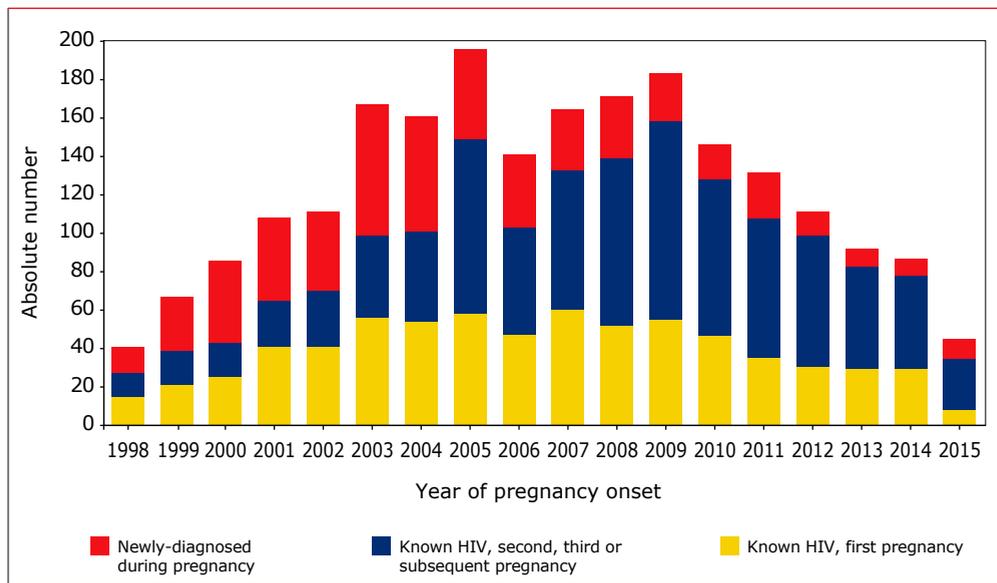
In total, 142 women were lost to follow up; this was more common in women of non-Dutch origin (12%) than in those of Dutch origin (6%). Of the women of non-Dutch origin, 106 were no longer in care in one of the HIV treatment centres because they had moved abroad.

### **Trends in number of pregnancies among women living with HIV**

The absolute annual number of pregnancies varied between a minimum of 41 pregnancies in 1998 and a maximum of 196 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 9 and 60 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 pregnancy in Amsterdam in 2003, which was later expanded into a national screening programme from 1 January 2004 onwards.

The majority of women were already aware of being HIV-positive at the time of their pregnancy, with 55% of the women having received an HIV diagnosis before the onset of pregnancy. The number of second, third or subsequent pregnancies increased from 12 in 1998 to a maximum of 103 in 2009 and declined thereafter (*Figure 6.1*).

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



### Pregnancy-related characteristics

Overall, 1,359 women accounted for 2,355 registered pregnancies. Fifty-five 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).

**Table 6.1: Characteristics of HIV-positive pregnant women registered and monitored by Stichting HIV Monitoring up to 1 May 2017**

	<b>Total n (%)</b>	<b>Dutch n (%)</b>	<b>Non-Dutch n (%)</b>
<b>Maternal characteristics</b>	1,359	245 (18)	1,114 (82)
<b>HIV diagnosis before pregnancy</b>	751 (55)	179 (73)	572 (51)
<b>Age at start of first pregnancy while HIV-positive (years*)</b>	29 (26-34)	30 (27-35)	29 (25-34)
<b>HIV transmission route</b>			
Heterosexual	1,277 (94)	217 (89)	1,060 (95)
Other	82 (6)	28 (11)	54 (5)
<b>Ever CDC-c** event</b>	240 (18)	40 (17)	205 (18)
<b>Deaths</b>	35 (3)	9 (4)	26 (2)
<b>Lost to follow up</b>	248 (19)	13 (6%)	129 (12%)
<b>Total number of pregnancies</b>	2,355	417	1,938
<b>Maximum number of pregnancies after HIV diagnosis</b>			
1	746 (55)	137 (55)	609 (55)
2	358 (26)	67 (26)	291 (26)
3	167 (12)	25 (15)	142 (13)
≥4	88 (6)	16 (7)	72 (6)
<b>Pregnancy outcome</b>			
Birth (live or stillbirth)	1,757 (75)	316 (76)	1,441 (74)
Miscarriage	130 (6)	26 (6)	104 (5)
Abortion	269 (11)	43 (10)	226 (11)
Abortion, no additional data	179 (8)	32 (8)	147 (8)
Unknown	20 (1)	0	20 (1)
<b>Mode of delivery</b>			
Vaginal	1,038 (59)	227 (72)	811 (56)
Caesarean	670 (38)	83 (26)	587 (41)
Unknown	49 (3)	6 (1)	43 (3)
<b>Pregnancy duration</b>			
≥37 weeks	1,422 (60)	266 (64)	1,156 (60)
32-37 weeks	202 (9)	30 (7)	172 (9)
<32 weeks	151 (6)	32 (8)	119 (6)
Missing	580 (25)	89 (21)	491 (25)
<b>Birth weight (grams, IQR*)</b>	3,090 (2,685-3,410)	3,150 (2,735-3,455)	3,080 (2,655-3,395)

	Total n (%)	Dutch n (%)	Non-Dutch n (%)
<b>Gender</b>			
Boy	915 (52)	158 (50)	757 (53)
Girl	825 (47)	156 (49)	669 (46)
Unknown	17 (1)	2 (1)	15 (1)
<b>Perinatal deaths</b>	60 (3)	11 (3)	49 (3)
Antepartum	34	6	28
Intrapartum	4	1	3
0-24 hours postpartum	15	3	12
1-7 days postpartum	4	1	3
>7 days postpartum	3		3
<b>First CD4 cell counts (cells/<math>\mu</math>l) in first pregnancy (median, IQR)</b>	410 (266-565)	530 (360-740)	384 (250-532)
<b>Start cART in first pregnancy</b>			
Before pregnancy	512 (38)	103 (42)	409 (37)
During pregnancy	734 (54)	114 (47)	620 (56)
No cART during pregnancy	112 (8)	28 (11)	84 (8)
<b>HIV RNA plasma levels before delivery in first pregnancy</b>			
HIV RNA available	991/1,076 <sup>^</sup> (92)	184/194 <sup>^</sup> (91)	807/882 <sup>^</sup> (90)
Undetectable	903 (91)	172 (93)	731(91)
Detectable <sup>#</sup>	88 (9)	12 (7)	76 (9)
Unknown	85	10	75

\*Median, interquartile range (IQR)

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

<sup>#</sup>based on the detection limit of the assay

<sup>^</sup>number of first pregnancies after HIV diagnosis that resulted in birth.

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

The outcome of all pregnancies that lasted at least 24 weeks was counted as a birth. As such, the 2,355 registered pregnancies resulted in 1,757 (75%) births (including both live births and stillbirths). One hundred and thirty pregnancies (6%) ended in miscarriage (loss of pregnancy before 24 weeks), and 269 (11%) ended through abortion (n=264) or ectopic pregnancy (n=5), with a known reason for abortion in 37 cases (6 medical, 32 non-medical). Another 179 (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, 915 (52%) boys and 825 (47%) girls were born, while for 17 infants the gender was not documented. Fifty-nine percent of the newborns were delivered vaginally. This was significantly more common in women of Dutch origin (72%) than in women of non-Dutch origin (56%) ( $p < 0.0001$ ). A total of 670 newborns (38%) were delivered by Caesarean section. Planned Caesarean delivery is known to reduce the risk of MTCT if the maternal viral load is detectable, but such a delivery is not beneficial if viral load suppression is achieved following successful treatment with cART<sup>166,167</sup>. We observed a decrease over time in the proportion of planned Caesarean deliveries in first pregnancies from 43% in 1999 to 15% in 2015 (Figure 6.2), which is equivalent to the level seen in the HIV-negative population<sup>168</sup>. Together with the decrease in planned Caesarean sections, the proportion of women with a viral load above 500 copies/ml at the time of delivery also decreased over time (from 31% in 1998 to 0% in 2015,  $p < 0.0001$ ) (Figure 6.3). Despite a difference in the rate of Caesarean deliveries between women of Dutch origin and those of non-Dutch origin, there was no significant difference between these two groups of women in terms of the proportion with a detectable HIV RNA load at the time of delivery (Table 6.1).

Figure 6.2: Percentage of pregnancies by mode of delivery over time.

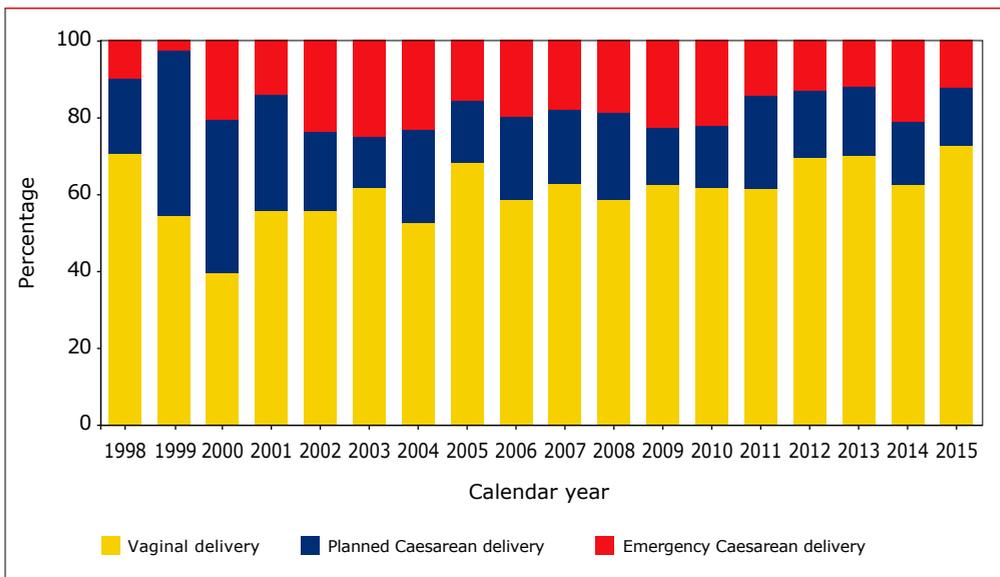
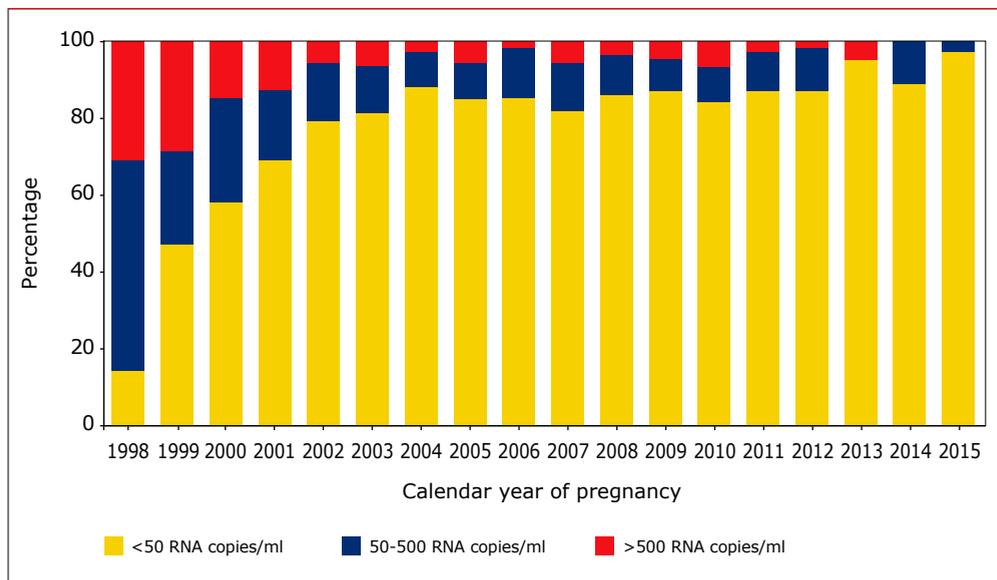


Figure 6.3: Distribution of women with HIV RNA levels <50 copies/ml, 50–500 copies/ml or >500 copies/ml at the time of delivery.



Overall, 81% of the pregnancies lasted at least 37 weeks. The median weight of newborns was 3,090 grams (IQR 2,685-3,410). Among newborns with a known birth weight and duration of pregnancy, a total of 378 (21%) were preterm births. The proportion of premature births varied from 27% in 1999 to 15% in 2015. In 2001, 8% were early-premature births (pregnancy duration between 24 and 32 weeks), while in 2012 this figure was 2.3%.

After delivery, four infants were admitted to medium or intensive care, while another 128 children remained under clinical observation. Congenital disorders were registered for five infants, one of whom had died. Perinatal death, including antepartum, occurred in 3% (n=60) of the births; 75% of these deaths occurred after a pregnancy duration of between 24 and 32 weeks. No significant differences in pregnancy duration, birth weight, and perinatal death were found between women of Dutch and non-Dutch origin. However, the observed median birth weight of infants born to pregnant women living with HIV appears to be lower than that of infants born to women of the general population in the Netherlands<sup>169</sup>.

Women of Dutch origin had a significantly higher first median CD4 count measured during pregnancy (median 530, IQR 360-740) than women of non-Dutch origin (median 384, IQR 250-532;  $p < 0.0001$ ). The majority of women used cART during their pregnancy: 38% had started cART before the onset of the pregnancy and 54% started while pregnant, 3% of whom started within the first 12 weeks and 65% within the first 24 weeks of the pregnancy. Finally, the proportion of women who were already receiving cART when they became pregnant was slightly higher in women of Dutch origin (42%) than in women of non-Dutch origin (37%).

### Mother-to-child transmission

Of the 1,757 children born from registered pregnancies from 1996 onwards, nine (0.5%) newborns were found to have acquired HIV through vertical transmission. The mothers of seven of these nine newborns had not received cART during pregnancy, despite five of these mothers having been diagnosed with HIV during pregnancy. The reasons why these mothers had not started cART are unknown. Of the remaining two mothers who had not received cART during 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 mothers of the remaining two children who had acquired HIV through vertical transmission had started cART during pregnancy and both had an undetectable HIV RNA level during delivery (<50 copies/ml). One of these mothers gave birth through vaginal delivery and the other underwent a Caesarean section. The infant born by Caesarean section was thought to have already acquired HIV *in utero*. Since two vertical transmissions of HIV occurred in pregnancies with an HIV RNA level below 50 copies/ml at time of delivery, the MTCT transmission rate among HIV RNA-suppressed pregnant women was 0.2% (2/821).

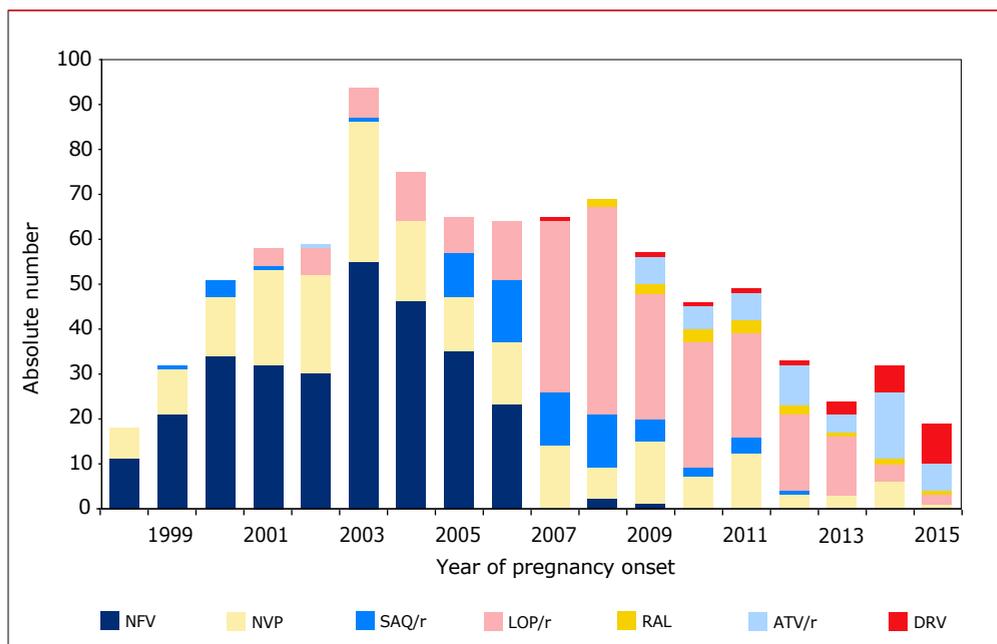
### Response to cART in pregnant women

Between 1998 and 2016, 1,666 pregnancies lasted more than 24 weeks. Combination antiretroviral therapy (cART) was used in 1,533 (92%) of these pregnancies; in 672 pregnancies, the women were already using cART at the time they became pregnant, while in 861 pregnancies, cART was started during pregnancy. In the remaining 133 pregnancies, cART was not used at any time during the pregnancy.

*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, although regimens containing raltegravir or atazanavir were also prescribed during

pregnancy from 2008 onwards, as well as darunavir-containing regimens from 2013 onwards. Finally, as raltegravir has been shown to rapidly decrease time to virological suppression, it is mainly added to a cART regimen in pregnant women whose HIV RNA level remains detectable in the last trimester of pregnancy<sup>170</sup>.

*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= nefinavir; DRV=darunavir.*

In terms of the NRTI backbone, the combination of zidovudine and lamivudine was used during 72% of the first registered pregnancies. However, the use of this combination decreased over time from 88% in 2001 to 0% in 2015. From 2011 onwards, emtricitabine in combination with tenofovir was used as a backbone in 27% of all first registered pregnancies and abacavir in combination with lamivudine was used in 2% of all first registered pregnancies.

As expected, women who started cART before pregnancy had significantly lower CD4 counts at treatment initiation than those who started cART during their pregnancy ( $p < 0.0001$ ). Furthermore, women who started cART before pregnancy

had significantly higher median pre-treatment HIV RNA levels than those who started cART during pregnancy ( $p < 0.0001$ ) (Table 6.2). This may be because a proportion of women only started cART during pregnancy to prevent MTCT, rather than for their own health benefit.

**Table 6.2: Characteristics of 1,192 HIV-positive pregnant women who initiated combination antiretroviral therapy (cART) between 1 January 1998 and 1 May 2017.**

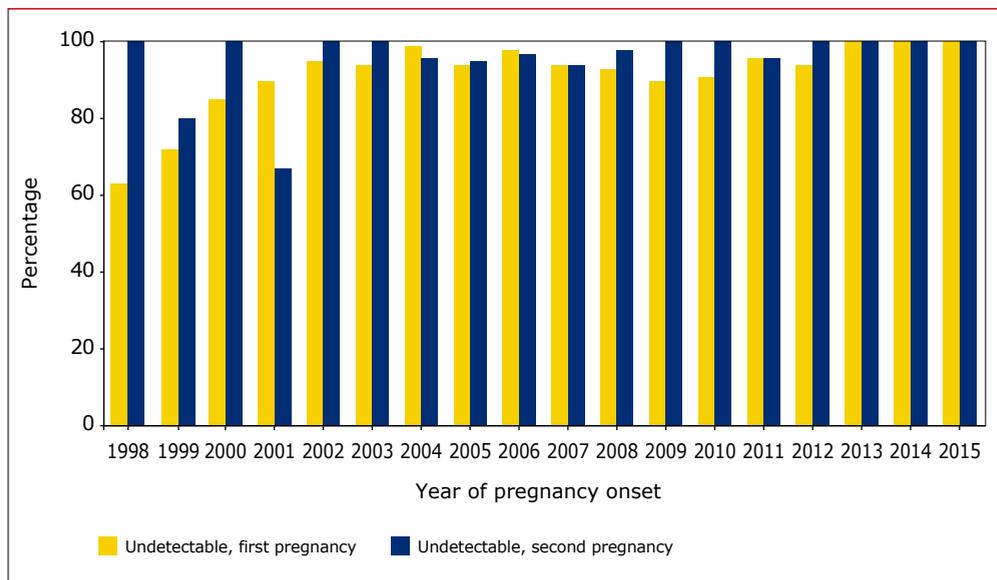
	cART initiation	
	Before pregnancy	During pregnancy
<b>Total women (n=1,192)</b>	501 (42)	691 (58)
<b>Age at start cART*</b>	29 (25-32)	29 (25-33)
<b>Region of origin</b>		
Netherlands	100 (20)	106 (15)
Other	401 (80)	585 (85)
<b>Calendar year of cART initiation</b>		
<2000	123 (25)	23 (3)
2001-2006	241 (48)	401 (58)
≥2007	137 (27)	267 (39)
<b>At start of cART</b>		
CD4 cell counts (cells/mm <sup>3</sup> )*	210 (100-300)	351 (210-510)
HIV RNA levels (log <sub>10</sub> copies/ml)*	4.7 (4.0-5.3)	4.0 (3.3-4.6)
<b>At parturition</b>		
CD4 cell counts (cells/mm <sup>3</sup> )*	450 (320-610)	464 (300-630)
HIV RNA levels (log <sub>10</sub> copies/ml)*	1.7 (1.6-1.7)	1.7 (1.7-2.0)
<b>Detectable HIV RNA levels<sup>#</sup></b>	49 (10)	70 (11)

\*Median, Interquartile Range (IQR)

<sup>#</sup>based on the detection limit of the assay.

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, 78% 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. Moreover, the proportion of women with an HIV RNA <500 copies/ml at the time of delivery increased from 67% in 1998 to 100% in 2016. Figure 6.5 shows the differences in undetectable HIV RNA levels at time of delivery between the first and second registered pregnancies. As illustrated in Figure 6.5, in more recent years close to all women had an HIV RNA level < 50 copies/ml at the time of delivery in both their first and second pregnancy.

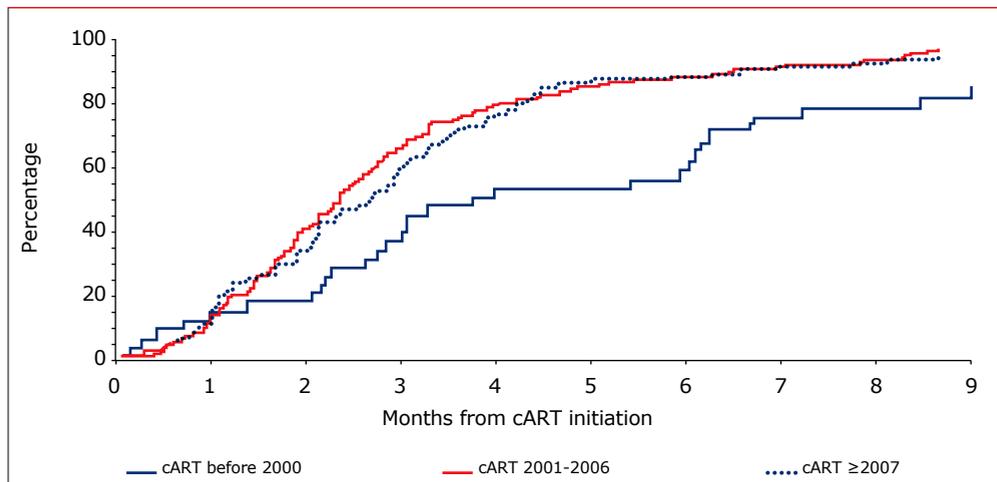
Figure 6.5: Proportion of women with an undetectable viral load at the time of delivery of the first or second pregnancy.



### 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) was compared in pregnant women who started cART during pregnancy before 2000, between 2001 and 2006, and from 2007 onwards. Six months after the start of cART, 87% of the women had achieved virological suppression with two consecutive HIV RNA levels of either <50 or 500 copies/ml. The most marked responses were observed in women who started cART during their pregnancy between 2001 and 2006 (90%, 95% confidence interval [CI] 85-93) and in women who started cART after 2007 (89%, 95% CI 83-94). A poorer response was seen in women who started cART during their pregnancy before 2000 (63%, 95% CI 49-73; p-value log-rank test 0.004, *Figure 6.6*). Finally, the time between cART initiation and virological suppression did not differ between the different cART regimens (p-value log-rank test: 0.52) (*Appendix Figure 6.1*).

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



Legend: cART=combination antiretroviral therapy.

## Virological response during pregnancy and after delivery

For the purpose of these analyses, we defined virological failure as two consecutive HIV RNA levels >500 copies/ml following initial suppression to below the level of quantification of the HIV-RNA assay used, and we considered all episodes of virological failure during pregnancy and the first year postpartum.

In total 7 women (0.6%) experienced virological failure during their pregnancy. One of these women belonged to the group of 501 (0.2%) women who were already using cART before the onset of the pregnancy and 6 (0.9%) belonged to the group of 691 women who started cART during their pregnancy between 1998 and 2016. Although virological failure was rare during pregnancy, we did observe a high rate of treatment discontinuation after delivery; of the 691 women who initiated cART during their pregnancy, 199 (29%) discontinued cART within one year after delivery. In the majority of cases, cART discontinuation was planned because cART had only been prescribed to prevent vertical transmission of HIV during pregnancy (138/199, 69%). However, these planned discontinuations all occurred prior to the recent change in treatment guidelines recommending universal treatment regardless of CD4 count. In addition, a further 30 women (15%) chose to discontinue cART themselves.

The proportion of women who first initiated cART during pregnancy and subsequently discontinued cART after delivery markedly declined over time

from 40% in 2000 to 7% in 2016, reflecting the recent change in treatment guidelines. Of the 492 (691 minus 199) women who continued cART following delivery, 120 (24%) 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 501 women who received cART before the onset of their pregnancy, 51 (10%) discontinued treatment within one year of delivery. For twenty-three (45%) women, treatment discontinuation was their own decision, and for another 8 women (16%) treatment discontinuation was planned due to the pregnancy having ended. However, this occurred primarily during the earlier years and has since become very rare. None of the women who continued to use cART post-partum experienced virological failure in the 12 months after giving birth.

## Summary and conclusions

The absolute number of pregnancies in HIV-positive women in the Netherlands has declined over time. This is likely a reflection 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. This is thought to be due to the economic crisis<sup>171</sup>, as well as a decrease in the number of women originating from sub-Saharan Africa (*Chapter 1*) as a result of stricter immigration laws.

The proportion of women achieving undetectable viraemia at time of delivery, the most important factor in preventing MTCT, has increased tremendously and is close to universal now. Consequently, MTCT has become extremely rare. The overall MTCT rate was 0.5% and was even lower in women who achieved full viral suppression (HIV RNA level <50 copies/ml) at time of delivery (0.2%), comparable to or even lower than that in other western European countries<sup>172,173,174,175</sup>.

Although earlier studies on whether exposure to cART might increase the risk of preterm birth were conflicting<sup>176</sup>, more recent studies have reported declines in preterm births in women living with HIV<sup>177,178</sup>. These declines have been 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 declined. Nevertheless, the proportion of preterm births in HIV-positive women remains higher than that seen in the general population<sup>168</sup>. Besides the higher proportion of pre-term births in HIV-1 positive women, we observed a lower median birth weight in children born to women living with HIV than that in children born to women in the general population in the Netherlands (3,090 gram versus 3,450 gram)<sup>169</sup>.

The proportion of women living with HIV 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-positive pregnant women, the proportion of Caesarean deliveries was higher than that reported in the Dutch population of HIV-positive women<sup>178</sup>. This may be because vaginal delivery has become more widely accepted in HIV-positive women in the Netherlands than in other European countries<sup>178</sup>.

Several studies have demonstrated that adherence to cART may deteriorate in the postpartum period<sup>179,180,181,182,183,184</sup>. A possible explanation for this phenomenon is that women may be more motivated during pregnancy to take medication to prevent vertical transmission than to take it for their own health. Our data showed that planned discontinuation of cART after a pregnancy had ended was common in the early years. However, with the change in treatment guidelines recommending treatment regardless of CD4 cell count, more pregnant women are continuing cART post-partum for their own health.

## Recommendations

As a result of changes in recent guidelines on HIV and pregnancy, it is likely that cART is being started earlier in pregnancy. This earlier initiation of cART may lead to a greater number of women achieving an undetectable HIV RNA level earlier in their pregnancy. Achieving viral suppression earlier in pregnancy should make it possible to now consider invasive procedures for genetic syndromes, such as amniocentesis in case of foetal anomalies on the 20-week ultrasound scan. However, exposure to cART in the first trimester may be associated with a lower birth weight and prematurity, and it is unknown whether longer exposure to cART is harmful to the foetus. Therefore, monitoring of pregnant women using cART during the first trimester of their pregnancy is 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 nausea from which many women suffer, particularly during the first 12 weeks of pregnancy, may lead to poorer adherence and ultimately treatment failure. Finally, women living with HIV who start cART during their pregnancy require a high level of clinical support not only during pregnancy but also after delivery. Therefore, continued monitoring of HIV-positive women after pregnancy is necessary to prevent a loss of motivation to adhere to cART and to ensure early detection of virological failure.

## 7. Quality of care

Colette Smit, Sonia Boender, Jan Prins, Kees Brinkman, Suzanne Geerlings, Frank Kroon, Peter Reiss

### Introduction

One of SHM's missions is to contribute to the quality of HIV care in the Netherlands. Through the collection of pseudonymised data from HIV-positive individuals in outpatient care in the currently 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 issued national guidelines for the treatment and monitoring of HIV-positive individuals in the Netherlands<sup>185</sup>. With these guidelines as a basis, we defined a set of indicators and used them to explore the quality of care in the Dutch HIV treatment centres and to gain insight into potential variation in outpatient care between HIV 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 HIV/AIDS practice guidelines<sup>185</sup>. The indicators were classified as volume, outcome or process indicators.

As noted in earlier studies, the number of patients in care (i.e., the centre volume) may have an impact on the reported indicators<sup>186,187,188</sup>. In particular, the small number of patients in some HIV treatment centres could result in less informative percentages, as a single deviating score on an indicator could result in a wide range of scores for a given indicator in such a low-volume centre. 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:  $\geq 700$  patients ( $n=8$  centres [red dots]); medium-sized: 400-700 patients ( $n=11$  centres [blue dots]); small:  $\leq 400$  patients ( $n=8$  centres [grey dots]).

### Volume indicator

To meet the requirements of the national certification process for HIV treatment centres in the Netherlands (*Harmonisatie Kwaliteitsbeoordeling in de Zorgsector [HKZ]*), HIV treatment centres are expected to enrol a minimum of approximately 20 new patients into care each year. Therefore, as a volume indicator, we quantified the number of patients newly entering care for the first time between 2012 and 2016 for each treatment centre.

### Outcome indicators

The outcome indicators included retention in care, initiation of combination antiretroviral therapy (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 entered care for the first time after being diagnosed with HIV in one of the Dutch HIV treatment centres between 2012 and 2015 and were still in care at least 18 months after entering care. Patients who died during this observation period were excluded from the denominator ( $n=50$ ). During the observation period, approximately 11% of the 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 not counted in either of the centres where they had been in care, but were included in a separate category; these patients are represented with a green dot in the figures.

Initiation of cART describes the overall percentage of those patients who entered care in 2012, 2013, 2014 or 2015 and who started cART within 6 months of entry into care. This indicator was stratified by CD4 cell count at entry into care: CD4  $\geq 500$  cells/mm<sup>3</sup>, CD4 350-500 cells/mm<sup>3</sup> and CD4  $< 350$  cells/mm<sup>3</sup>.

Viral suppression was assessed by two indicators. The first indicator was defined as the percentage of *treatment-naïve* patients with a plasma HIV RNA level  $< 400$  copies/ml at six months after the start of cART. The HIV RNA measurement closest to six months after the start of cART was chosen, with a minimum of three months and a maximum of nine months. The target suppression rate was set at  $\geq 90\%$ . This indicator is part of the HKZ certification process and was developed jointly with the NVHB<sup>89</sup> during the development of the HKZ, with use of the Delphi method.

The second indicator for viral suppression was the percentage of *all* HIV-positive individuals on cART for at least six months with a plasma HIV RNA level  $< 100$  copies/ml. This indicator was calculated for the calendar years 2012, 2013, 2014, 2015 and 2016.

### Process indicators

The process indicators were calculated for two scenarios: before the start of cART and after the start of cART.

To calculate the process indicators *prior to cART initiation*, we included all patients who had entered care between 2012 and 2015. Only patients who entered care for the first time and were in care for at least 12 months were included; patients who had switched treatment centres were not counted as newly entering care, as they had remained in care elsewhere. Of note, 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, 2014 or 2015 for whom the following measurements were available in the six months after entry into care: CD4, plasma HIV RNA, total cholesterol, screening for the presence of hepatitis C virus (HCV) co-infection and hepatitis B co-infection (HBV). When looking at the proportion of patients with available cholesterol measurements, we stratified patients according to age at the time they entered care (<50 years and ≥50 years).

To calculate the process indicators *following cART initiation*, we included patients who had started cART in 2012, 2013, 2014 or 2015. The indicators were defined as the percentage of patients in whom the following measurements were carried out at least once within approximately 12 months after cART initiation: CD4 cell count, plasma HIV RNA and total cholesterol (stratified by age in the specific calendar of observation, <50 years and ≥50 years).

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, 2013 and 2014. We calculated the proportion with repeat HCV serology or HCV RNA within approximately 12 months after entering care. It is worth noting that data on HCV-related risk-taking behaviour are not available to SHM, and therefore this indicator may well overestimate the number of MSM that should have been repeatedly screened for HCV.

The second of the MSM-specific indicators was derived for all MSM who entered care in 2012, 2013 and 2014, and provides the proportion of men for whom syphilis serology was repeated within approximately 12 months after entry into care.

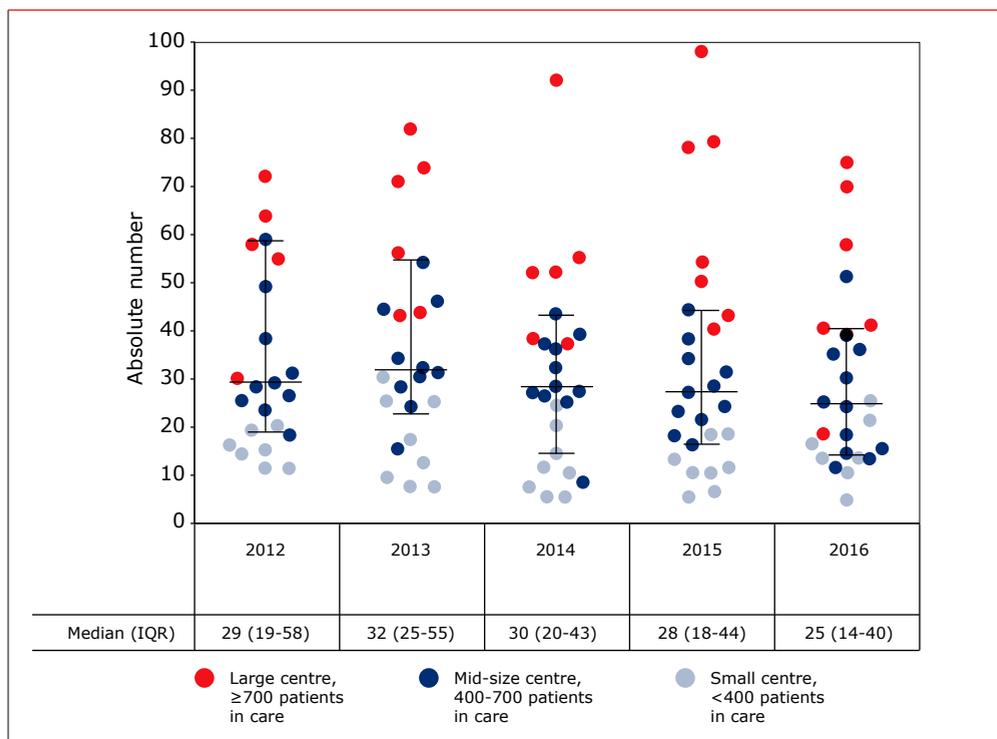
As smaller centres had a smaller number of MSM entering care in each year, we increased the sample size by presenting the overall scores for all centres, not stratified by calendar year of entering care.

## Results

### Volume indicator

The numbers of patients who newly entered care in 2012-2016 across the HIV treatment centres are shown in *Figure 7.1*. The median number of patients annually entering care varied between 32 in 2013 and 25 in 2016. The minimum number ranged from 11 patients in 2012 to 4 in 2016.

*Figure 7.1: Annual number of individuals newly entering care per HIV treatment centre in the Netherlands in 2012-2016.*



*Legend: IQR=interquartile range.*

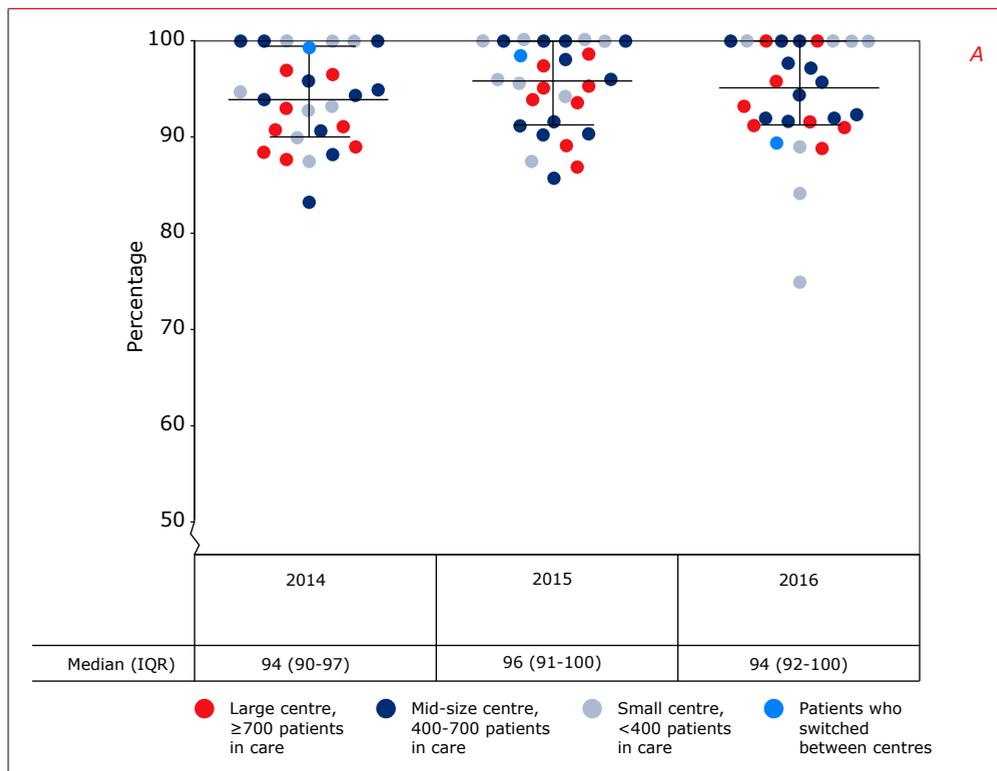
## Outcome indicators

### Retention in care

In 2012, 1,159 patients newly entered care at one of the HIV treatment centres in the Netherlands. Overall, 1,084 of these 1,159 patients (94%) were documented as being retained in care after 1 June 2014. In 2013, 1,136 patients newly entered care, and 1,076 (95%) of those were retained in care after 1 June 2015; 93% of those who entered care in 2014 were still in care in 2016. *Figure 7.2A* shows the variation in retention rate across treatment centres for 2014, 2015 and 2016. The median retention rate was 94% in 2014 and 2016 and 96% in 2015, with a minimum of 75% and a maximum of 100%.

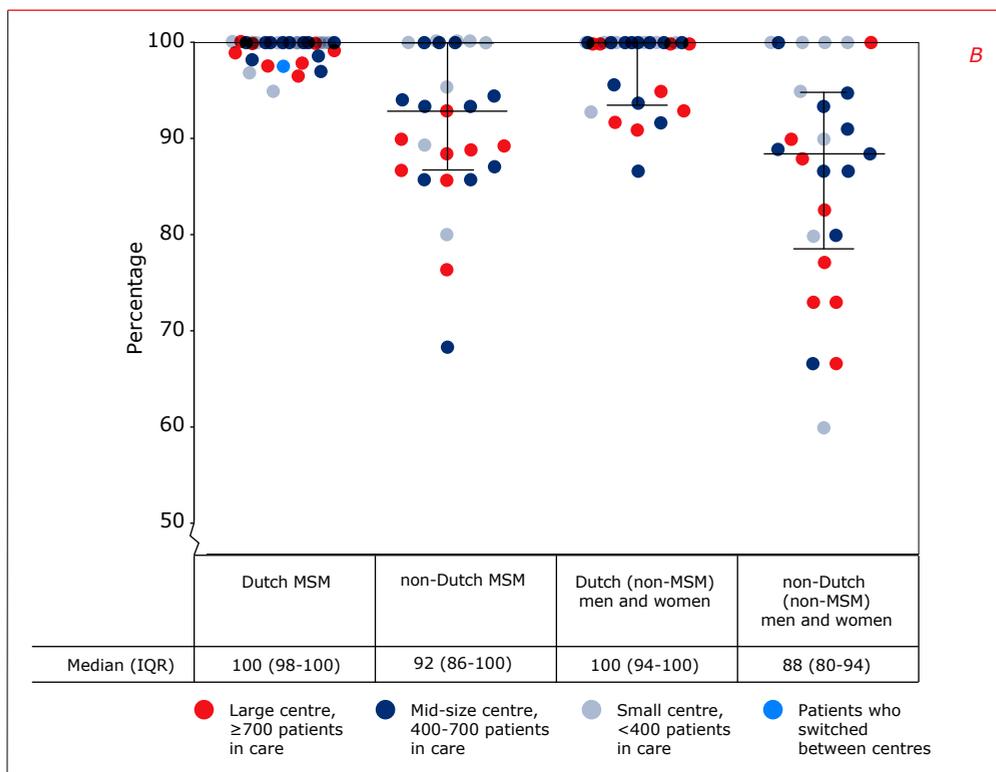
*Figure 7.2B* shows the retention rates stratified by MSM vs non-MSM and region of origin (Dutch vs non-Dutch). Retention in care rates were highest in Dutch MSM (98%) and Dutch (non-MSM) men and women (93%) compared to non-Dutch MSM (89% and non-Dutch (non-MSM) men and women patients (85%, Chi square test  $P < 0.0001$ ). Also among MSM, higher retention rates were observed compared to among non-MSM (median 97% vs median 89%,  $p < 0.0001$ ).

Figure 7.2: Retention in care, defined as the percentage of patients who newly-entered care in 2012, 2013 or 2014 and were still known to be in care in 2014, 2015 and 2016, respectively. Retention rates are presented as the median and interquartile range across all HIV treatment centres. Retention in care is presented (A) over time and (B) by HIV transmission group and origin.



Legend: IQR=interquartile range.

Figure 7.2B: Retention in care by HIV transmission group and origin, defined as the percentage of patients who newly-entered care in 2012, 2013 or 2014 and were still known to be in care in 2014, 2015 and 2016, respectively. Retention rates are presented as the median and interquartile range across all HIV treatment centres.



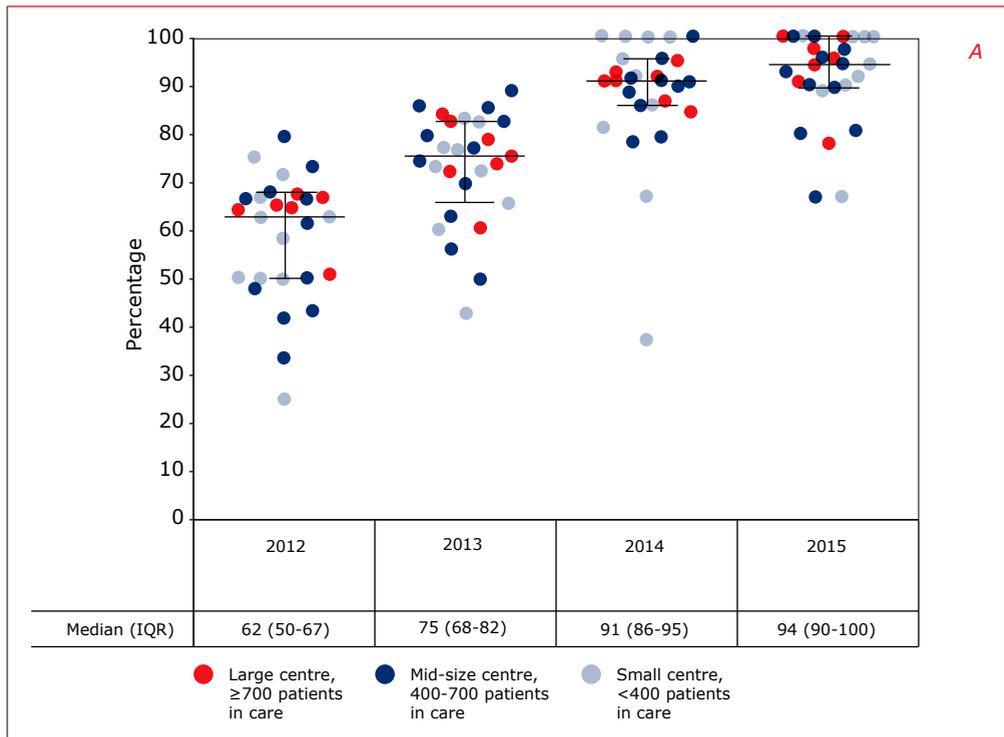
Legend: IQR=interquartile range.

### Initiation of cART

Figure 7.3 shows the percentages of patients starting cART within six months after entering care. Overall, a median of 62% of the patients who entered care in 2012 started cART within six months of entry, and this proportion increased to 94% among patients who entered care in 2015. In terms of variation across HIV treatment centres, the lowest percentage of patients starting cART within six months was 25% for 2012, 42% in 2013, 38% in 2014 and 67% in 2015. When stratified by CD4 cell count, the percentage of patients starting cART within six months of entering care was lower for the CD4 cell categories  $> 500$  cells/mm<sup>3</sup> and 350-500 cells/mm<sup>3</sup>, compared with the CD4 cell category of  $< 350$  cells/mm<sup>3</sup>. This difference between CD4 cell categories decreased in 2014 and 2015, as most of the patients entering care these

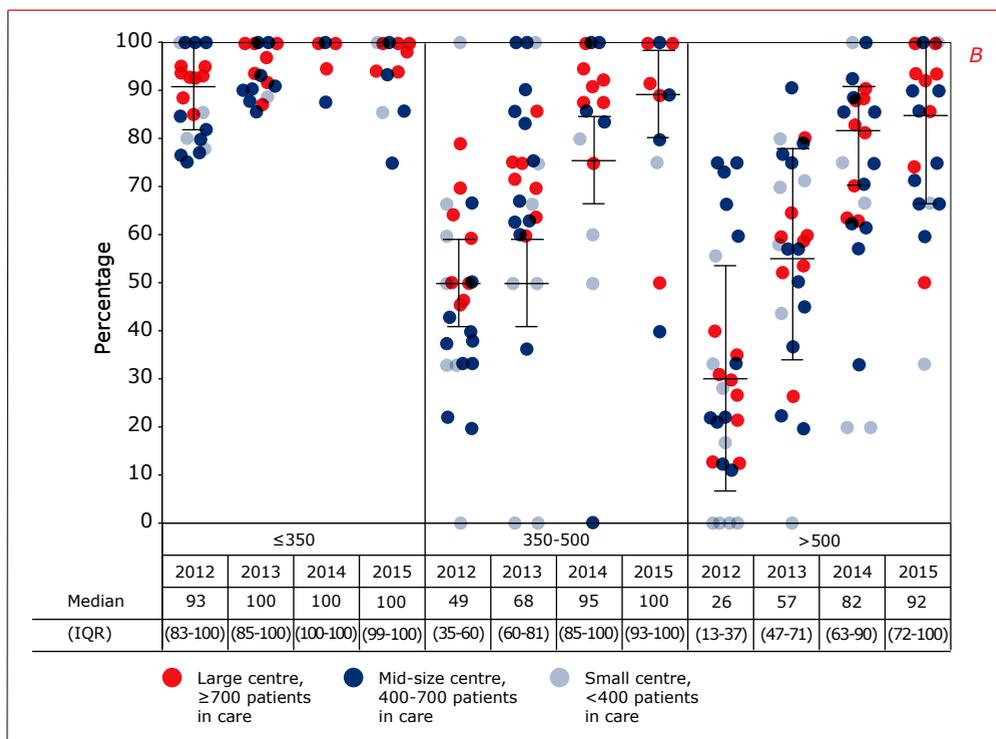
years started treatment within six months (2014: 82%, 95% and 100% for the CD4 cell categories >500, 350-500 and <350 cells/mm<sup>3</sup>, respectively; and 2015: 92%, 100% and 100% for the CD4 cell categories >500, 350-500 and <350 cells/mm<sup>3</sup>, respectively); nonetheless, considerable variation remained between HIV treatment centres.

*Figure 7.3: The percentage of patients who entered care between 2012–2015 and started combination antiretroviral therapy (cART) within six 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.*

Figure 7.3B: The percentage of patients who entered care between 2012–2015 and started combination antiretroviral therapy (cART) within six months after entry. Percentages categorised by CD4 cell count at entry are presented as the percentage of patients starting cART across all HIV treatment centres.

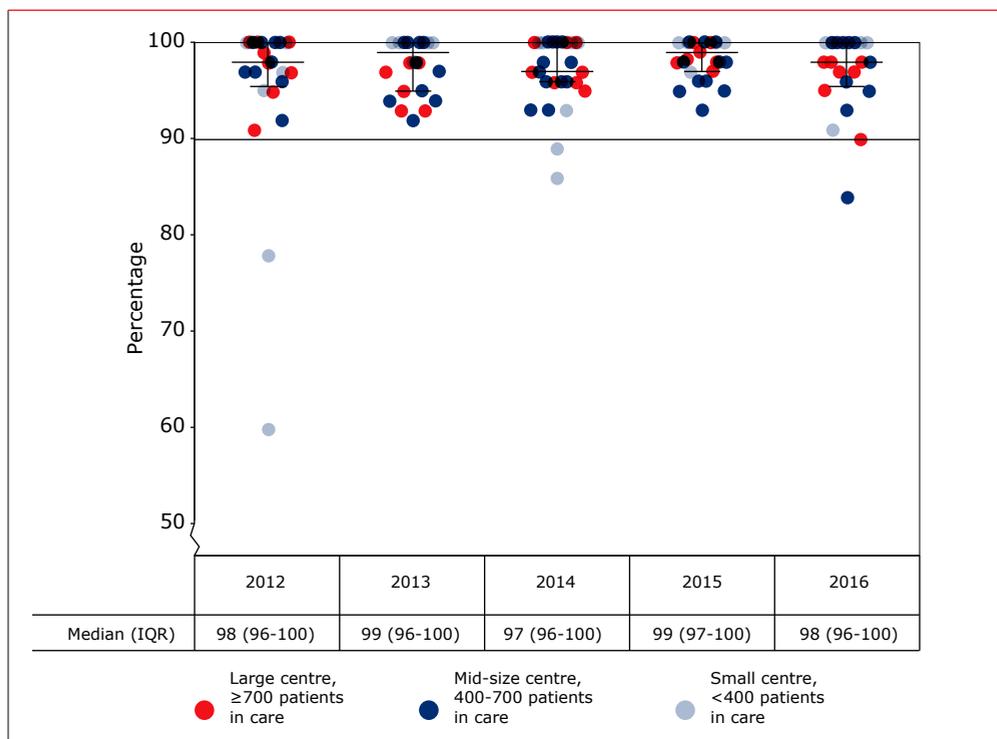


Legend: IQR=interquartile range.

### 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 2012-2016 (Figure 7.4). The median percentages varied between 97% and 99% between 2012 and 2016. In 2012 and 2014, in two small treatment centres and in one mid-sized centre in 2016, 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-naïve 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.

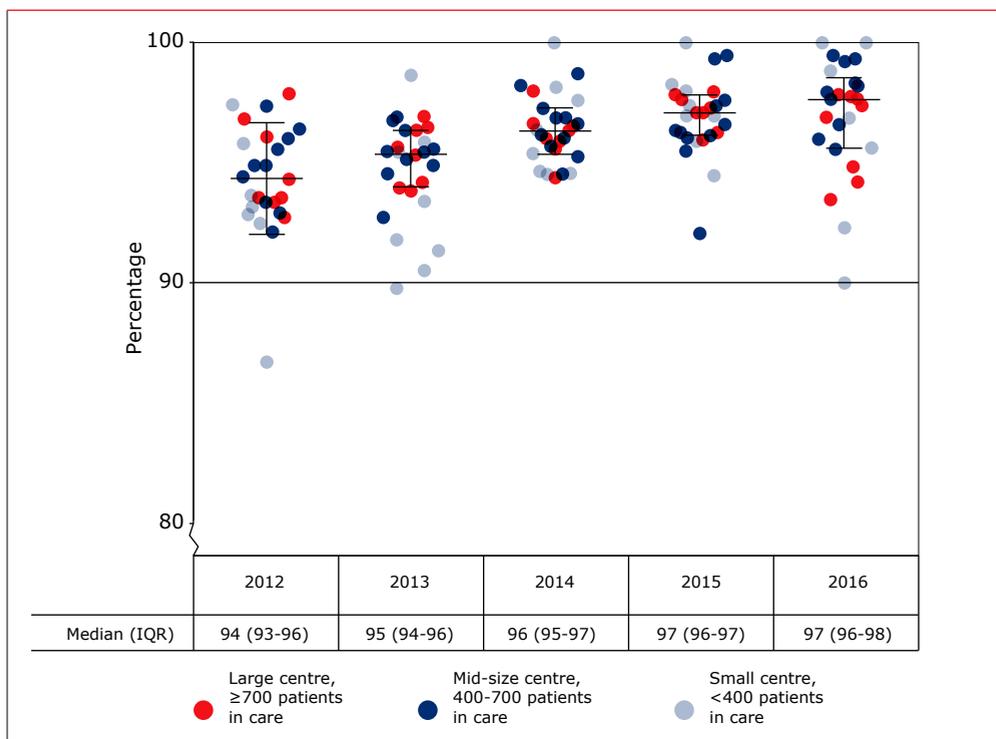


Legend: IQR=interquartile range.

The second viral suppression indicator is the percentage of all HIV-positive individuals in care who were on cART for at least six months and had an HIV RNA level <100 copies/ml. This indicator was calculated for the calendar years 2012-2016 (Figure 7.5). In all calendar years, the median percentage was more than 90%, with limited variation according to centre size. Only in 2012, one small centre had less than 90% of the patients with an HIV RNA level < 100 copies/ml.

Overall and not stratified by treatment centre, the proportion of patients with long-term viral suppression was lower in patients of non-Dutch origin compared to those originating from the Netherlands (95% vs 98%, Chi square test  $p < 0.0001$ ). Furthermore, higher suppression rates after more than six months of cART use were observed in MSM, compared to non-MSM (98% vs 94%,  $p < 0.0001$ ).

Figure 7.5: The percentage of all HIV-positive individuals 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 2012–2016 and is presented as the percentage across all HIV treatment centres.



Legend: IQR=interquartile range.

## Process indicators

### Prior to start of cART

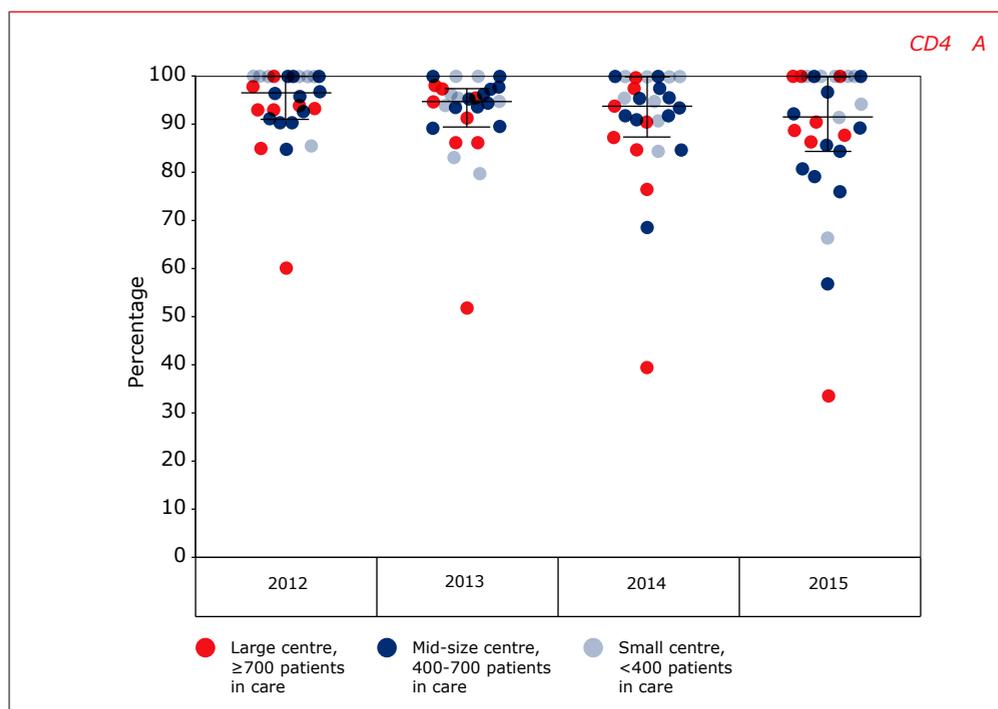
Figure 7.6 shows the variation in plasma HIV RNA, CD4 cell count, total cholesterol (stratified by age at first visit), as well as HCV and HBV screening across the HIV treatment centres in the Netherlands in patients who newly entered care in 2012-2015. The median percentages of patients tested for plasma HIV RNA and CD4 cell count within six months after entering care was greater than 90% in all years, with the exception of HIV RNA in 2012. However, there was considerable inter-centre variation in the percentage of patients tested for CD4 in all years and in HIV RNA in 2012 and 2013. Also, there was considerable inter-centre variation in the patients with a cholesterol measurement; the variation was wider among the patients less than 50 years of age at time of their first clinical visit compared to

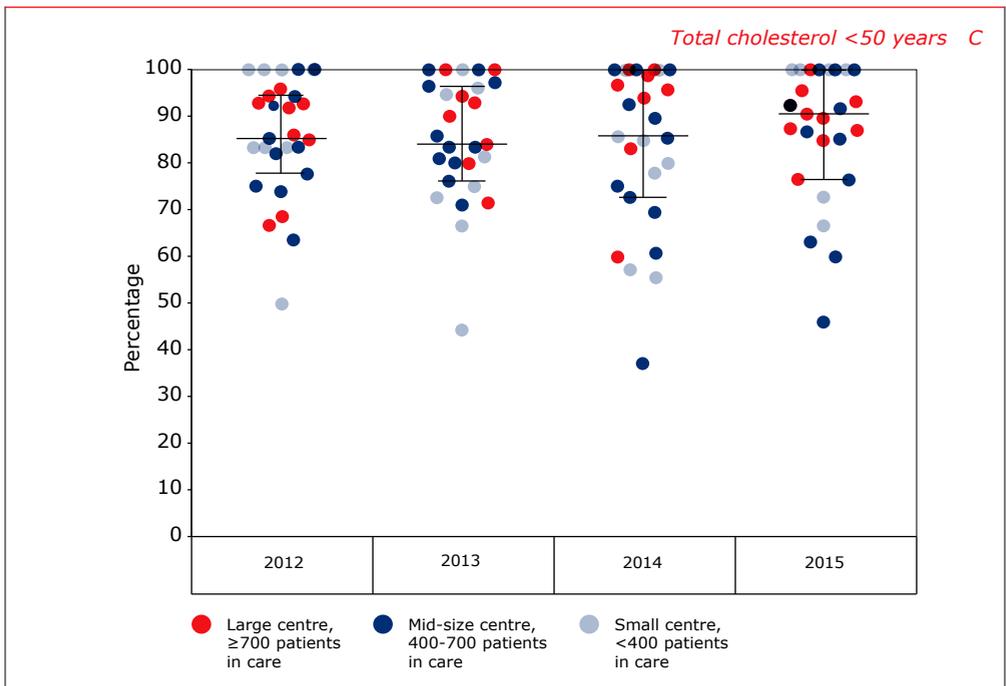
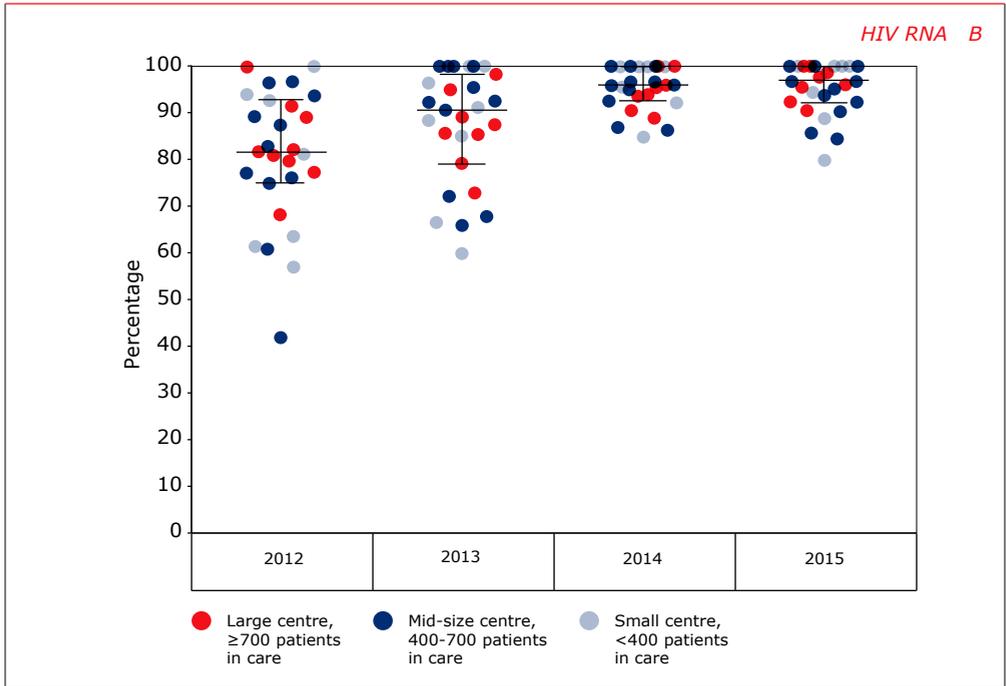
patients 50 years or more. Although in the majority of centres all patients 50 years of age or more had a cholesterol measurement, there were still centres in which less than 90% of the patients above 50 years of age had an available cholesterol measurement.

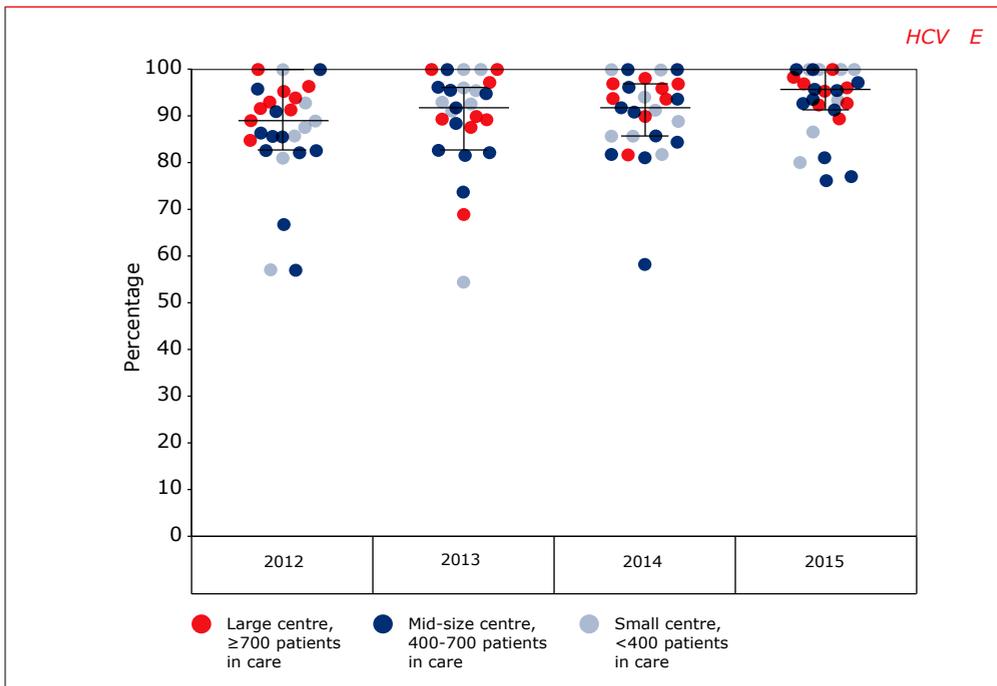
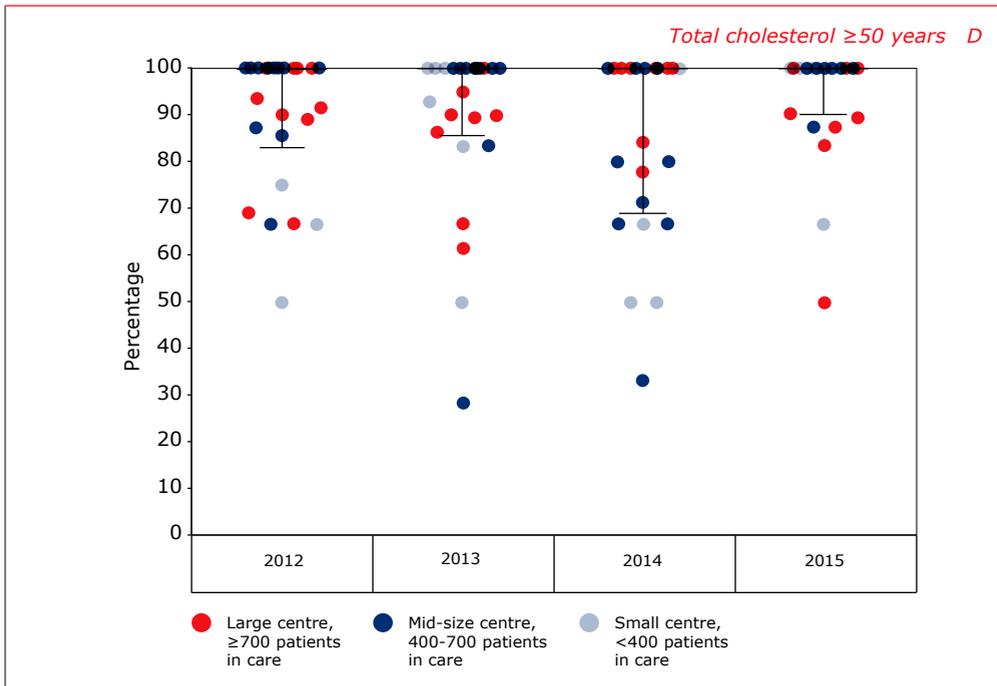
In terms of HCV screening, the maximum percentage of patients screened for HCV was 100% in all years, while the minimum rates were between 7% (2013) and 76% (2015). Overall, patients who were screened for HCV during their first year in care were more often MSM ( $p=0.002$ ). Among the patients who were not screened for HCV during their first six months in care, 45% of these had subsequently been tested for HCV subsequently: for this group the median time between entry into care and their first HCV test was 17 months (IQR: 12-25 months).

The maximum percentage of patients screened for HBV was 100% in all years, while minimum rates were 55% in 2013 and 70% in 2012.

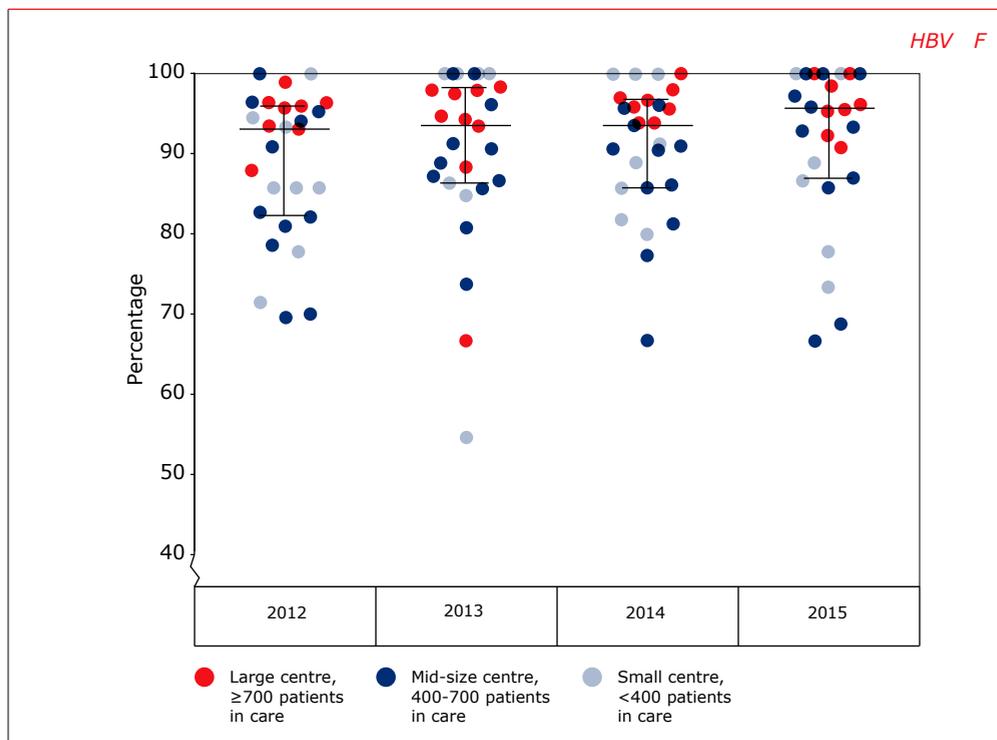
*Figure 7.6: Percentages of patients who newly entered care in Dutch HIV treatment centres in 2012–2015, with assessment within six months of (A) plasma CD4 cell count, (B) HIV RNA, (C) total cholesterol in patients aged <50 years at entry in care, (D) total cholesterol in patients aged  $\geq$ 50 years at entry in care, (E) hepatitis C, and (F) hepatitis B.*







Legend: HCV=hepatitis C.

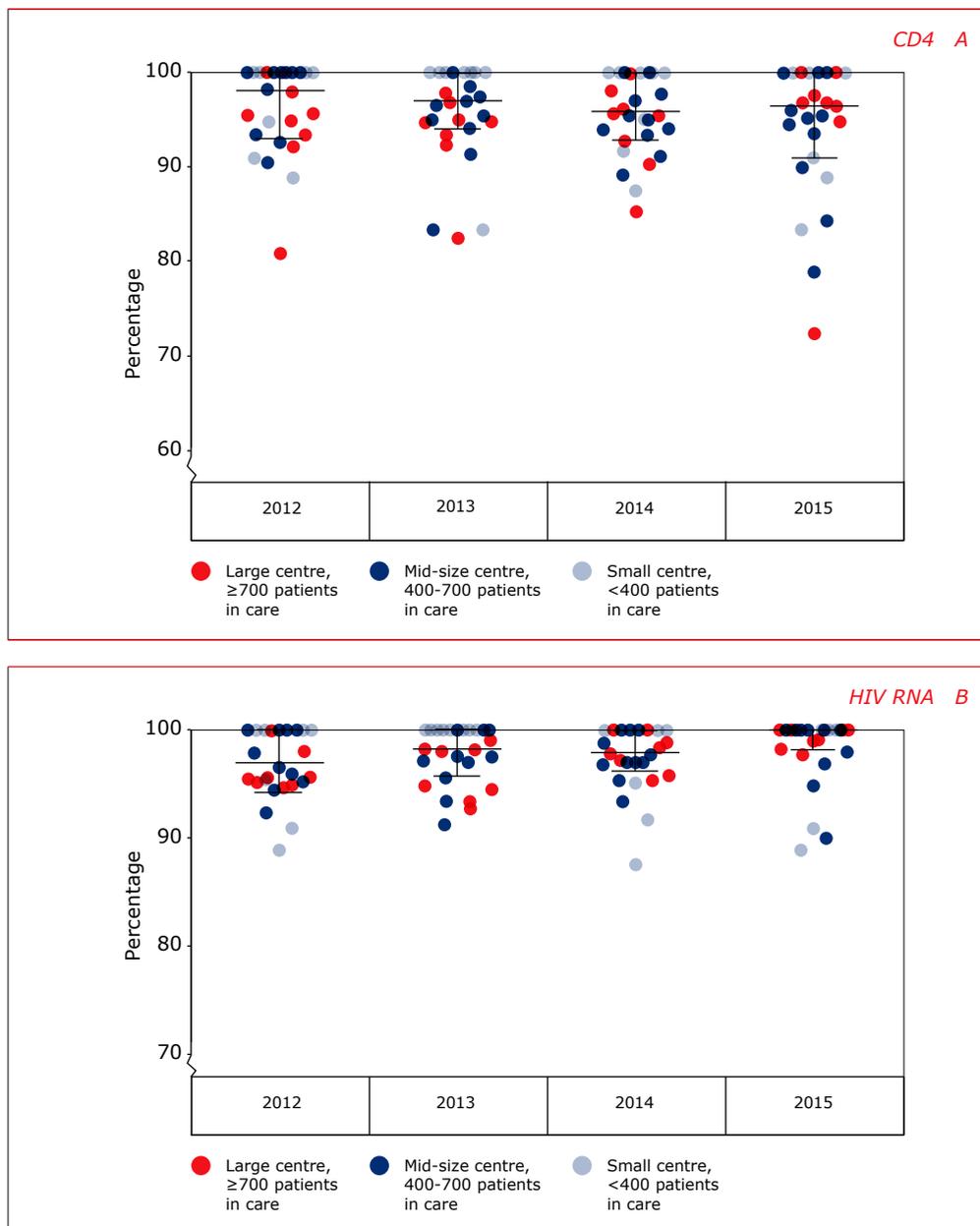


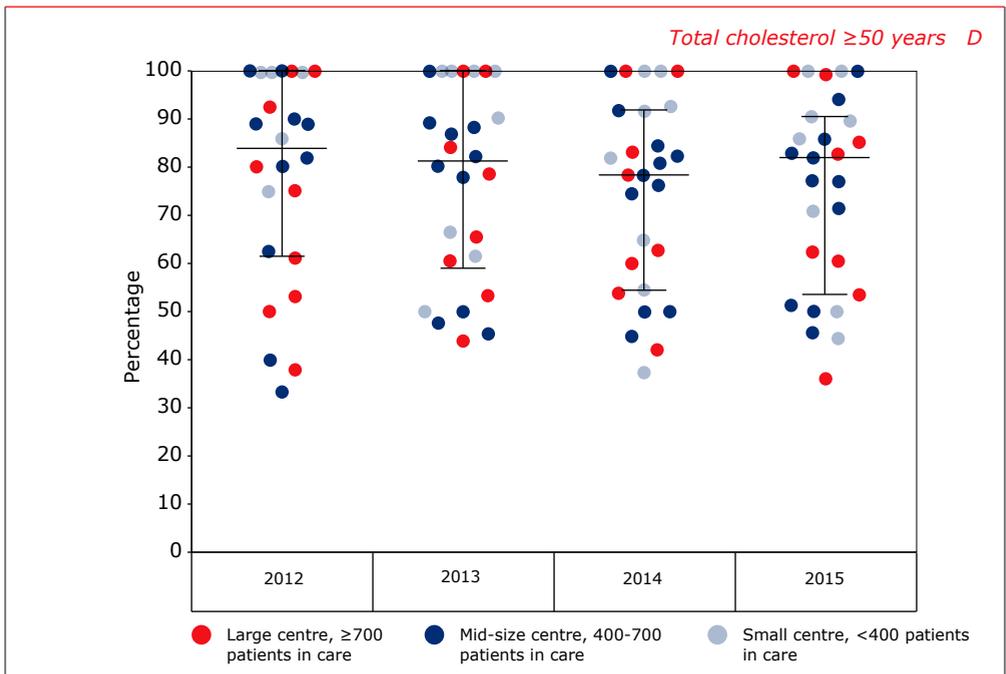
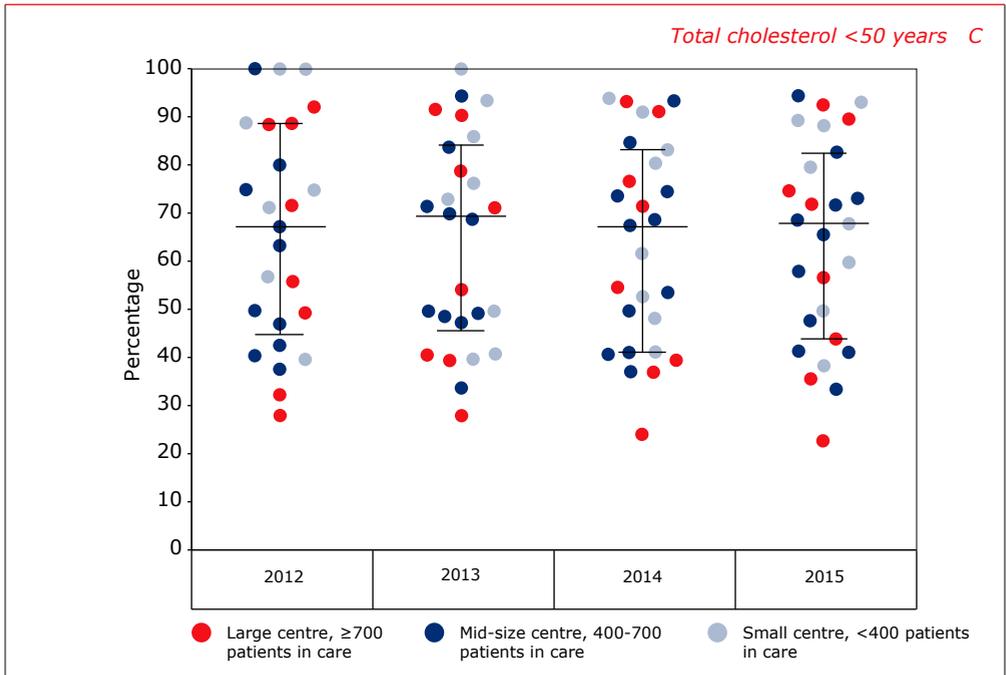
Legend: HBV=hepatitis B.

### 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, and total cholesterol (stratified by age) once within 13 months after cART initiation for all patients who initiated cART between 2012 and 2015 and who were still in care 12 months after starting cART. CD4 count and HIV RNA were assessed within 12 months after the start of cART in the majority of patients, although, for CD4 count, there was a minimum assessment rate of 72% in one HIV treatment centre. Unlike the assessment of CD4 count and HIV RNA, the assessment of total cholesterol following treatment initiation showed a large variation between treatment centres, irrespective of centre size and time-updated age (Figures 7.7C and 7.7D).

Figure 7.7: Percentages of patients in HIV treatment centres in the Netherlands who initiated combination antiretroviral therapy (cART) in 2012–2015, with assessment of (A) plasma CD4 cell count, (B) HIV RNA, (C) total cholesterol in patients aged <50 years at entry in care, and (D) total cholesterol in patients aged ≥50 years at entry in care within 13 months after start of cART.

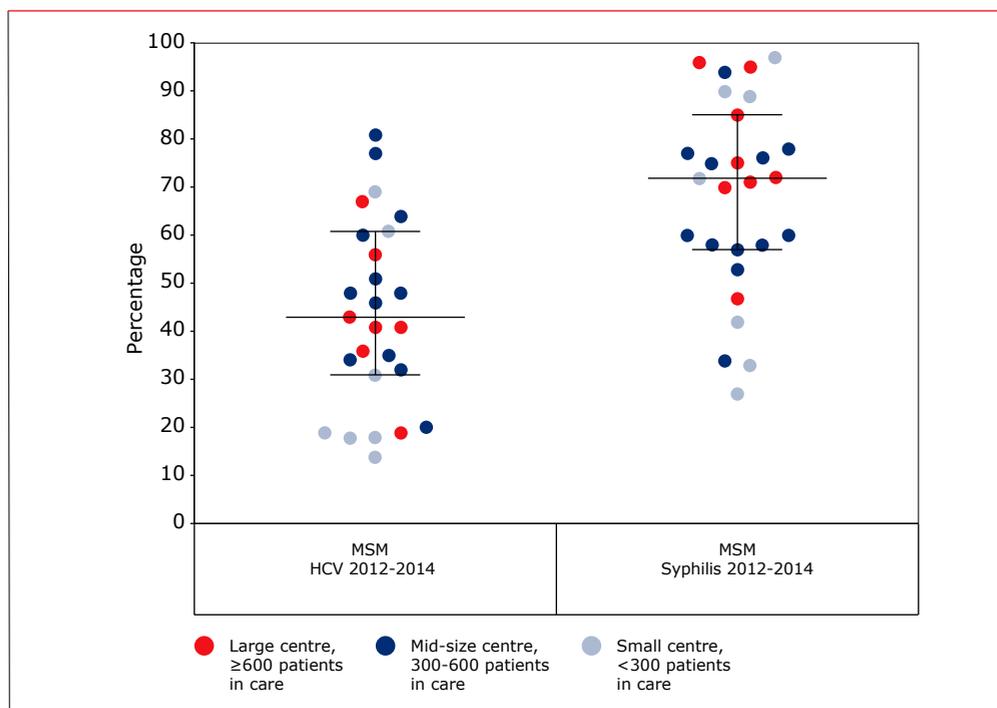




### Repeat screening for hepatitis C and syphilis in MSM

Between 2012 and 2014, 2,139 MSM newly entered care; of those, 1,960 (92%) were screened for the presence of HCV in the first year after entering care. Fifty-four (3%) of the 1,960 MSM tested positive for HCV. The remaining 1,906 (97%) 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 within 12 months for HCV among MSM who were HCV-negative at entry into care.

*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 into care and for syphilis among all MSM who entered care in one of the HIV treatment centres in 2012 and 2014.*



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

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 41%; the maximum percentage was 81%, while one centre carried out repeat HCV tests in only 14% of MSM who were HCV-negative at entry into care. In total 1,051 MSM were not repeatedly screened for the presence

of HCV. Of note, for 110 out of these 1,051 (10%) MSM, repeat HCV screening could not be documented despite having at least one elevated alanine aminotransferase level ( $\geq 75$  u/l) during the observation period. A high degree of variation was also observed between HIV treatment centres for repeat screening for syphilis among MSM during follow up. The maximum percentage of patients undergoing repeat syphilis screening was 97%, and the minimum was 27%, with a median of 70%.

## Key findings

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

- Most HIV treatment centres see more than 20 new patients per year. However, some 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.
- After exclusion of patients who died, overall and treatment centre-specific retention-in-care rates are generally high. However, lower retention rates were observed among patients of non-Dutch origin compared to patients born in the Netherlands.
- Over time, the proportion of patients initiating cART within six months after entering care clearly increased. However, considering that current guidelines recommend treatment for all patients regardless of CD4 count<sup>185</sup>, it is worth noting that relatively lower proportions for the start of cART within six months were observed for patients who entered care with a CD4 cell count  $>350$  CD4 cells/mm<sup>3</sup>; this was observed in small, mid-sized and large treatment centres.
- Viral suppression rates within six months after the start of cART were high; the median suppression rate was 98% in 2016, and among all patients who had been using cART for six months or longer, the median viral suppression rate was 97% in 2016.
- Although a large variation was observed in total cholesterol levels, HBV and HCV screening before the start of cART, the median proportions of patients being screened for cholesterol, HBV and HCV are increasing over time.
- In MSM who entered care between 2012 and 2014 and who were HCV-negative at entry into care, the rate of repeat HCV screening varied widely, from 14% to 81%. Of note, although the guidelines recommend repeated screening for HCV in MSM who report behaviour that may increase their risk of acquiring HCV, we are 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 between 2012 and 2014, repeat syphilis screening varied considerably from 27% to 97%.

## Conclusion

Overall, retention in care was high, but it was lower for patients of non-Dutch origin, which was also observed in the continuum of care presented in *Chapter 1* of this report. Of note, some of these patients of non-Dutch origin who were considered not retained in care may have moved abroad. Viral suppression rates in the first six months on cART, as well as with longer 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 entered care in earlier calendar years. However, although the proportion of patients starting cART within six months after entering care has increased, the rate of starting treatment among patients who entered care with CD4 cell counts above 350 cells/mm<sup>3</sup> needs further improvement in several centres. A large variation in the assessment of total cholesterol after cART initiation was also observed and may result in a large number of centres with inadequate data to calculate the CVD risk profile.

The variation in repeated HCV screening may, to some extent, be explained by physicians applying a policy of targeted screening only, in which they are guided by the presence of incident transaminase elevations. This is supported by the observation that 90% of the MSM not screened for HCV did not have elevated transaminase levels. However, in 10% of the MSM with clinically significant elevation of transaminases, HCV infection was not excluded by performing HCV testing. Furthermore, differences in the MSM population with respect to known risk-taking behaviour for HCV acquisition might contribute to the inter-centre variation in HCV screening.

Quality of care covers several aspects of health care<sup>190,191</sup>. As such, the wide range of indicators used in this analysis offers broad coverage of various aspects of HIV care and provides insight into care provision among the different treatment centres. Nonetheless, data reliability remains an important issue, and it should be recognised that some of the reported variation may have been introduced incidentally by missing data.

Finally, the variation between treatment centres may be used as a benchmark to compare centres and, accordingly, identify aspects that allow improvement. Therefore, we encourage treatment centres to scrutinise their individual indicator results to identify elements of care that may need improvement. In 2016, HIV treatment centres first received their centre-specific indicators compared to the blinded scores of other centres. Subsequently, many centres approached SHM for more specific data regarding their scores, and it is hoped such feedback may assist them in further improving their provision of care.

# Special reports

## 8. The Amsterdam Cohort Studies on HIV infection: annual report 2016

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 2016, the cohorts reached 32 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 32 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, in turn, 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 (*Gemeentelijke 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 AMC's Department of Experimental Immunology. 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, RIVM-CIb*).

### Ethics statement

The ACS have 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 2016

#### The cohort of men who have sex with men

As of 31 December 2016, 2,736 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 2,736 MSM, 607 were HIV-positive at entry into the study, and 251 seroconverted during follow up. In total, the GGD Amsterdam was visited 57,467 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  $\leq 30$  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 Centre. 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 those who seroconverted for HIV

during follow up within the cohort continue to return for study visits 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 2016, 630 HIV-negative, and 64 HIV-positive MSM were in active follow up within the ACS (6-monthly visits to the GGD Amsterdam for STI testing, including HIV). Of these 64 HIV-positive MSM, 62 filled in behavioural questionnaires. Apart from the HIV-positive MSM visiting the GGD Amsterdam, 267 HIV-positive MSM were followed outside the GGD Amsterdam at the Jan van Goyen Medical Centre or the HIV Focus Centre in Amsterdam. Behavioural questionnaires were filled in by 20 of these men. The median age of the total group of MSM was 44.5 years (interquartile range [IQR] 37.3-52.1), 8.2% were non-Dutch, and 72.8% had attained a high level of education. The majority of the participants (84.6%) were residents of Amsterdam. In 2016, 23 new HIV-negative MSM were recruited. The median age in this group was 23.9 years (IQR 23.2-26.6).

### **The cohort of drug users**

As of 31 December 2016, 1,680 people who use drugs (PWUD) were included in the ACS and contributed 28,194 visits. 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 also HIV-negative participants, underwent a medical examination. Blood was collected for diagnostic tests and storage.

In 2014, the cohort was closed for new participants and 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 consisted of PWUD who visited the GGD Amsterdam once a year to complete questionnaires with no testing and blood sampling. Group 2, the focus group, consisted of PWUD who were 1) HIV positive; 2) hepatitis C virus (HCV) seroconverters; 3) multiple-exposed, non-infected with HIV and HCV, and 4) a random control group. This group visited the GGD Amsterdam twice a year for testing and blood sampling and to fill out questionnaires, as in previous years. Regular follow up of drug users continued until February 2016. Finally, all drug users who had ever participated in the ACS were invited for an end-of-study interview. A total of 182 end-of-study interviews were held between February and July 2016, after which the follow up of drug users was successfully ended.

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 2016, 576 deaths had been confirmed among PWUD. The median age of the PWUD who visited the ACS in 2016 was 55 (IQR 49-59), 8.1% had attained a high level of education, and 63.4% were born in the Netherlands.

## ACS Biobank

The ACS visits, together with data collection from several subgroup studies and affiliated studies embedded in the ACS, have resulted in a large collection of stored samples. 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 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 HIV-positive and HIV-exposed children at the Emma Kinderziekenhuis in the AMC until 2008. All stored samples are available for ACS research.

## Subgroup studies and affiliated studies

### AGE<sub>n</sub>IV cohort study

The AGE<sub>n</sub>IV cohort study, a collaboration between the AMC Department of Infectious Diseases, Department of Global Health, 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-positive individuals aged  $\geq 45$  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 complete a questionnaire at intake and follow-up questionnaires every 2 years afterwards. In total, 598 HIV-1-positive participants and 550 HIV-negative individuals completed a baseline visit between October 2010 and September 2012. HIV-1-positive participants were included through the AMC HIV outpatient clinic and HIV-uninfected participants from similar risk groups through the STI clinic of the GGD Amsterdam (n=486) or the ACS (n=64). All participants were aged  $\geq 45$  years and were as comparable as possible with respect to age, gender, ethnicity, and risk behaviour. By the end of 2016, 437 HIV-1-positive participants and 457 HIV-negative individuals had completed the third follow-up visit. In October 2016 the fourth round of study visits started, which is expected to continue until summer 2019.

### 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 (n=459) and HIV-positive (n=40) participants of the ACS who were in active follow up, and also among patients of the STI clinic of GGD Amsterdam and 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-positive 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-positive MSM population. This study, the H2M2, is an Aids Fonds-supported project and a collaboration between the GGD Amsterdam, AMC, DC Klinieken Oud-Zuid, the RIVM-CIb, DDL diagnostic laboratories and VUmc. The study includes a subset of the HIV-positive participants of the ACS (n=19). In 2016, initial analyses showed that among 193 HIV-positive MSM, neither persistence of anal HPV infection nor HPV viral load in the anal mucosa nor anti-HPV antibodies in serum were good predictors of anal high-grade dysplasia.

Since September 2014, collection of anal and genital swabs has been resumed in all consenting ACS participants. The key aim of this second new study (the H2M3 study), which builds on the H2M study, is to examine long-term incidence and clearance of anal and penile hrHPV infections. The H2M3 study is a collaboration between GGD Amsterdam, ACS, and Crucell. Between September 2014 and November 2015, 700 men provided samples for HPV testing during ACS cohort visits. Of these, 434 (62%) were already participating in the H2M study (recruited 2010-2011), and 266 (38%) were new participants who joined the ACS after inclusion in the H2M study had ended. Samples at two time points (6 months apart) have been tested in the laboratory for HPV DNA, and initial analyses have been conducted. This study found that one-third of MSM had not cleared an anal HPV-16 infection after four years; thus, persistence of anal HPV is common. Twenty-two percent of men who were not infected with HPV-16 at baseline acquired an anal HPV-16 infection over a four-year period. So, even in highly pre-exposed men, the incidence rate of hrHPV infections is high.

### AMPrEP project in H-TEAM

The Amsterdam pre-exposure prophylaxis (AMPrEP) project is a prospective, longitudinal, open-label demonstration study. The aim of the study is to assess the uptake and acceptability of daily versus event-driven PrEP among MSM and transgender persons (TG) at increased risk for HIV infection, as part of a comprehensive HIV reduction package offered at a large STI clinic.

In total, 374 MSM and 2 TG were enrolled between August 2015 and May 2016 at the STI outpatient clinic of the GGD Amsterdam. In 2016, 35 ACS participants also participated in the AMPrEP project at their own initiative. Participants were asked to return for follow-up visits one month after the PrEP start visit and then every three months. At every visit participants fill in questionnaires on risk behaviour, adherence and general wellbeing and are screened for STI and HIV. Participants will be provided with PrEP until June 2018.

The AMPrEP project is part of the HIV Transmission Elimination Amsterdam (H-TEAM) initiative, a multidisciplinary and integrative approach to stop the epidemic ([www.hteam.nl](http://www.hteam.nl)).

## The HIV epidemic

### HIV incidence

In 2016, 3 MSM participating in the ACS seroconverted for HIV. The observed HIV incidence among MSM has remained relatively stable in recent years and was 0.5 per 100 person years in 2016. The HIV incidence in PWUD has been stable since 2008, with between zero to less than one case per 100 person years. As follow up was restricted to a selection of PWUD and inclusion stopped in 2014, followed by closure of the cohort in 2016, 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 2016 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), 1985–2016.

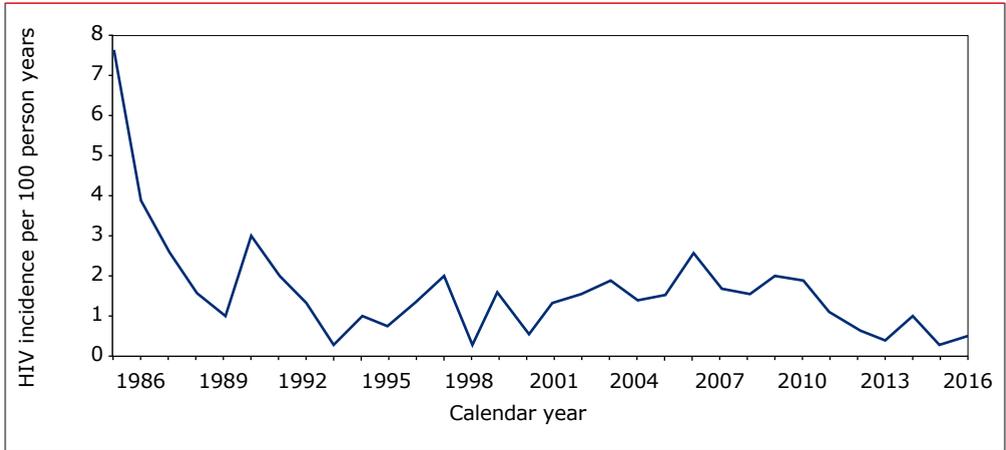
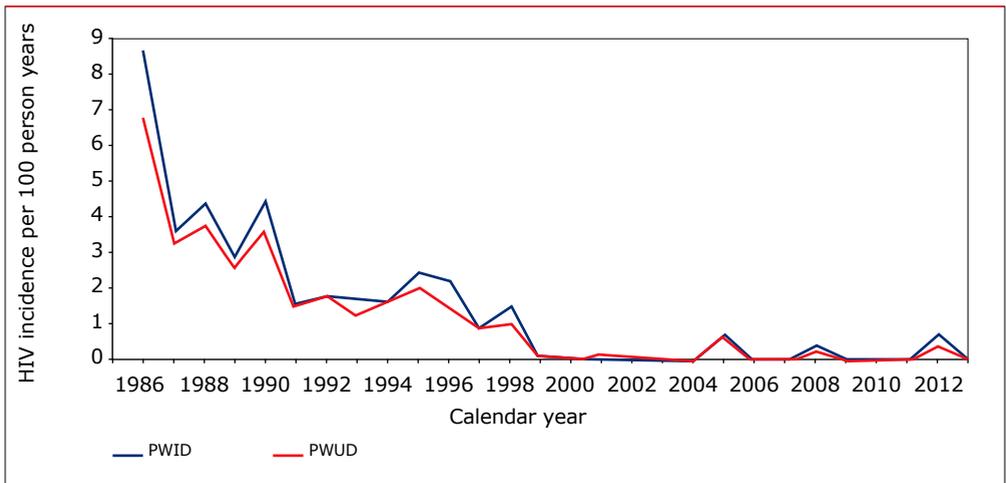


Figure 8.2: HIV incidence per calendar year in the Amsterdam Cohort Studies (ACS) among people who use drugs, 1986–2013.



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

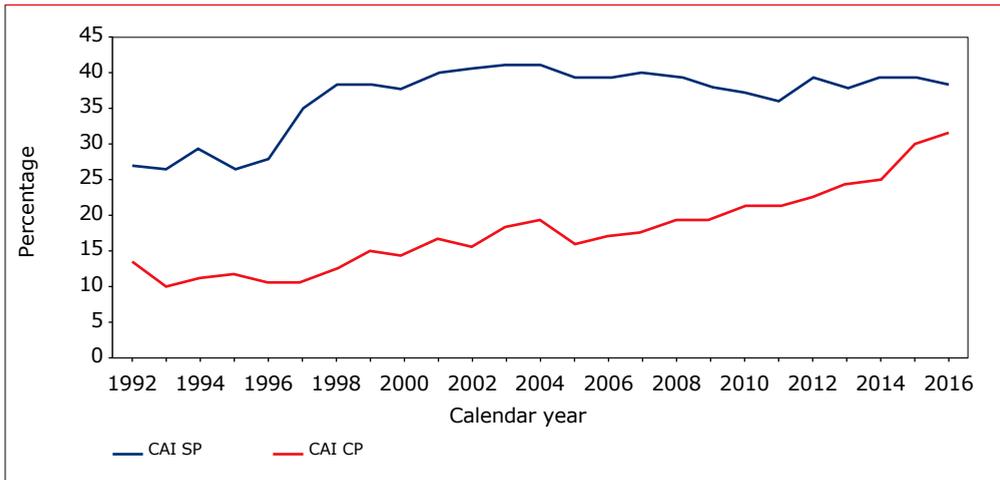
### Combination antiretroviral therapy (cART) uptake

Of all 320 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 2016, treatment data were available for 317 men. Of these, 314 (99%) received some form of antiretroviral therapy. Of the 308 MSM for whom viral load results were available in 2016, 286 (93%) had a viral load of <50 copies/ml (M2000rt assays).

### Risk behaviour of MSM in ACS

Information from the questionnaires completed by 610 HIV-negative MSM during cohort visits in 2016 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 participating in the ACS, especially CAI 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 who have sex with men (MSM) with a casual and/or steady partner, 1992–2016.



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

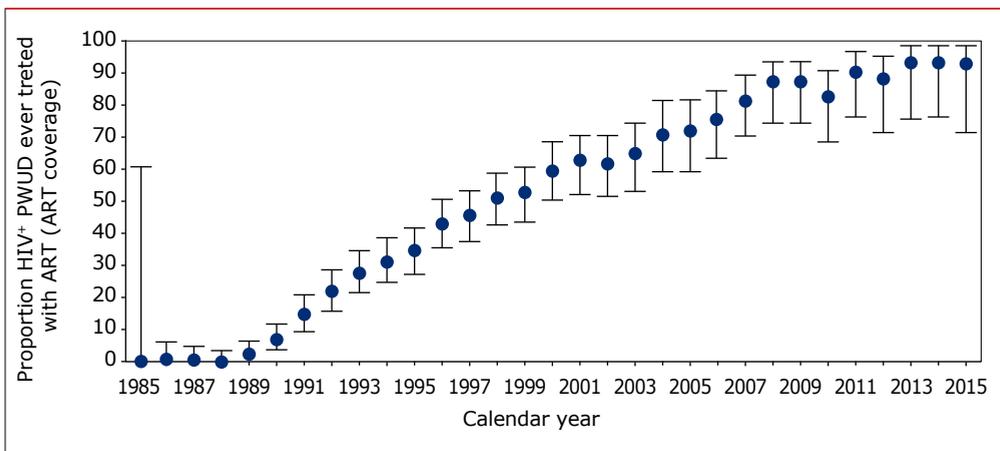
### STI screening among MSM in ACS

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 2016, a total of 665 MSM from the ACS were screened for STI. The overall prevalence of any STI (i.e., chlamydia, gonorrhoea, syphilis, or HCV) was 15.9% (99/621) among HIV-negative MSM and 29.5% (13/44) among HIV-positive MSM.

### HIV and HCV treatment uptake among PWUD in ACS

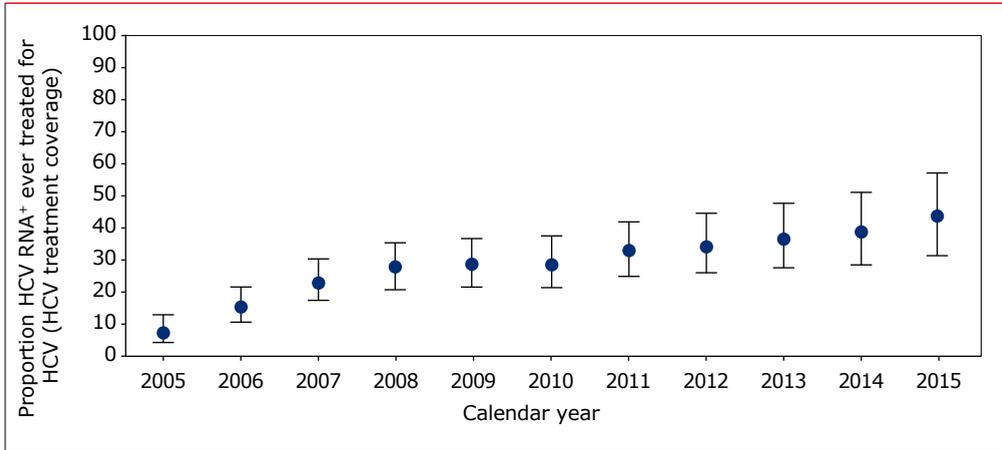
ART coverage increased over time, from 5.7% in 1990 and 42.2% in 1996 to 91.7% in 2015 (see *Figure 8.4*). The proportion of PWUD initiating ART ranged from 4.8% in 1990 to 33.3% in 2011. At eight years after HIV seroconversion, the cumulative probability of ART uptake was 42.5% in the pre-cART era and 61.5% in the cART era. HCV treatment initiation peaked in 2006 (9.7%). HCV treatment coverage was 43.9% in 2015 (see *Figure 9.5*), but lower among HIV co-infected (23.5%) than HCV mono-infected PWUD (52.5%). In 2015, 3.0% initiated HCV treatment with direct-acting antivirals<sup>192</sup>.

*Figure 8.4: The proportion of HIV-positive people who use drugs (PWUD) participating in the Amsterdam Cohort Studies (ACS) ever treated with ART, 1989–2015<sup>92</sup>.*



*Legend: PWUD=people who use drugs; ART=antiretroviral therapy.*

Figure 8.5: The proportion HCV RNA-positive people who use drugs (PWUD) participating in the Amsterdam Cohort Studies (ACS) ever treated for HCV, 2005–2015<sup>192</sup>.

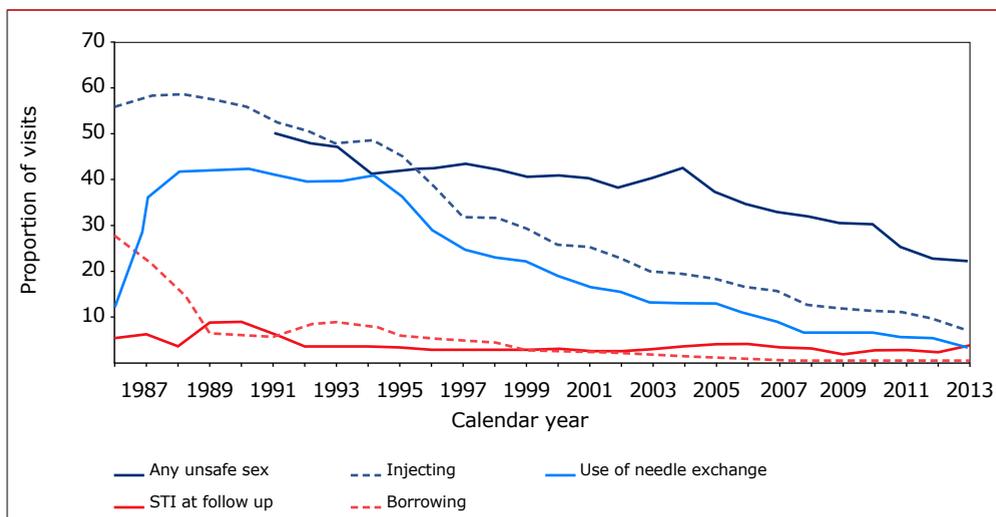


Legend: HCV=hepatitis C virus.

#### Risk behaviour of PWUD in ACS

As follow up was restricted to a selection of PWUD and inclusion stopped in 2014, and the cohort was closed in 2016, 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 8.6*).

Figure 8.6: Proportion of visits per calendar year at which injecting and high-risk sexual behaviour was reported amongst people who use drugs (PWUD) who were HIV-negative on entry to the Amsterdam Cohort Studies (ACS), 1986–2013.



Legend: STI=sexually transmitted infection.

## ACS 2016 research highlights

### IP-10, a marker of HIV-1 disease progression

Elevated blood CXCL10/IP-10 levels during primary HIV-1 infection have been described as an independent marker of rapid disease onset and one that is more robust than peak viraemia or CD4 cell nadir. IP-10 enhances the recruitment of CXCR3+ cells, which include major HIV target cells, raising the question whether it promotes the establishment of viral reservoirs. Data from four cohorts of HIV+ patients were analysed, allowing us to study IP-10 levels before infection (data from ACS), as well as during controlled and uncontrolled viraemia (data from ANRS cohorts). Pre-existing elevated IP-10 levels, but not sCD163, were associated with rapid CD4 T-cell loss upon HIV-1 infection. During primary HIV infection, IP-10 levels, and to a lesser extent IL-18 levels, correlated with cell-associated HIV DNA, while 26 other inflammatory soluble markers did not. IP-10 levels tended to differ between HIV controllers with detectable and undetectable viraemia<sup>193</sup>.

### New target to tackle HIV

Monoclonal antibodies were isolated from an elite neutraliser from the ACS. We found an antibody with very potent neutralising properties. Using negative stain electron microscopy and other techniques, we found that this antibody bound to a novel target epitope, showing the fusion peptide on the envelope glycoprotein needed to infect target cells as a site of vulnerability. In addition, we also constructed soluble native-like envelope glycoproteins from early virus variants of the same elite neutraliser. The availability of a native-like Env trimer and a broadly neutralising antibody (bNAb) from the same elite neutraliser opens new avenues for HIV vaccine design aimed at generating similar bNAbs against a key functional site on HIV<sup>194</sup>.

### The power of the ACS: tracing the origin of the hepatitis B virus (HBV) G variant in Amsterdam

HBV genotype G (HBV-G) is an aberrant genotype with little sequence divergence, suggesting that it has a recent origin. HBV-G is also strongly associated with people who inject drugs (PWID) and MSM. To estimate the prevalence and possible time of introduction of HBV-G into the MSM community in Amsterdam, we retrospectively analysed 226 blood plasma samples from HBsAg positive MSM enrolled in the ACS dating from 1984-1999 using HBV genotype-specific PCR assays. Of the 226 ACS samples, 149 were HBV DNA positive. Of those, 104 were HBV-A+, 5 were HBV-G+ and 40 showed a dual infection with HBV-A and HBV-G. Infection with HIV-1 was significantly associated with a lower HBV DNA plasma viral load (pVL), but not with the prevalence of HBV-G. Early virus isolates from 1985 already contained the typical HBV-G characteristics: stopcodons in the preCore region and a 36-nt insert in the core gene. In addition, a G1776A mutation was observed in half of the strains. Thus, HBV-G was introduced into the Amsterdam MSM community before 1985. These early isolates show extremely limited sequence variation with modern isolates, suggesting a low evolutionary rate. HBV-G acquisition was independent of HIV-1 infection, but HIV-1 infection was associated with a significantly reduced HBV pVL, indicating a beneficial effect of initial HIV-1 infection on HBV replication<sup>195</sup>.

### Group sex

The association between group sex and lower condom use during anal sex and higher proportions of STI were assessed and compared to dyadic sex among HIV-negative MSM between 2009 and 2012. The sample consisted of 465 MSM who either reported *both* group and dyadic sex (at n=706 visits) or dyadic sex *only* (at n=1339 visits) in the preceding six months. Logistic regression with generalised estimating equations was used to investigate the association between sexual setting (group versus dyadic sex), CAI, and STI. Group sex was reported at 35%

(706/2045) of visits. Condomless sex was more often reported during dyadic than group sex (odds ratio [OR] 3.64; 95% CI 2.57–5.16). Men who had group sex were more likely to be diagnosed with gonorrhoea compared to men with dyadic sex (OR 1.71; 95% CI 1.08–2.97), but this effect was not retained in the multivariable model. Results demonstrate that MSM are more likely to use condoms during group sex than dyadic sex. Thus, for some, group sex may not necessarily be risky for HIV infection compared with dyadic sex. However, group sex may be a higher-risk setting for acquiring STIs other than HIV, such as gonorrhoea<sup>200</sup>.

### Cost-effectiveness of HCV treatment among PWID

The cost-effectiveness of four HCV treatment strategies among PWID and treatment scale-up were assessed. An individual-based mathematical model was used describing HIV and HCV transmission and disease progression among PWID in a declining HCV epidemic, as observed in Amsterdam, and a stable HCV epidemic. We assessed the incremental cost-effectiveness ratio (ICER, costs in /quality-adjusted life year (QALY)) of four treatment strategies: 1) PegIFN/RBV; 2) sofosbuvir/RBV for genotype 2±3 and dual DAA for genotype 1±4; 3) Dual DAA for all genotypes; 4) Dual DAA with 3x treatment uptake. In both types of epidemic, dual DAA therapy was the most cost-effective strategy. In the declining epidemic, dual DAA yielded an ICER of 344/QALY, while in the stable epidemic dual DAA led to cost-savings. Scaling-up treatment was also highly cost-effective. We conclude that HCV treatment with DAA-containing regimens is a highly cost-effective intervention among PWID<sup>196</sup>.

### Steering committee

In 2016, the steering committee met three times. Twelve proposals for use of data and/or samples (serum/PBMC) were submitted to the committee: six from the AMC Medical Microbiology department, four from the AMC Experimental Immunology, and 2 from GGD Amsterdam. Eight of the proposals were collaborations with groups outside the ACS. Nine requests were approved, and three were declined even after revision.

## Publications in 2016 that include ACS data

1. **Motives of Dutch men who have sex with men for daily and intermittent HIV pre-exposure prophylaxis usage and preferences for implementation: A qualitative study.** [Bil JP, van der Veldt WM, Prins M, Stolte IG, Davidovich U. \*Medicine \(Baltimore\)\*. 2016;95\(39\):e4910](#)
2. **Changing incidence and risk factors for Kaposi sarcoma by time since starting antiretroviral therapy: Collaborative analysis of 21 European cohort studies.** [Cancer Project Working Group for the Collaboration of Observational HIV Epidemiological Research Europe \(COHERE\) study in EuroCoord. \*Clin Infect Dis\*. 2016; 63\(10\):1373-1379](#)
3. **The neutralizing antibody response in an individual with triple HIV-1 infection remains directed at the first infecting subtype.** [Cornelissen M, Euler Z, Van den Kerkhof TLGM, Van Gils MJ, Boeser-Nunnink BDM, et al. \*AIDS Res Hum Retroviruses\*. 2016;32\(10-11\):1135-1142](#)
4. **Widespread hepatitis B virus genotype G (HBV-G) infection during the early years of the HIV-1 epidemic in Dutch men having sex with men.** [Cornelissen M, Zorgdrager F, Bruisten SM, Bakker M, Berkhout B, van der Kuyl AC. \*BMC Infect Dis\*. 2016; 16:268](#)
5. **HCV mono-infection and HIV/HCV coinfection enhance T-cell immune senescence in injecting drug users early during infection.** [Grady BP, Nanlohy NM, van Baarle D. \*Immun Ageing\*. 2016;13:10](#)
6. **Higher rates of triple-class virological failure in perinatally HIV-infected teenagers compared with heterosexually infected young adults in Europe.** [Judd A, Lodwick R, Noguera-Julian A, Gibb DM, Butler K, et al. Pursuing Later Treatment Options II \(PLATO II\) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe \(COHERE\) in EuroCoord. \*HIV Med\*. Sept. 2016 \[Epub ahead of print\]](#)
7. **Hepatitis C virus broadly neutralizing monoclonal antibodies isolated 25 years after spontaneous clearance.** [Merat SJ, Molenkamp R, Wagner K, Koekkoek SM, van de Berg D, et al. \*PLoS One\*. 2016;11\(10\):e0165047](#)
8. **The effect of HIV infection on anal and penile human papillomavirus incidence and clearance: a cohort study among MSM.** [Mooij SH, van Santen DK, Geskus RB, van der Sande MA, Coutinho RA, et al. \*AIDS\*. 2016;30\(1\):121-32.](#)

9. **Limiting cumulative HIV viremia copy-years by early treatment reduces risk of AIDS and death.** Olsen AD, Walker AS, Suthar AB, Sabin C, Bucher HC, et al. CASCADE Collaboration in EuroCoord. *J Acquir Immune Defic Syndr.* 2016;73:100-108
10. **A novel astrovirus-like RNA virus detected in human stool.** Oude Munnink BB, Cotten M, Canuti M, Deijs M, Jebbink MF, et al. *Virus Evol.* 2016;2(1):vew005
11. **A novel genus in the order Picornavirales detected in human stool.** Oude Munnink BB, Cotten M, Deijs M, Jebbink MF, Bakker M, et al. *J Gen Virol.* 2015;96(11):3440-3
12. **Interferon lambda 4 genotype is associated with jaundice and elevated aminotransferase levels during acute hepatitis C virus infection: findings from the InC3 Collaborative.** Page K, Mirzazadeh A, Rice TM, Grebely J, Kim AY, et al. *Open Forum Infect Dis.* 2016;3:ofw024
13. **The impact of transient combination antiretroviral treatment in early HIV infection on viral suppression and immunologic response in later treatment.** Pantazis N, Touloumi G, Meyer L, Olson A, Costagliola D, et al. CASCADE Collaboration in EuroCoord. *AIDS.* 2016;30(6):879-888
14. **Kaposi sarcoma risk in HIV-infected children and adolescents on combination antiretroviral therapy from sub-Saharan Africa, Europe, and Asia.** Pediatric AIDS-Defining Cancer Project Working Group for IeDEA Southern Africa, TAPHOD, and COHERE in EuroCoord. *Clin Infect Dis.* 2016;63(9):1245-1253
15. **Elevated basal pre-infection CXCL10 in plasma and in the small intestine after infection are associated with more rapid HIV/SIV disease onset.** Ploquin MJ, Madec Y, Casrouge A, Huot N, Passaes C, et al. *PLoS Pathog.* 2016;12(8):e1005774
16. **Historical trends in the hepatitis C virus epidemics in North America and Australia.** Rodrigo C, Eltahla AA, Bull RA, Grebely J, Dore GJ, et al. InC3 Study Group. *J Infect Dis.* 2016;214(9):1383-1389
17. **The effects of alcohol on spontaneous clearance of acute hepatitis C virus infection in females versus males.** Tsui JJ, Mirzazadeh A, Hahn JA, Maher L, Bruneau J, et al. *Drug Alcohol Depend.* 2016;169:156-162

18. **Is group sex a higher-risk setting for HIV and other sexually transmitted infections compared with dyadic sex among men who have sex with men?** Van den Boom W, Davidovich U, Heuker J, Lambers F, Prins M, et al. *Sex Transm Dis.* 2016;43(2):99-104
19. **HIV-1 escapes from N332-directed antibody neutralization in an elite neutralizer by envelope glycoprotein elongation and introduction of unusual disulfide bonds.** Van den Kerkhof TL, de Taeye SW, Boeser-Nunnink BD, Burton DR, Kootstra NA, et al. *Retrovirology.* 2016;13(1):48
20. **Probability of N332 glycan occupancy on HIV-1 gp120 modulates sensitivity to broadly neutralizing antibodies.** Van den Kerkhof TLGM, Van Gils MJ, Boeser-Nunnink BD, Burger, JA, Schuitemaker H, Sanders RW. *AIDS.* 2016;30(14):2179-84
21. **An HIV-1 antibody from an elite neutralizer implicates the fusion peptide as a site of vulnerability.** Van Gils MJ, Van den Kerkhof TLGM, Ozorowski G, Cottrell CA, Sok D, et al. *Nature Microbiology* 2016;2:16199
22. **Cost-effectiveness of hepatitis C treatment for people who inject drugs and the impact of the type of epidemic; extrapolating from Amsterdam, the Netherlands.** Van Santen DK, de Vos AS, Matser A, Willems SB, Lindenburg K, et al. *PLoS One.* 2016;11(10):e0163488
23. **Children and young people with perinatal HIV in Europe: epidemiological situation in 2014 and implications for the future.** Writing group for the Kids to Adults Working Group and Data Management and Harmonisation Group in EuroCoord. *Euro Surveill.* 2016;21(10):1-7

#### Theses in 2016 that include ACS data

Laurentia Setiawan – 19 April 2016:  
**HIV-1 adaptation to the host.**  
 Supervisor: Prof. T.B.H. Geijtenbeek (AMC); co-supervisor: Dr. N.A. Kootstra (AMC).

Bas Oude Munnink – 22 June 2016:  
**The challenges of virus discovery in human fecal samples.**  
 Supervisor: Prof. M.D. de Jong (AMC); co-supervisor: Dr. L van der Hoek (AMC).

Tom van den Kerkhof – 21 April 2016:  
**HIV-1 vaccine design: Learning from natural infection.**  
 Supervisor: Prof. J. Schuitemaker (AMC); co-supervisor: Dr R.W Sanders (AMC).

Joost Vanhommerig – 23 September 2016: **Epidemiology and diagnosis of acute hepatitis C virus infection.** Supervisor: Prof. M. Prins (AMC/GGD Amsterdam); co-supervisors: Dr. C.J. Schinkel (AMC) and Dr. S.M. Bruisten (GGD).

Titia Heijman – 22 december 2016: **From insights into STI testing strategies to sexual risk dynamics in MSM.** Supervisor: Prof. M. Prins (AMC/GGD Amsterdam); co-supervisors: Dr. E. Davidovich (GGD Amsterdam) and Dr. I.G. Stolte (GGD Amsterdam).

## 9. Curaçao

Diederik van de Wetering, Gonneke Hermanides, Ashley Duits, Ard van Sighem

### Introduction

For more than 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 and gives 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.

#### In memoriam Carel Nicolaas Winkel

1948-2016

Cai Winkel, the first HIV physician in Curaçao, passed away in November 2016 at the age of 68. For more than 25 years, Winkel ran the only HIV outpatient clinic in Curaçao. He made combination antiretroviral therapy available for all people living with HIV on the island, tirelessly taking care of every patient. He was co-founder of AIDS Stichting Nederlandse Antillen. He was always willing to participate in the many international and national initiatives to combat the HIV epidemic or to improve the HIV care in Curaçao. He supported the Epidemiology Department of the GGD in Curaçao in anonymous surveillance reporting and made national online monitoring of HIV treatment possible in collaboration with SHM. Winkel was an inspiring mentor for medical students and health care workers at the St Elisabeth Hospital. In addition to his clinical work, Winkel had many other interests that gave him a wide network of friends. He will be remembered for his affectionate personality, loyalty and great hospitality and will be missed by his patients, friends, family and the community of Curaçao.

### People in clinical care

In total, 580 (55%) of all 1,054 registered patients remained in clinical care by the end of 2016. People were considered to be in clinical care if they visited their treating physician in 2016 or had a CD4 count or HIV RNA measurement in that year and were still living in Curaçao. Of the 474 individuals who were no longer in clinical care, 175 (17%) were known to have died, and 10 (2%) to have moved abroad, while 2 people were diagnosed with HIV only in 2017. Thus, 287 individuals, or 27%

of all registered patients, were considered lost to follow up. Loss to care was lowest for people originating from the former Dutch Antilles: 29% of those who entered HIV care between 2006 and 2015 were estimated to be lost to care after five years. Of the individuals originating from Haiti or the Dominican Republic, 37% were lost to care after five years, as were 39% of individuals originating from other regions. *Table 9.1* summarises the characteristics of the 580 HIV-positive individuals in clinical care in Curaçao at the end of 2016.

*Table 9.1: Characteristics of the 580 HIV-positive individuals in clinical care in Curaçao by the end of 2016.*

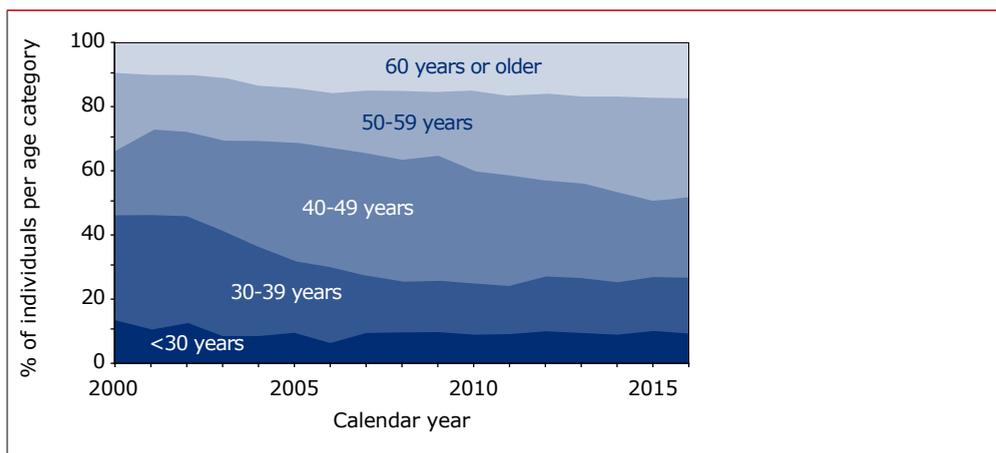
	Men (n=356, 61%)		Women (n=224, 39%)		Total (n=580)	
	n	%	n	%	n	%
<b>Transmission</b>						
MSM	143	40	-	-	143	25
Heterosexual	165	46	207	92	372	64
Other/unknown	48	13	17	8	65	11
<b>Current age (years)</b>						
0-12	0	0	0	0	0	0
13-17	0	0	0	0	0	0
18-24	14	4	10	4	24	4
25-34	51	14	28	13	79	14
35-44	73	21	41	18	114	20
45-54	112	31	77	34	189	33
55-64	71	20	42	19	113	19
65-74	29	8	19	8	48	8
≥75	6	2	7	3	13	2
<b>Country of origin</b>						
Former Netherlands Antilles	292	82	141	63	433	75
Dominican Republic	8	2	40	18	48	8
Haiti	20	6	23	10	43	7
The Netherlands	13	4	1	0	14	2
Other	23	6	19	8	42	7
<b>Years aware of HIV infection</b>						
<1	29	8	11	5	40	7
1-2	46	13	23	10	69	12
3-4	51	14	32	14	83	14
5-10	85	24	53	24	138	24
10-20	107	30	80	36	187	32
>20	35	10	23	10	58	10
Unknown	3	1	2	1	5	1

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

## Ageing population

The median age of the population in clinical care by the end of 2016 was 49 (interquartile range [IQR], 39-57) years 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 individuals after the introduction of combination antiretroviral treatment (cART). As a result, almost half of all people currently in care (48%) are 50 years or older, including 49% of men and 46% of women; 17% of the individuals are 60 years or older. The median age of people diagnosed with HIV between 2005 and 2016 was 40 (IQR, 30-49) years and did not change over time; 23% were 50 years or older at the time of diagnosis.

*Figure 9.1: Increasing age of the HIV-positive population in clinical care in Curaçao over calendar time. In 2000, 13% of the people in care were younger than 30 years of age, whereas 28% were 50 years or older. In 2016, these proportions were 9% and 48%, respectively, while 17% of people in care were 60 years of age or older. The proportion of people in clinical care as of 31 December 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.*



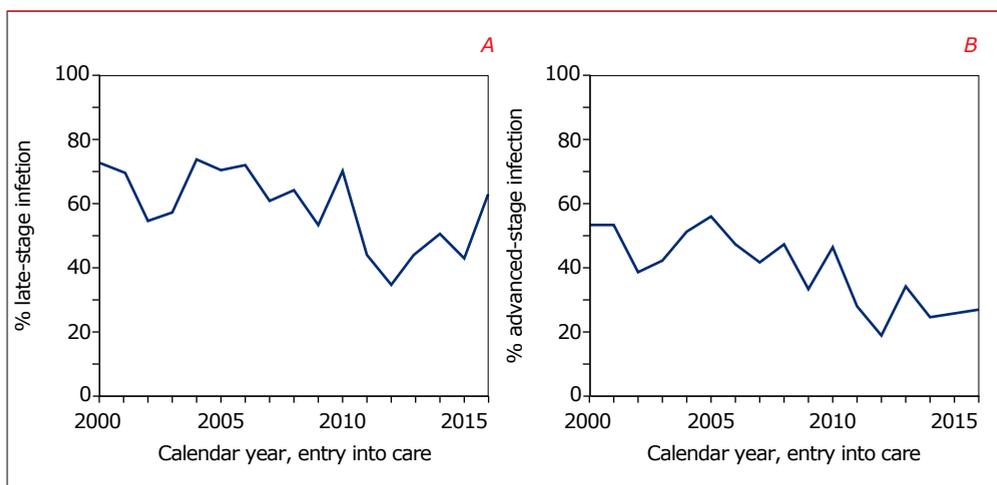
## Duration of infection

People in clinical care by the end of 2016 had been diagnosed with HIV a median of 8.3 (IQR, 3.7-14.5) years previously. Thus, a large group (42%) of those in care had been living with HIV for more than 10 years, while 10% had done so for more than 20 years. The median time since diagnosis was 7.3 years for men who have sex with men (MSM), 8.6 years for other men, and 8.8 years for women.

## Late presentation and start of treatment

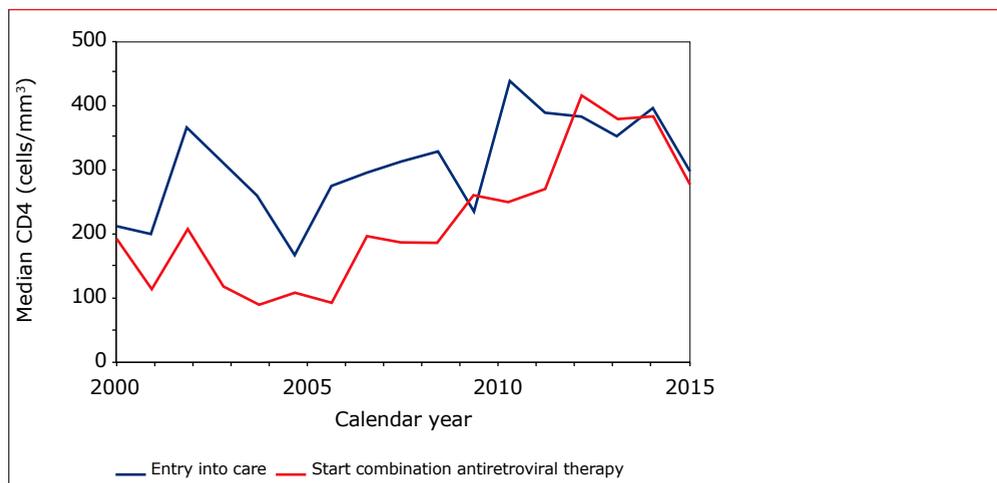
Overall, 58% of the people who have entered care since 2000 were late presenters, i.e., individuals either presenting for care with a CD4 count below 350 cells/mm<sup>3</sup> or presenting with an AIDS-defining event regardless of CD4 count<sup>3</sup>. Although the proportion of late presenters has decreased over time, 52% of individuals entering care in 2014 or later were late presenters (*Figure 9.2; Appendix Table 9.1*). In addition, the proportion of people presenting for care with advanced HIV disease, i.e., with a CD4 count less than 200 cells/mm<sup>3</sup> or AIDS, has decreased over time and has been at an average of 25% since 2014.

*Figure 9.2: Proportion of people classified as presenting with (A) late-stage or (B) advanced-stage HIV infection at the time of entry into care. From 2000 (2014) onwards, 58% (52%) presented with late HIV disease while 38% (25%) were advanced presenters. Late-stage HIV infection: CD4 counts below 350 cells/mm<sup>3</sup> or having AIDS, regardless of CD4 count. Advanced-stage HIV infection: CD4 counts below 200 cells/mm<sup>3</sup> or having AIDS.*



In recent years, there has been an increase in CD4 cell counts at the start of cART (*Figure 9.3; Appendix Table 9.1*). Between 2014 and 2016, 26% of the people for whom a CD4 count was available at the start of cART had less than 200 CD4 cells/mm<sup>3</sup>, 24% had CD4 counts between 200 and 349 cells/mm<sup>3</sup>, 29% had CD4 counts between 350 and 499 cells/mm<sup>3</sup>, and 28% had CD4 counts of 500 cells/mm<sup>3</sup> or higher. During the same period, 98% of the people entering care with less than 350 cells/mm<sup>3</sup>, 91% of those with CD4 counts between 350 and 499 cells/mm<sup>3</sup>, and 92% of patients with 500 CD4 cells/mm<sup>3</sup> or more received treatment within six months.

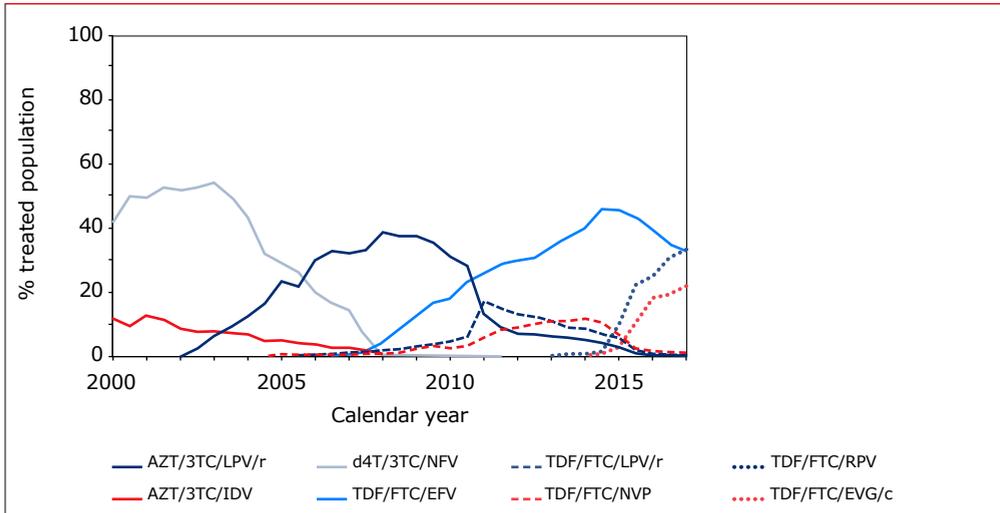
**Figure 9.3:** Changes over calendar time in median CD4 counts at entry into care and at the start of combination antiretroviral therapy (cART). Between 2000 and 2016, the median CD4 count at the time of entry into care increased from 214 cells/mm<sup>3</sup> (interquartile range [IQR], 105–407) to 302 (164–541) cells/mm<sup>3</sup>. During the same period, CD4 counts at start of cART increased from 195 cells/mm<sup>3</sup> (69–336) to 281 (146–463) cells/mm<sup>3</sup>.



## Combination treatment

In total, 898 (85%) of the 1,054 registered patients started cART (*Appendix Table 9.1*). Over time, there have been clear shifts in the treatment regimens prescribed in Curaçao (*Figure 9.4*). Around 2008, a combination of zidovudine/lamivudine and ritonavir-boosted lopinavir was frequently prescribed. At the end of 2016, the most commonly prescribed regimens were a combination of tenofovir/emtricitabine with either rilpivirine, efavirenz, or cobicistat-boosted elvitegravir. Of the 575 patients who started cART and were still in care by the end of 2016, 31% were being treated with tenofovir/emtricitabine/rilpivirine, 31% with tenofovir/emtricitabine/efavirenz, and 27% with tenofovir/emtricitabine/cobicistat-boosted elvitegravir. The majority of the patients (95%) used a once-daily regimen.

**Figure 9.4:** Percentage of people treated with combination antiretroviral therapy (cART) by specific regimens over calendar time. At the end of 2016, 33% of the patients were receiving RPV/TDF/FTC, 33% TDF/FTC/EFV, and 22% TDF/FTC/EVG/c.

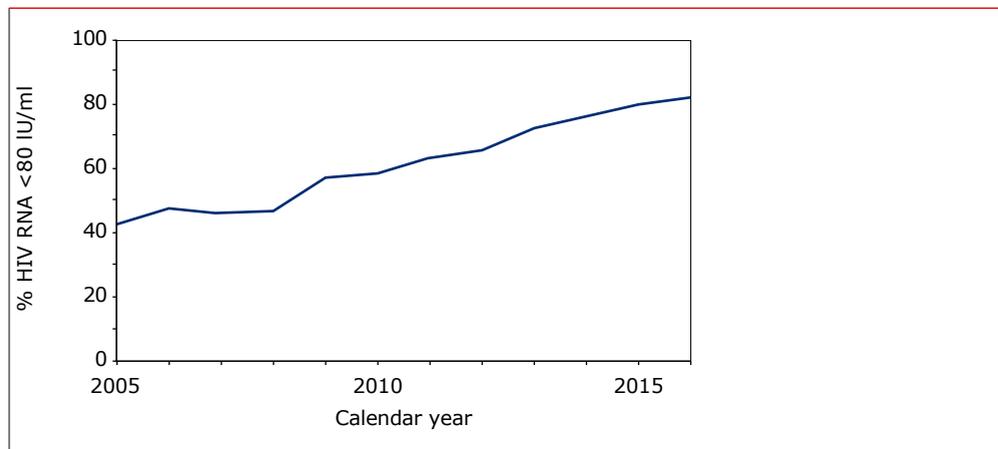


**Legend:** AZT=zidovudine; 3TC=lamivudine; LPV/r=ritonavir-boosted lopinavir; d4T=stavudine; NFV=nelfinavir; TDF=tenofovir disoproxil fumarate; FTC=emtricitabine; RPV=rilpivirine; IDV=indinavir; EFV=efavirenz; NVP=nevirapine; EVG/c=cobicistat-boosted elvitegravir.

### Treatment outcome

In the total population still in care, the median current CD4 count was 515 (IQR, 340-691) cells/mm<sup>3</sup>. CD4 counts were similar between MSM (556 [IQR, 392-747] cells/mm<sup>3</sup>) and women (555 [409-735] cells/mm<sup>3</sup>), but men who acquired their infection via other modes of transmission had lower CD4 counts (415 [265-618] cells/mm<sup>3</sup>). Among individuals with a viral load measurement, the proportion with HIV RNA levels less than 80 IU/ml increased from 43% in 2005 to 82% in 2016 (Figure 9.5). Altogether, 15% of the individuals had ever been diagnosed with an AIDS-defining disease; 38% of these individuals were diagnosed with AIDS concurrently with their HIV diagnosis.

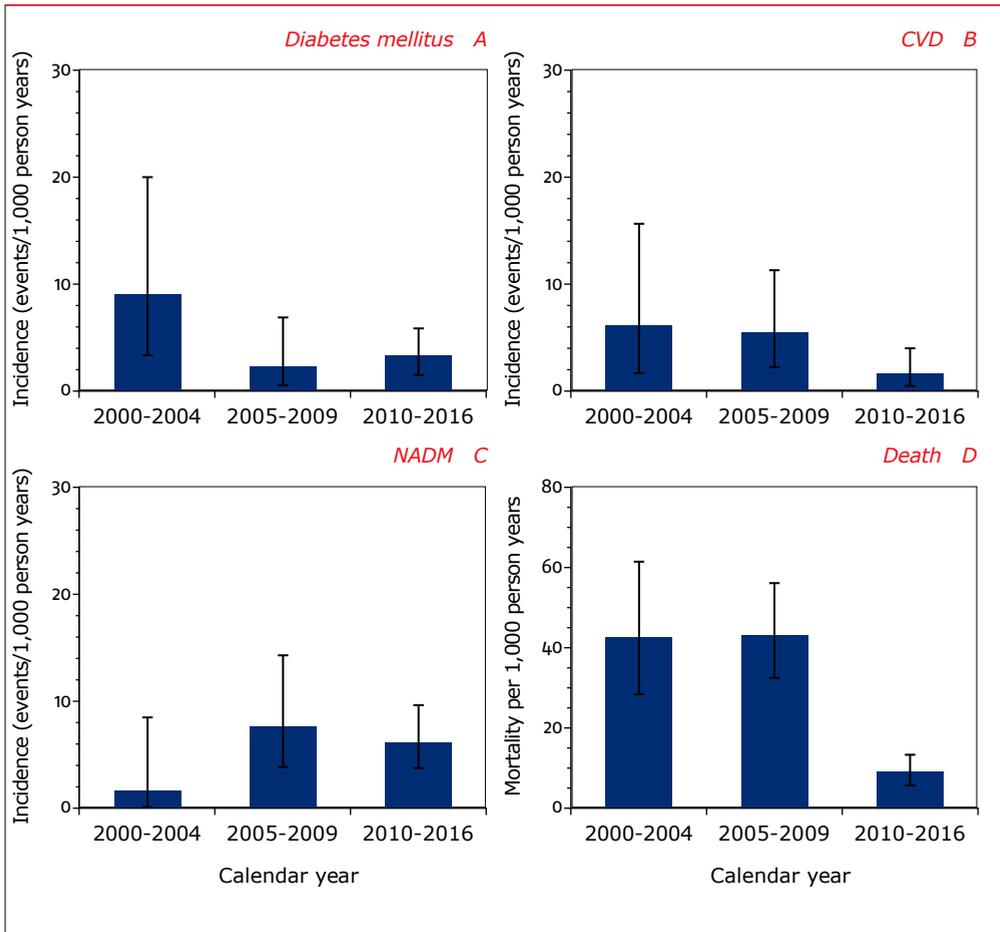
Figure 9.5: Proportion of people in care with HIV RNA <80 IU/ml at their last viral load measurement in each calendar year.



### 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<sup>197,198</sup>. In total, there were 19 cases of diabetes mellitus, 16 cases of cardiovascular disease (8 strokes and 8 myocardial infarctions), and 30 non-AIDS defining malignancies, including 4 cases of cervical dysplasia, 3 prostate cancer, 2 bladder cancer, and 2 anal cancer (Figure 9.6A-C).

**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 (The Data Collection on Adverse Events of Anti-HIV Drugs) protocol for collecting non-AIDS-defining malignancies.



### Mortality

Mortality rates after start of cART were 43 (28-62) 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 9 (6-13) per 1,000 person years, which may be a result of the introduction of guidelines to start cART earlier in infection before clinical

complications occur. However, the decrease in mortality could, in part, also be a consequence of under-ascertainment of deaths in the significant number of patients being lost to follow up.

## Conclusion

In recent years, HIV-positive individuals in Curaçao appear to be diagnosed increasingly earlier in their infection, as the proportion of people 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 individuals in Curaçao has improved considerably over the years, although adherence to treatment is still not optimal, as illustrated by the relatively low proportion of individuals with a suppressed viral load. Finally, the high proportion of patients lost to care is worrisome and may be affected by underreporting of death and/or emigration.

## Recommendations

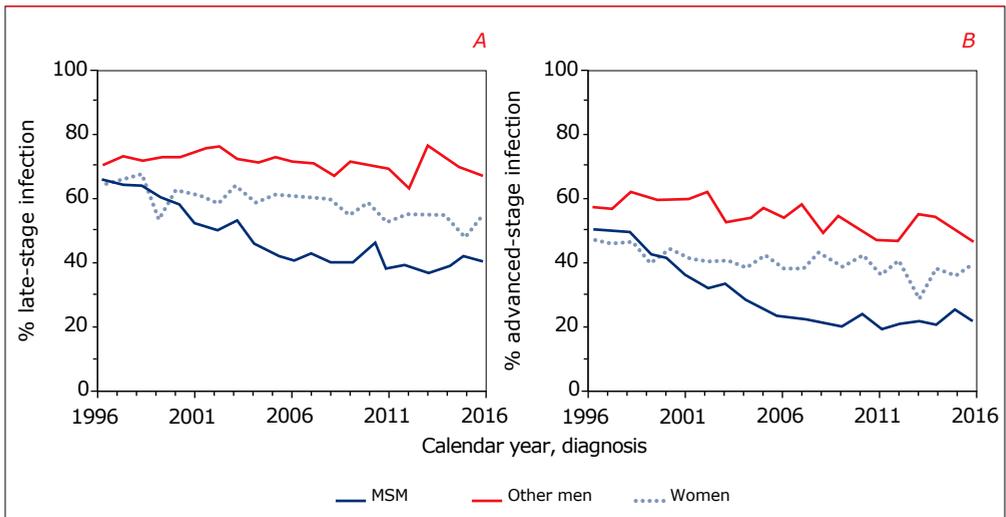
Curaçao is in a unique position in the Caribbean, in that data from HIV-positive individuals in care are regularly collected and monitored; however, it is important that the quality of these data is maintained. Special attention should be paid to the collection of data from people who interrupt care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

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

# Appendix figures and tables

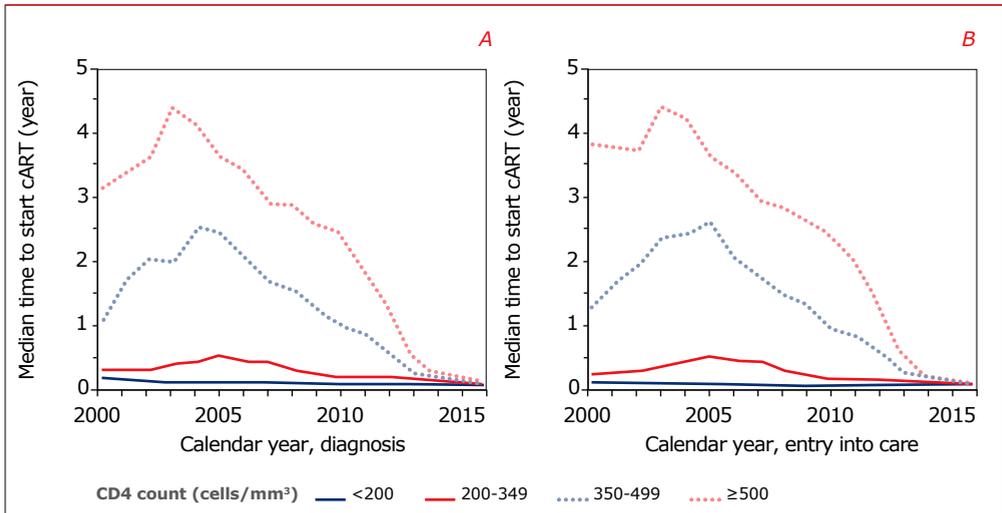
Appendix figures and tables are listed by chapter

*Appendix Figure 1.1: Proportion of individuals classified as presenting with (A) late-stage or (B) advanced-stage HIV infection at the time of HIV diagnosis. From 1996 (2014) onwards, 52% (46%) were diagnosed with late-stage HIV infection: men who have sex with men (MSM) 44% (39%), other men 71% (69%), and women 58% (51%). Overall, 34% (28%) were diagnosed with advanced-stage HIV infection: MSM 26% (21%), other men 54% (50%), and women 39% (37%). Late-stage HIV infection: CD4 counts below 350 cells/mm<sup>3</sup> or having AIDS, regardless of CD4 count. Advanced-stage HIV infection: CD4 counts below 200 cells/mm<sup>3</sup> or having AIDS.*

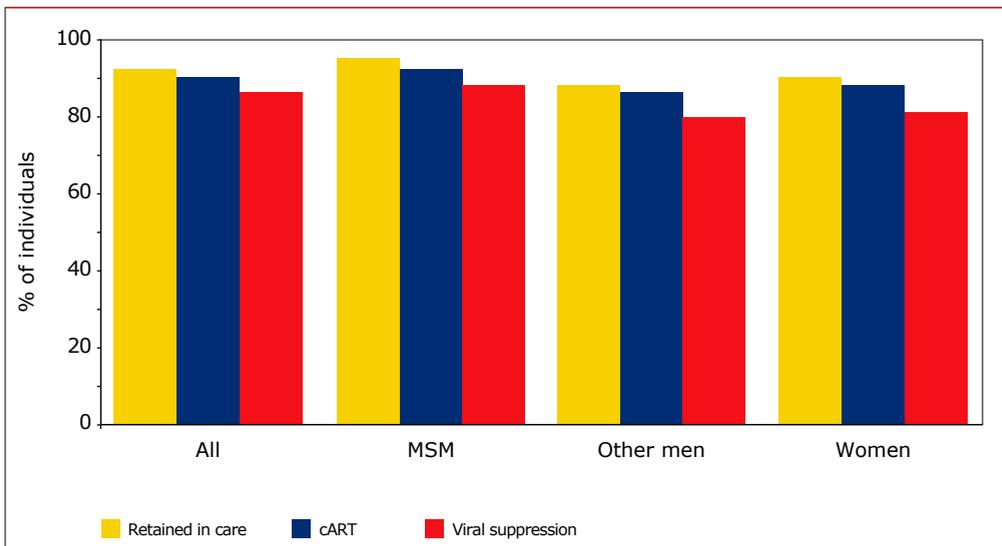


*Legend: MSM=men who have sex with men.*

**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.

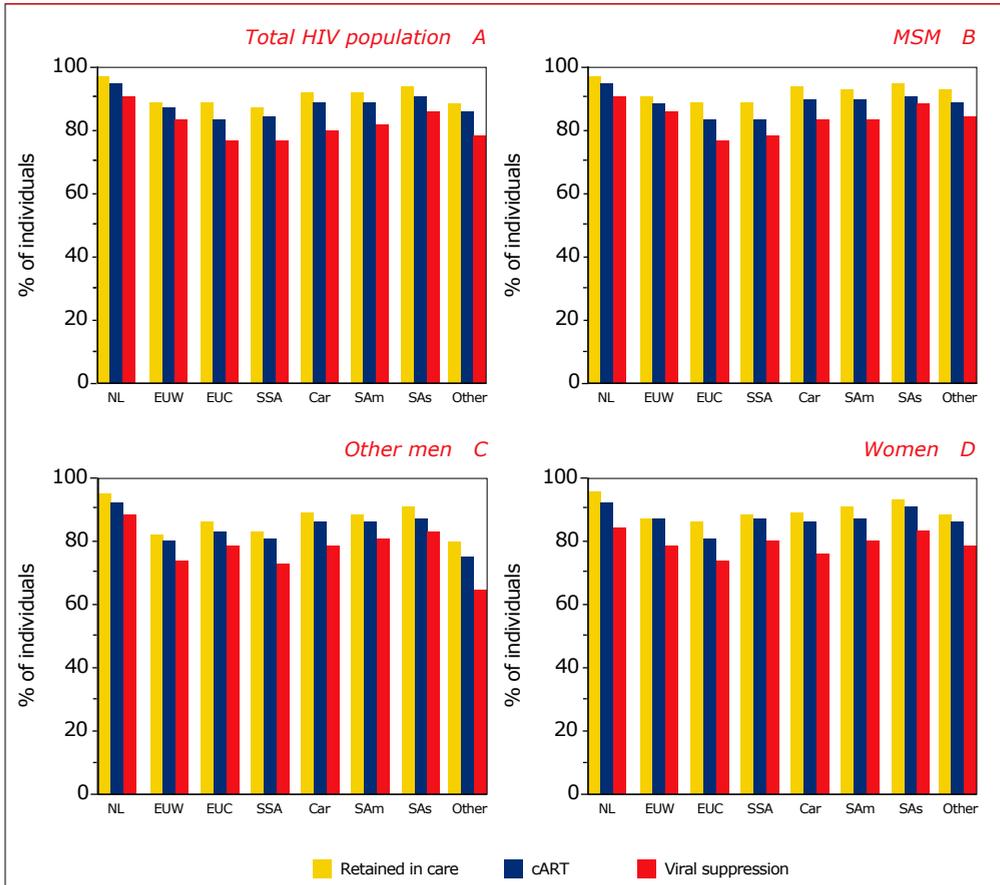


**Appendix Figure 1.3:** Continuum of HIV care by transmission risk group. Proportions are given relative to the number of people diagnosed and linked to care.



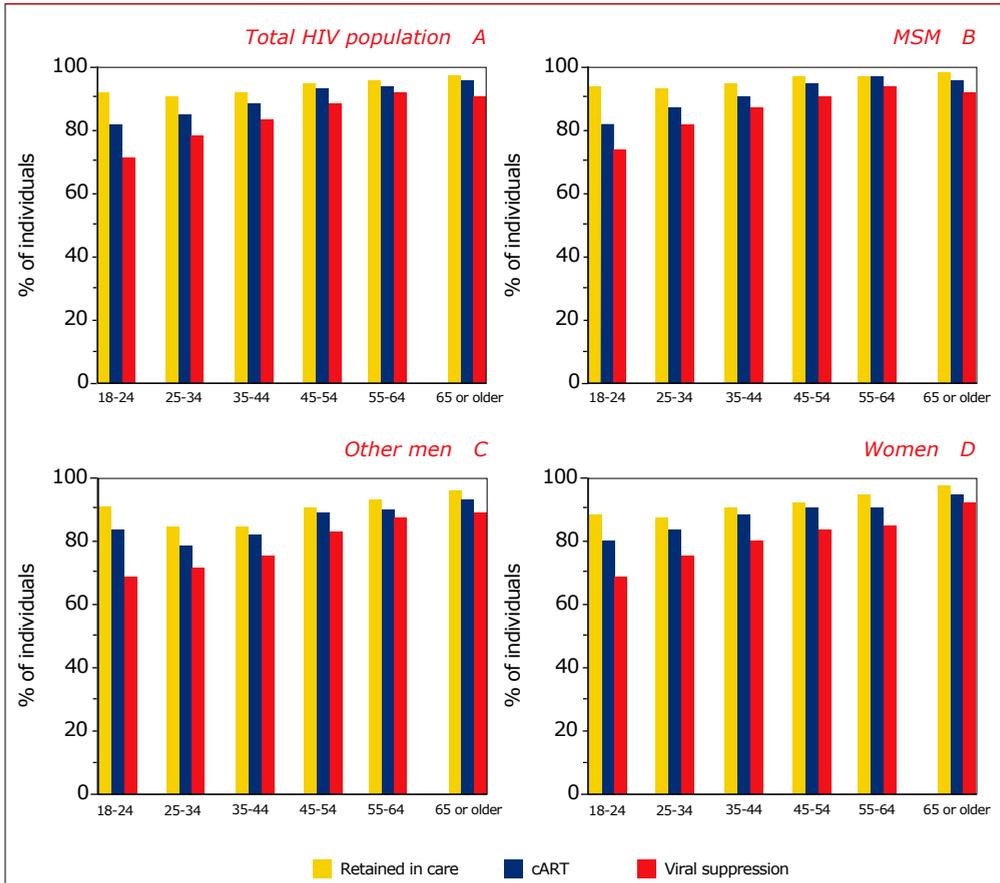
**Legend:** MSM=men who have sex with men; cART=combination antiretroviral therapy.

**Appendix Figure 1.4:** Continuum of HIV care by region of origin for (A) the total HIV-1-positive population and for (B) men who have sex with men, (C) other men, and (D) women. Proportions are given relative to the number of people diagnosed and linked to care.



**Legend:** NL=the Netherlands; EUW=western Europe; EUC=central Europe; SSA=sub-Saharan Africa; Car=Caribbean; SAm=South America; SAs=South and South-East Asia; Other=other regions of origin; cART=combination antiretroviral therapy.

**Appendix Figure 1.5: Continuum of HIV care by age group for (A) the total HIV-1-positive population and for (B) men who have sex with men, (C) other men, and (D) women. Proportions are given relative to the number of people diagnosed and linked to care.**



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

**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 2015 and 2016 had not yet been finalised at the time of writing.**

Year of diagnosis	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
≤1995	2,272	267	390	285	134
1996	385	90	83	31	8
1997	447	114	127	39	10
1998	332	109	113	22	7
1999	357	107	137	19	7
2000	380	163	195	18	5
2001	451	167	217	16	5
2002	474	167	251	16	3
2003	460	180	277	23	5
2004	590	203	263	10	4
2005	639	197	261	17	2
2006	686	163	197	10	5
2007	779	158	212	12	4
2008	866	177	180	6	1
2009	782	159	181	9	0
2010	790	181	165	6	1
2011	776	145	150	4	1
2012	712	147	143	6	1
2013	736	115	130	2	2
2014	607	108	116	1	0
2015	557	125	117	1	0
2015*	574	129	121	1	0
2016	491	95	92	1	0
2016*	545	105	102	1	0
2017	83	16	22	0	0
<b>Total</b>	<b>14,652</b>	<b>3,353</b>	<b>4,019</b>	<b>554</b>	<b>205</b>

\*Projected numbers

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

	Blood or blood products		Other/unknown		Children		Total
	Men	Women	Men	Women	Men	Women	
	62	22	176	53	53	37	3,751
	3	4	36	6	12	3	661
	7	3	41	8	9	9	814
	6	5	30	8	8	8	648
	9	4	19	7	11	13	690
	3	4	35	4	14	29	850
	8	5	40	8	15	34	966
	14	7	61	4	18	21	1,036
	9	3	61	14	17	21	1,070
	4	3	65	10	14	12	1,178
	3	7	61	10	11	10	1,218
	4	7	57	4	7	11	1,151
	2	6	50	7	7	12	1,249
	5	3	54	6	14	17	1,329
	2	1	49	10	13	15	1,221
	6	3	41	7	19	16	1,235
	8	8	58	4	11	9	1,174
	5	3	37	10	7	14	1,085
	11	1	41	6	6	4	1,054
	7	4	42	8	5	6	904
	3	1	40	5	5	5	859
	3	1	41	5	5	5	885
	7	0	35	6	4	4	735
	8	0	39	7	4	4	816
	0	0	4	0	0	0	125
	<b>188</b>	<b>104</b>	<b>1,133</b>	<b>205</b>	<b>280</b>	<b>310</b>	<b>25,003</b>

**Appendix Table 1.2: Region of origin of the 24,413 adult HIV-1-positive individuals with a recorded date of diagnosis stratified according to year of HIV diagnosis.**

	MSM		Other men			
	<2014	≥2014	Total	<2014	≥2014	Total
The Netherlands	9,098 70.5%	1,181 68.0%	10,279 70.2%	2,090 44.1%	283 58.4%	2,373 45.4%
Sub-Saharan Africa	189 1.5%	30 1.7%	219 1.5%	1,265 26.7%	88 18.1%	1,353 25.9%
Western Europe	1,037 8.0%	92 5.3%	1,129 7.7%	271 5.7%	15 3.1%	286 5.5%
Central Europe	262 2.0%	84 4.8%	346 2.4%	144 3.0%	16 3.3%	160 3.1%
Eastern Europe	87 0.7%	14 0.8%	101 0.7%	65 1.4%	5 1.0%	70 1.3%
South America	875 6.8%	110 6.3%	985 6.7%	381 8.0%	31 6.4%	412 7.9%
Caribbean	454 3.5%	79 4.5%	533 3.6%	203 4.3%	19 3.9%	222 4.2%
South and South-East	385 3.0%	50 2.9%	435 3.0%	121 2.6%	10 2.1%	131 2.5%
Asia	527 4.1%	98 5.6%	625 4.3%	203 4.3%	18 3.7%	221 4.2%
Other/unknown						

Legend: MSM=men who have sex with men.

<b>Women</b>			
	<b>&lt;2014</b>	<b>≥2014</b>	<b>Total</b>
	1,108	145	1,253
	26.6%	39.1%	27.6%
	1,790	117	1,907
	43.0%	31.5%	42.1%
	220	6	226
	5.3%	1.6%	5.0%
	81	7	88
	1.9%	1.9%	1.9%
	46	8	54
	1.1%	2.1%	1.2%
	379	38	417
	9.1%	10.2%	9.2%
	215	11	226
	5.2%	3.0%	5.0%
	244	25	269
	5.9%	6.7%	5.9%
	79	14	85
	1.9%	3.8%	2.1%

Appendix Table 1.3: Characteristics of the 19,035 people living with HIV and in care as of December 2016.

	MSM	Heterosexual		IDU	
	Men	Men	Women	Men	Women
	n=11,928	n=2,377	n=3,104	n=224	n=84
<b>Current age [years]</b>					
0-12	0 0.0%	0 0.0%	0 0.0%	0 0.0%	0 0.0%
13-17	4 0.0%	0 0.0%	1 0.0%	0 0.0%	0 0.0%
18-24	199 1.7%	16 0.7%	37 1.2%	0 0.0%	0 0.0%
25-34	1,432 12.0%	221 9.3%	497 16.0%	4 1.8%	2 2.4%
35-44	2,547 21.4%	488 20.5%	1,017 32.8%	36 16.1%	10 11.9%
45-54	4,131 34.6%	853 35.9%	955 30.8%	92 41.1%	34 40.5%
55-64	2,548 21.4%	538 22.6%	415 13.4%	79 35.3%	34 40.5%
65-74	929 7.8%	222 9.3%	144 4.6%	13 5.8%	4 4.8%
≥75	138 1.2%	39 1.6%	38 1.2%	0 0.0%	0 0.0%
<b>Current age 50 years or older</b>					
No	6,132 51.4%	1,150 48.4%	2,085 67.2%	74 33.0%	17 20.2%
Yes	5,796 48.6%	1,227 51.6%	1,019 32.8%	150 67.0%	67 79.8%
<b>Current age 60 years or older</b>					
No	9,899 83.0%	1,911 80.4%	2,776 89.4%	180 80.4%	68 81.0%
Yes	2,029 17.0%	466 19.6%	328 10.6%	44 19.6%	16 19.0%

	Blood or blood products		Other / unknown		Total	
	Men n=151	Women n=89	Men n=795	Women n=283	Men n=15,475	Women n=3,560
0	0	0	57	77	57	77
0.0%	0.0%	0.0%	7.2%	27.2%	0.4%	2.2%
1	2	2	43	26	48	29
0.7%	2.2%	2.2%	5.4%	9.2%	0.3%	0.8%
3	1	1	46	41	264	79
2.0%	1.1%	1.1%	5.8%	14.5%	1.7%	2.2%
18	10	10	87	32	1,762	541
11.9%	11.2%	11.2%	10.9%	11.3%	11.4%	15.2%
24	22	22	115	38	3,210	1,087
15.9%	24.7%	24.7%	14.5%	13.4%	20.7%	30.5%
55	29	29	214	37	5,345	1,055
36.4%	32.6%	32.6%	26.9%	13.1%	34.5%	29.6%
26	16	16	142	26	3,333	491
17.2%	18.0%	18.0%	17.9%	9.2%	21.5%	13.8%
22	6	6	73	5	1,259	159
14.6%	6.7%	6.7%	9.2%	1.8%	8.1%	4.5%
2	3	3	18	1	197	42
1.3%	3.4%	3.4%	2.3%	0.4%	1.3%	1.2%
69	53	53	449	232	7,874	2,387
45.7%	59.6%	59.6%	56.5%	82.0%	50.9%	67.1%
82	36	36	346	51	7,601	1,173
54.3%	40.4%	40.4%	43.5%	18.0%	49.1%	32.9%
117	75	75	648	267	12,755	3,186
77.5%	84.3%	84.3%	81.5%	94.3%	82.4%	89.5%
34	14	14	147	16	2,720	374
22.5%	15.7%	15.7%	18.5%	5.7%	17.6%	10.5%

	MSM		Heterosexual		IDU	
	Men	Men	Women	Men	Women	
	n=11,928	n=2,377	n=3,104	n=224	n=84	
<b>Region of origin</b>						
Netherlands	8,669 72.7%	1,136 47.8%	913 29.4%	132 58.9%	41 48.8%	
Sub-Saharan Africa	164 1.4%	636 26.8%	1,304 42.0%	4 1.8%	0 0.0%	
Western Europe	744 6.2%	80 3.4%	71 2.3%	24 10.7%	27 33.1%	
South America	749 6.3%	209 8.8%	307 9.9%	11 4.9%	1 1.2%	
Caribbean	453 3.8%	121 5.1%	162 5.2%	5 2.2%	1 1.2%	
South and South-East Asia	355 3.0%	39 1.6%	207 6.7%	9 4.0%	1 1.2%	
Other	748 6.3%	149 6.3%	131 4.2%	39 17.4%	13 15.5%	
Unknown	46 0.4%	7 0.3%	9 0.3%	0 0.0%	0 0.0%	
<b>Years aware of HIV infection</b>						
<1	473 4.0%	92 3.9%	87 2.8%	1 0.4%	0 0.0%	
1-2	1,107 9.3%	211 8.9%	226 7.3%	2 0.9%	0 0.0%	
3-4	1,336 11.2%	224 9.4%	227 7.3%	2 0.9%	3 3.6%	
5-10	3,505 29.4%	624 26.3%	720 23.2%	18 8.0%	3 3.6%	
10-20	3,818 32.0%	1,025 43.1%	1,502 48.4%	85 37.9%	21 25.0%	
>20	1,683 14.1%	197 8.3%	330 10.6%	116 51.8%	57 67.9%	
Unknown	6 0.1%	4 0.2%	12 0.4%	0 0.0%	0 0.0%	

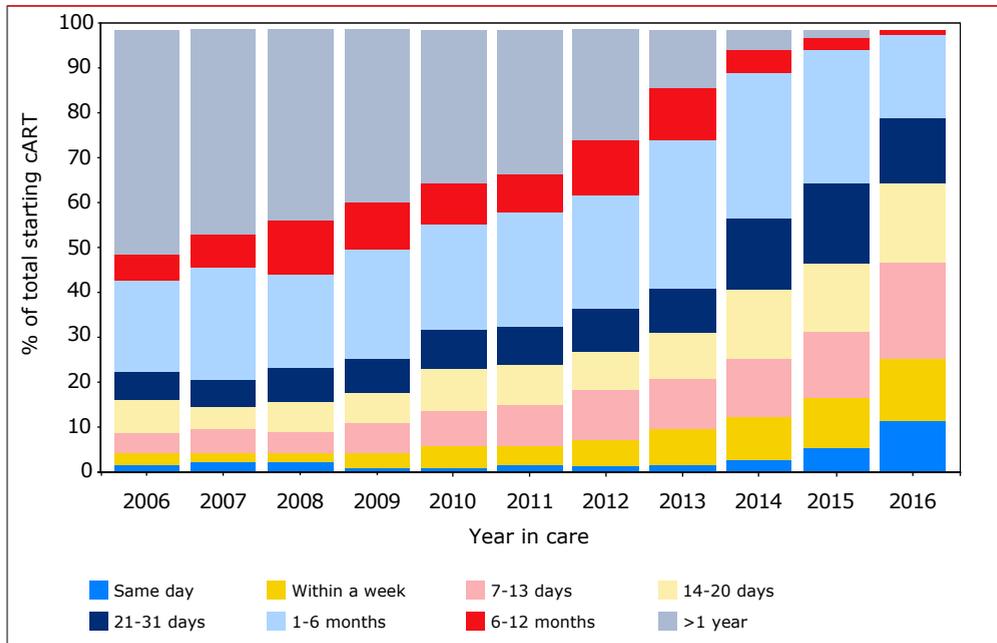
	Blood or blood products		Other / unknown		Total	
	Men	Women	Men	Women	Men	Women
	n=151	n=89	n=795	n=283	n=15,475	n=3,560
	97	17	360	102	10,394	1,073
	64.2%	19.1%	45.3%	36.0%	67.2%	30.1%
	29	38	225	105	1,058	1,447
	19.2%	42.7%	28.3%	37.1%	6.8%	40.6%
	3	3	31	25	882	126
	2.0%	3.4%	3.9%	8.8%	5.7%	3.5%
	3	9	37	13	1,009	330
	2.0%	10.1%	4.7%	4.6%	6.5%	9.3%
	4	4	35	1	618	168
	2.6%	4.5%	4.4%	0.4%	4.0%	4.7%
	6	11	27	8	436	227
	4.0%	12.4%	3.4%	2.8%	2.8%	6.4%
	9	7	75	26	1,020	177
	6.0%	7.9%	9.4%	9.2%	6.6%	5.0%
	0	0	5	3	58	12
	0.0%	0.0%	0.6%	1.1%	0.4%	0.3%
	7	0	32	7	605	94
	4.6%	0.0%	4.0%	2.5%	3.9%	2.6%
	8	4	75	18	1,403	248
	5.3%	4.5%	9.4%	6.4%	9.1%	7.0%
	14	2	65	28	1,641	260
	9.3%	2.2%	8.2%	9.9%	10.6%	7.3%
	21	20	191	75	4,359	818
	13.9%	22.5%	24.0%	26.5%	28.2%	23.0%
	48	42	321	106	5,297	1,671
	31.8%	47.2%	40.4%	37.5%	34.2%	46.9%
	51	21	99	44	2,146	452
	33.8%	23.6%	12.5%	15.5%	13.9%	12.7%
	2	0	12	5	24	17
	1.3%	0.0%	1.5%	1.8%	0.2%	0.5%

	MSM	Heterosexual		IDU	
	Men n=11,928	Men n=2,377	Women n=3,104	Men n=224	Women n=84
Current CD4 count [cells/mm <sup>3</sup> ], median / IQR	670 510-870	571 410-790	670 490-870	510 335-827	590 370-832
Current CD8 count [cells/mm <sup>3</sup> ], median / IQR	860 640-1180	840 600-1177	770 573-1050	857 570-1200	886 671-1125
Current HIV RNA <200 copies/ml					
No	503 4.2%	144 6.1%	209 6.7%	14 6.3%	7 8.3%
Yes	10,904 91.4%	2,137 89.9%	2,755 88.8%	193 86.2%	67 79.8%
Current HIV RNA <100 copies/ml					
No	605 5.1%	170 7.2%	243 7.8%	14 6.3%	5 6.0%
Yes	10,802 90.6%	2,111 88.8%	2,721 87.7%	193 86.2%	69 82.1%
Ever AIDS	2,125 17.8%	714 30.0%	676 21.8%	81 36.2%	35 41.7%
AIDS at diagnosis	1,129 9.5%	509 21.4%	395 12.7%	18 8.0%	6 7.1%
Current treatment					
cART	11,642 97.6%	2,307 97.1%	3,013 97.1%	229 98.2%	84 100.0%
Non-cART	18 0.2%	2 0.1%	2 0.1%	0 0.0%	0 0.0%
Not started	268 2.2%	68 2.9%	89 2.9%	4 1.8%	0 0.0%

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

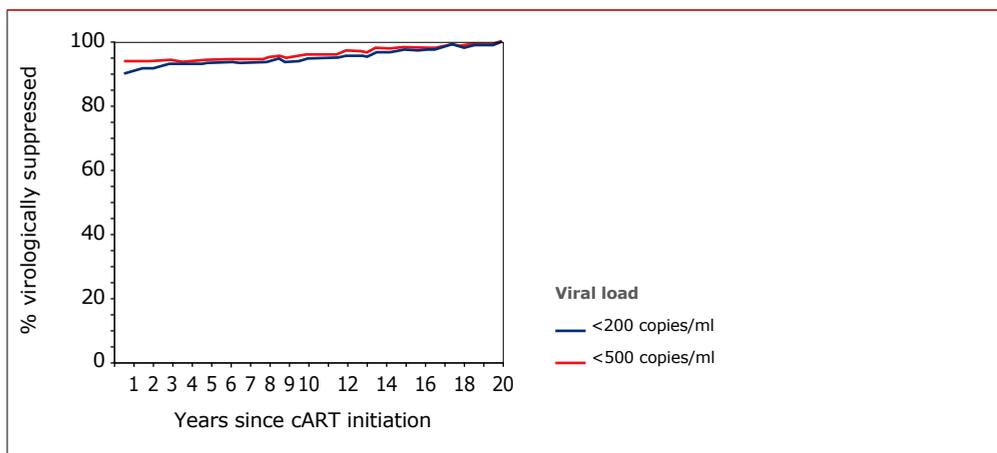
	Blood or blood products		Other / unknown		Total	
	Men	Women	Men	Women	Men	Women
	<b>n=151</b>	<b>n=89</b>	<b>n=795</b>	<b>n=283</b>	<b>n=15,475</b>	<b>n=3,560</b>
	558	737	550	750	650	680
	370-750	544-980	400-790	530-1050	480-854	490-880
	800	890	840	740	860	780
	530-1100	635-1290	590-1170	480-1000	630-1180	573-1050
	7	8	52	24	720	282
	4.6%	9.0%	6.5%	8.5%	4.7%	7.9%
	140	77	689	239	14,063	3,217
	92.7%	86.5%	86.7%	84.5%	90.9%	90.4%
	7	7	61	23	857	244
	4.6%	7.9%	7.7%	8.1%	5.5%	6.9%
	140	78	680	240	13,926	3,142
	92.7%	87.6%	85.5%	84.8%	90.0%	88.2%
	50	24	278	81	3,248	816
	33.1%	27.0%	35.0%	28.6%	21.0%	22.9%
	31	12	196	43	1883	456
	20.5%	13.5%	24.7%	15.2%	12.2%	12.8%
	146	89	773	278	15,088	3,464
	96.7%	100.0%	97.2%	98.2%	97.5%	97.3%
	0	0	1	2	21	4
	0.0%	0.0%	0.1%	0.7%	0.1%	0.1%
	5	0	21	3	366	92
	3.3%	0.0%	2.6%	1.1%	2.4%	2.6%

Appendix Figure 2.1: Time between entry into HIV care and initiation of combination antiretroviral therapy (cART) for those starting cART in 2006–2016\*.



Legend: cART=combination antiretroviral therapy.

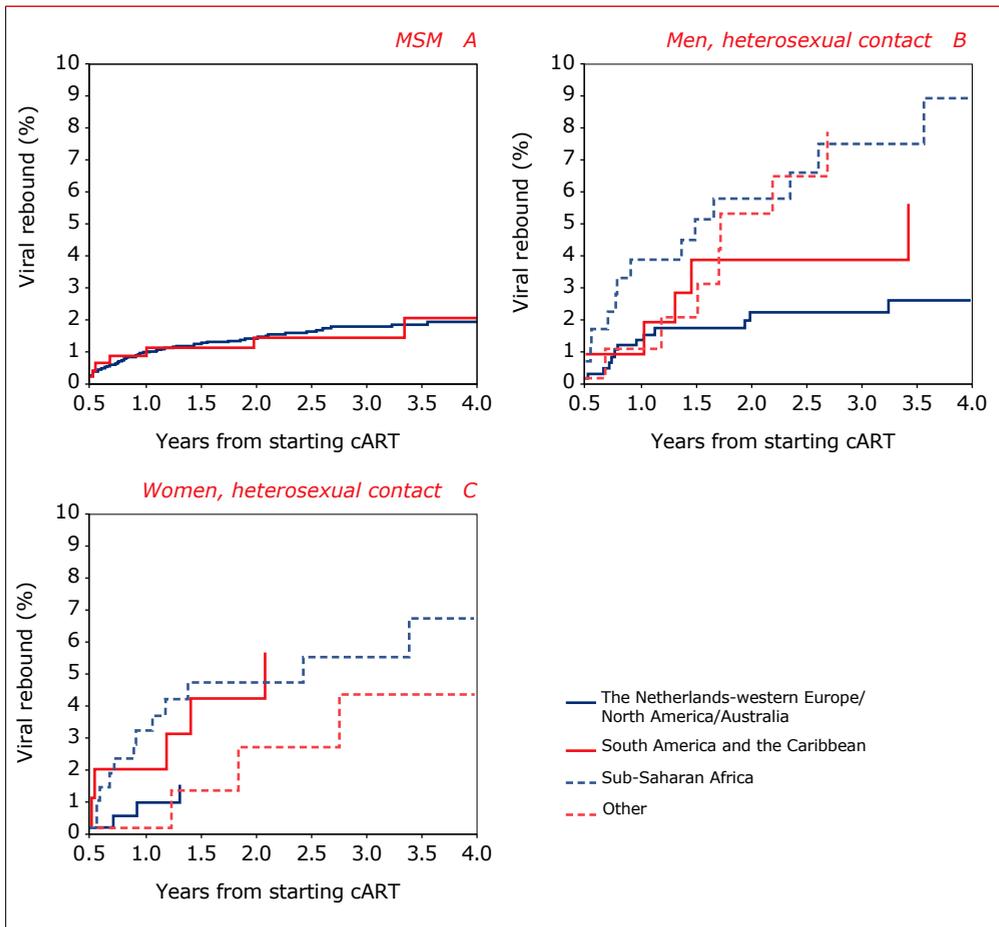
Appendix Figure 2.2: Viral suppression since combination antiretroviral therapy initiation.



Legend: cART=combination antiretroviral therapy.

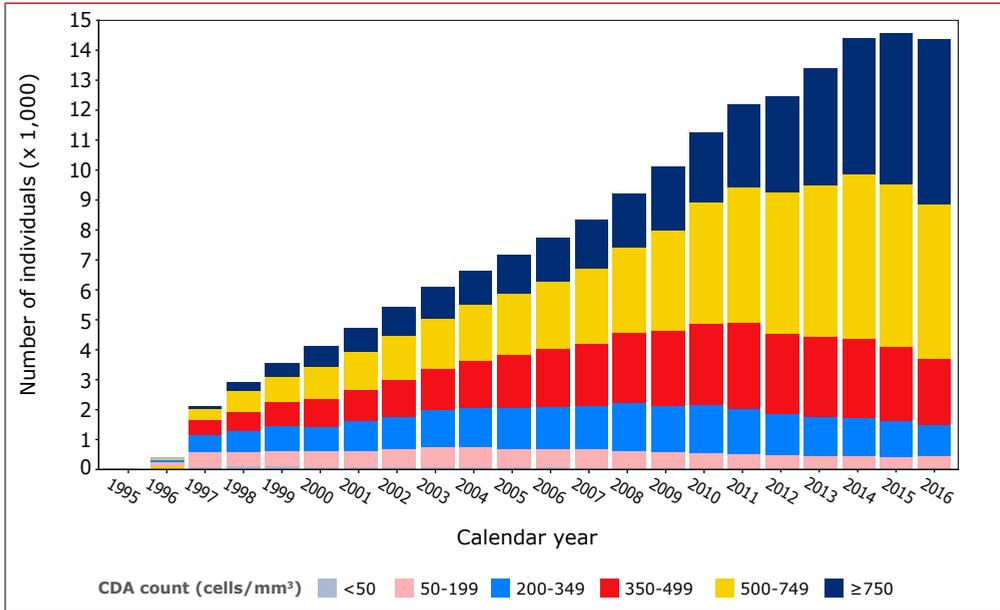
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**Appendix Figure 2.3:** Kaplan–Meier estimates of viral rebound according to transmission risk group and region of origin, among previously ART-naïve individuals receiving cART since 2011: A) Men who have sex with men; B) Men, heterosexual contact; C) Women, heterosexual contact.



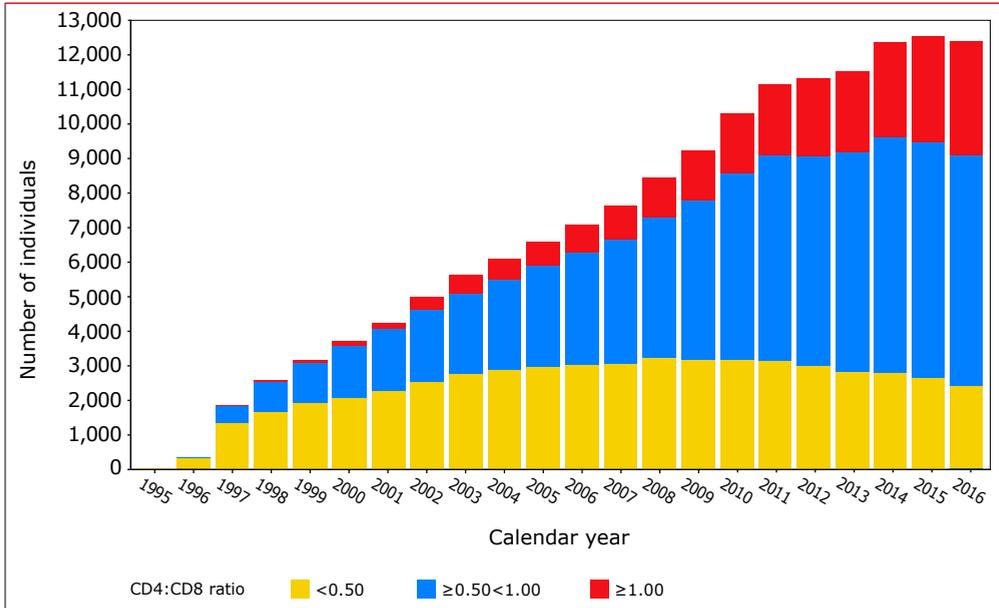
**Legend:** cART=combination antiretroviral therapy.

Appendix Figure 2.4: Last available CD4 cell count (cells/mm<sup>3</sup>) in each calendar year after the start of combination antiretroviral therapy.



Note: Numbers for 2016 may increase slightly because data collection is not yet complete.

Appendix Figure 2.5: Last available CD4:CD8 ratio in each calendar year after the start of combination antiretroviral therapy.



**Appendix Table 2.1: Combination antiretroviral therapy (cART) regimen used in 2016 by HIV-positive individuals who ever started cART diagnosed before 1990.**

Regimen	n	%
TDF/FTC/EFV	31	5.8
TDF/FTC/NVP	70	13.0
TDF/FTC/RPV	17	3.2
TDF/FTC/DRV/b	31	5.8
TDF/FTC/ATV/r	16	3.0
TDF/FTC/LPV	1	0.2
TDF/FTC/EVG/c	10	1.9
TDF/FTC/DTG	10	1.9
TDF/FTC/RAL	12	2.2
ABC/3TC/DTG	38	7.1
TAF/FTC/EVG/c	22	4.1
TAF/FTC/RPV	2	0.4
TAF/FTC/DTG	5	0.9
Other: 2NRTI+NNRTI	64	11.9
Other: 2NRTI+PI	35	6.5
Other: 2NRTI+INST	9	1.7
Other: PI+INSTI	12	2.2
Other: NRTI+PI+INSTI (3 ARVs)	17	3.2
Other: NRTI+PI+INSTI (4 ARVs)	18	3.4
Other	110	20.5
Not on cART	8	1.5

*Legend: ARV=antiretroviral drug; /r=ritonavir-boosted; /c=cobicistat-boosted; 3TC=lamivudine; b=boosted (cobicistat or ritonavir); cART=combination antiretroviral therapy; ABC=abacavir; ATV=atazanavir; DRV=darunavir; DTG=dolutegravir; EFV=efavirenz; EVG=elvitegravir; FTC=emtricitabine; LPV=lopinavir; NVP=nevirapine; PI=protease inhibitor; RAL=raltegravir; RPV=rilpivirine; TAF=tenofovir alafenamide; TDF=tenofovir disoproxil fumarate; NRTI=nonnucleoside reverse transcriptase inhibitor; NNRTI=non-NRTI; INSTI=integrase inhibitor.*

**Appendix Table 2.2: CD4 cell count at combination antiretroviral therapy initiation by calendar year 2011–2016.**  
Numbers are median [IQR] or n (%).

Year of cART initiation	2011	2012	2013	2014	2015	2016	Total (2011–2016)
CD4 cell count available at cART initiation	1,084 (100.0)	1,100 (100.0)	1,280 (100.0)	1,231 (100.0)	946 (100.0)	399 (100.0)	6,040 (100.0)
Median CD4 cell count/mm <sup>3</sup>	300 [188–380]	324 [190–430]	369 [244–497]	400 [255–560]	400 [200–580]	370 [171–550]	350 [210–490]
CD4 cell count (cells/mm <sup>3</sup> )							
<50	86 (7.9)	109 (9.9)	92 (7.2)	72 (5.9)	80 (8.5)	52 (13.0)	491 (8.1)
50–199	199 (18.4)	177 (16.1)	158 (12.3)	158 (12.8)	156 (16.5)	58 (14.5)	906 (15.0)
200–349	433 (39.9)	345 (31.4)	331 (25.9)	245 (19.9)	167 (17.7)	72 (18.1)	1,593 (26.4)
350–499	244 (22.5)	284 (25.8)	383 (29.9)	348 (28.3)	222 (23.5)	88 (22.1)	1,569 (26.0)
≥500	122 (11.3)	185 (16.8)	316 (24.7)	408 (33.1)	321 (33.9)	129 (32.3)	1,481 (24.5)

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

*Appendix Table 2.3: Annual proportion of available sequences with evidence of high-level resistance after virological failure from individuals who received combination antiretroviral therapy and were previously antiretroviral drug-naïve by antiretroviral drug.*

*A) High-level resistance to nucleoside reverse transcriptase inhibitors*

Calendar year	Number of sequences	Emtricitabine/lamivudine	Zidovudine	Stavudine	Abacavir	Didanosine	Tenofovir
2000	70	61.4	14.3	12.9	8.6	10.0	1.4
2001	96	62.5	16.7	17.7	13.5	17.7	5.2
2002	176	55.7	21.0	22.2	18.2	19.9	5.7
2003	248	57.3	17.7	24.6	20.2	22.6	8.9
2004	218	51.8	17.0	21.1	22.5	20.6	7.8
2005	206	46.1	16.0	21.4	18.5	19.4	5.8
2006	203	40.4	16.8	23.2	18.7	19.2	8.4
2007	225	37.8	14.2	19.1	15.1	14.7	5.8
2008	241	35.7	12.0	17.4	14.1	14.9	5.8
2009	245	33.5	13.5	14.7	10.2	11.4	3.7
2010	237	29.5	8.0	11.8	11.0	11.8	3.8
2011	151	25.2	6.6	10.6	10.6	10.6	5.3
2012	115	32.2	0.9	7.8	11.3	9.6	6.1
2013	99	27.3	1.0	8.1	8.1	8.1	6.1
2014	103	23.3	1.9	6.8	7.8	6.8	4.9
2015	119	19.3	2.5	8.4	9.2	8.4	6.7
2016	82	25.6	1.2	4.9	7.3	6.1	2.4

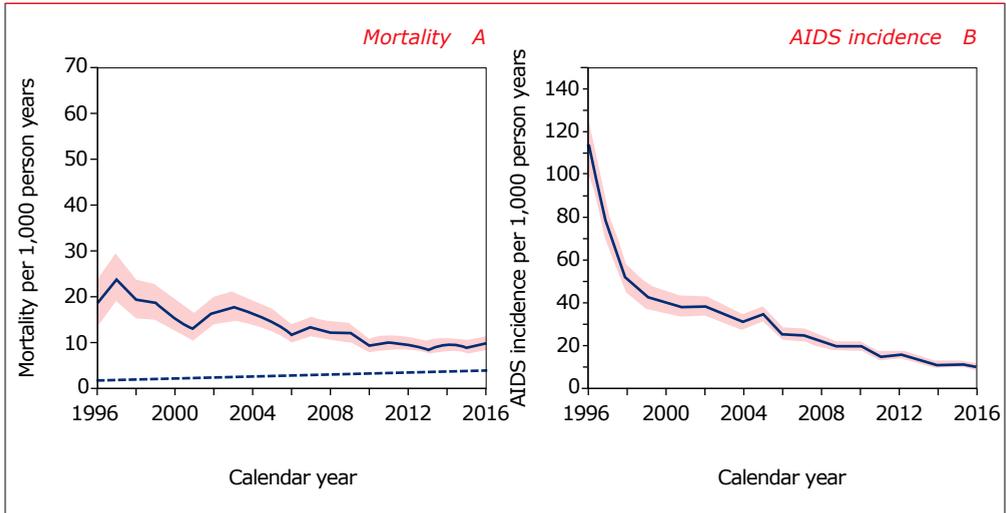
**B) High-level resistance to non-nucleoside reverse transcriptase inhibitors**

Calendar year	Number of sequences	Nevirapine	Efavirenz	Etravirine	Rilpivirine
2000	70	24.3	15.7	1.4	11.4
2001	96	28.1	20.8	1.0	9.4
2002	176	33.0	24.4	0.0	13.6
2003	248	35.5	28.2	0.0	14.1
2004	218	44.0	34.4	3.7	16.1
2005	206	32.5	25.7	0.5	14.6
2006	203	44.3	31.5	1.5	12.3
2007	225	35.1	25.8	1.3	13.3
2008	241	34.0	30.3	1.2	10.8
2009	245	33.1	26.1	1.6	10.6
2010	237	27.9	22.4	1.3	8.4
2011	151	24.5	17.9	0.7	6.6
2012	115	32.2	27.0	1.7	7.0
2013	99	33.3	27.3	2.0	13.1
2014	103	29.1	26.2	0.0	2.9
2015	119	21.9	16.0	2.5	8.4
2016	82	18.3	13.4	0.0	7.3

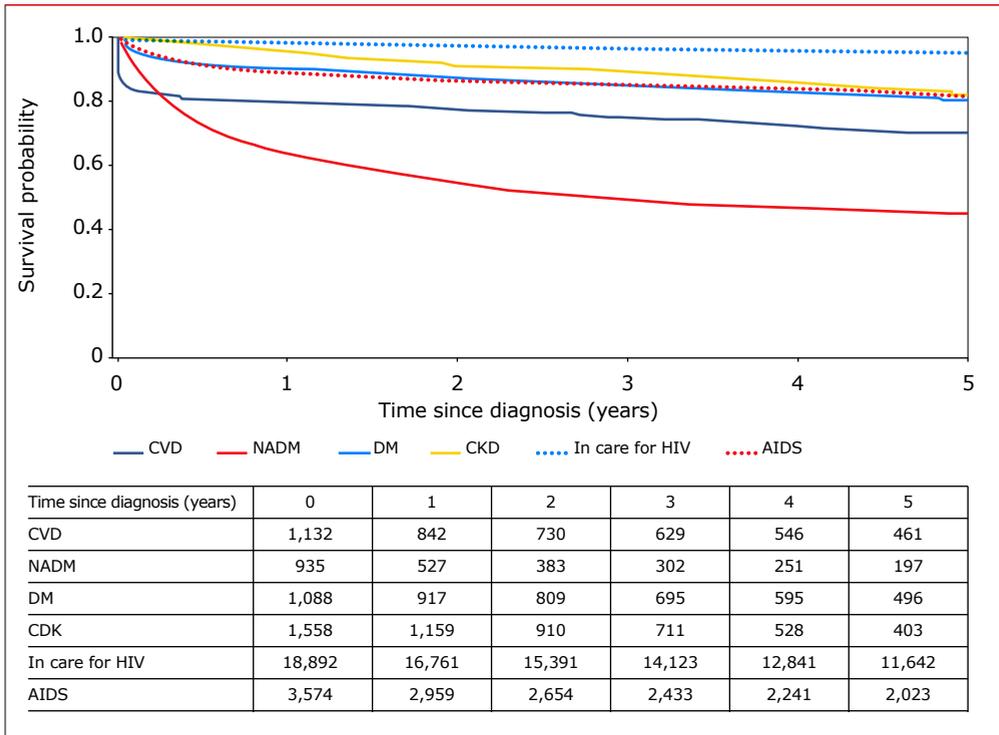
**C) High-level resistance to protease inhibitors.**

Calendar year	Number of sequences	Nelfinavir	Saquinavir	Indinavir	Atazanavir	Fosamprenavir	Lopinavir	Tipranavir	Darunavir
2000	70	48.6	5.7	4.3	5.7	2.9	2.9	1.4	0.0
2001	96	40.6	13.5	7.3	10.4	6.3	6.3	1.0	0.0
2002	176	26.7	7.4	4.6	4.0	2.3	2.3	0.0	0.0
2003	248	15.7	6.5	5.2	4.4	3.6	4.8	1.2	0.0
2004	218	13.8	3.7	4.6	4.1	2.8	1.8	0.5	0.0
2005	206	17.5	2.4	1.0	2.9	1.9	0.5	0.5	0.0
2006	203	11.3	3.9	3.9	4.4	3.0	3.0	1.5	0.0
2007	225	8.4	3.6	3.1	5.3	2.7	1.8	0.9	0.0
2008	241	7.1	2.5	2.5	3.3	3.7	1.7	0.4	0.0
2009	245	11.0	3.7	4.9	3.7	4.9	3.7	0.4	0.0
2010	237	6.8	3.0	3.0	3.0	3.8	1.3	0.0	0.0
2011	151	6.0	2.0	2.0	2.0	1.3	0.7	0.0	0.0
2012	115	4.4	1.7	2.6	0.9	0.9	1.7	0.0	0.0
2013	99	3.0	0.0	0.0	0.0	1.0	0.0	0.0	0.0
2014	103	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2015	119	0.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0
2016	82	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

**Appendix Figure 3.1:** (A) Annual mortality and (B) incidence of AIDS in 24,684 HIV-1-positive individuals in the Netherlands after HIV diagnosis 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-matched and gender-matched individuals from the general population in the Netherlands.

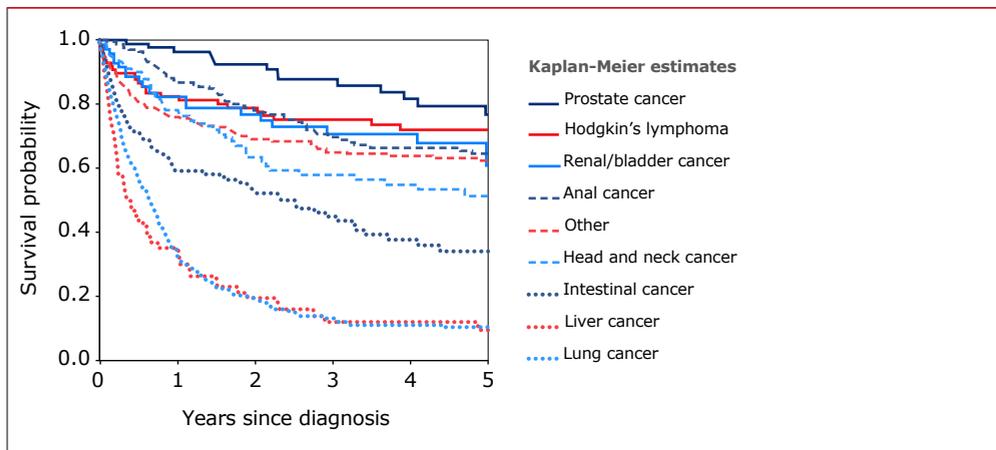


**Appendix Figure 3.2:** Estimated 5-year survival following the diagnosis of cardiovascular disease (CVD), non-AIDS defining malignancy (NADM), diabetes mellitus (DM), chronic kidney disease (CKD). Two reference groups are included: survival from date of entry into HIV care (after 1 January 2000), and from date of first AIDS diagnosis (after 1 January 2000). The numbers below the graph represent the number of subjects per stratum at risk at each time point.

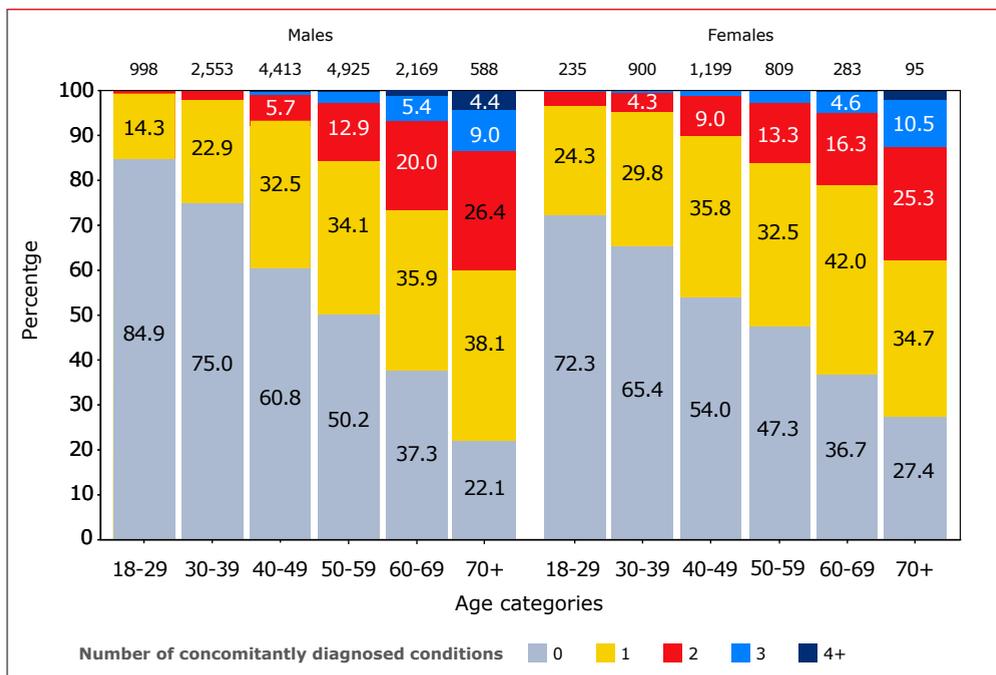


**Legend:** CVD=cardiovascular disease; NADM=non-AIDS defining malignancy; DM=diabetes mellitus; CKD=chronic kidney disease.

Appendix Figure 3.3: Estimated 5-year survival following the diagnosis of the most common non-AIDS defining malignancies diagnosed between 1 January 2000 and 31 December 2016.

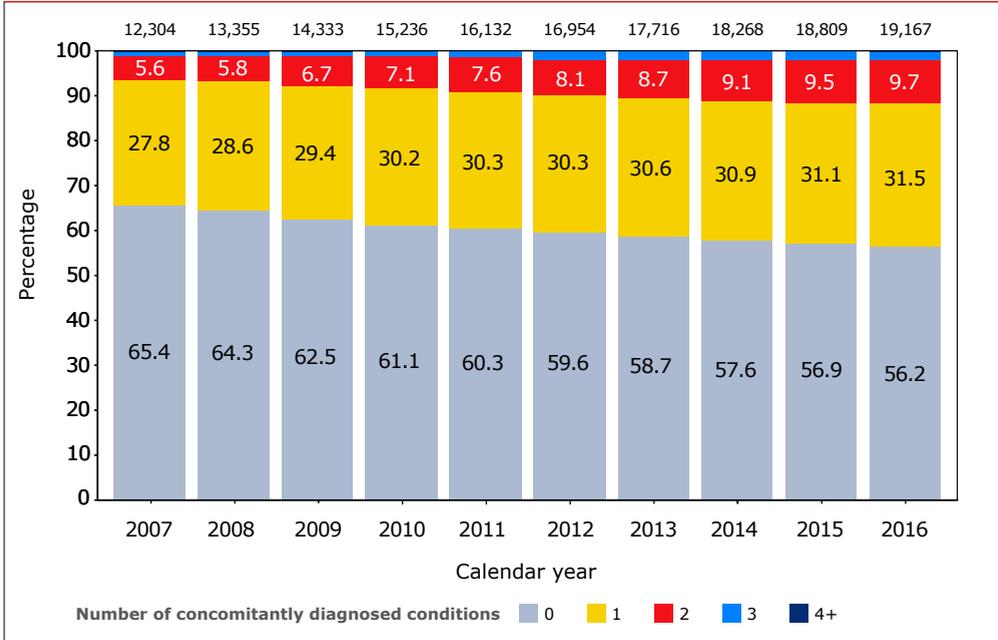


Appendix Figure 3.4: Prevalence of non-HIV/AIDS multimorbidity by gender in the adult population in 2016. The numbers on top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per age category.



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**Appendix Figure 3.5: Prevalence of non-HIV/AIDS multimorbidity in the adult population.** The numbers on top of each bar represent the number of individuals contributing data to that age category. The numbers in the stacked bars represent percentages, with all stacked bars adding up to 100% per calendar year.



*Appendix Table 3.1: Annual number of cases of death and first AIDS events among 24,684 HIV-1-positive individuals in the Netherlands recorded up to May 2016.*

Calendar year	AIDS			Death	
	Number of AIDS events	AIDS $\geq$ 6 weeks after diagnosis	AIDS $\geq$ 4 weeks after start of cART	Number of deaths	Number of deaths $\geq$ 6 weeks after start of cART
1996	362	225	24	52	24
1997	301	148	53	87	63
1998	238	97	40	84	69
1999	229	112	57	91	89
2000	242	93	59	85	81
2001	248	122	59	83	79
2002	295	115	63	120	81
2003	288	126	68	142	118
2004	280	130	60	145	122
2005	349	158	80	142	117
2006	278	138	73	123	98
2007	297	147	78	152	125
2008	274	139	84	153	132
2009	270	122	71	161	142
2010	284	115	73	130	117
2011	230	110	70	151	135
2012	262	124	81	155	144
2013	224	101	72	149	140
2014	189	82	55	165	151
2015	208	96	79	159	150
2016	151	60	51	159	150

*Legend: cART=combination antiretroviral therapy.*

**Appendix Table 3.2: Absolute number of causes of death among HIV-1-positive individuals during the periods 1996–2000, 2001–2005, 2006–2010, and 2011–2016.**

Causes of death	1996–2000	2001–2005	2006–2010	2011	2012	2013	2014	2015	2016
<b>AIDS</b>									
AIDS – infection	68	120	149	35	15	23	17	7	1
AIDS – malignancy	58	64	61	3	13	10	5	13	4
AIDS – unclassifiable	98	64	20	3	4	.	4	9	12
<i>Total</i>	224	248	230	41	32	33	26	29	17
<b>Non-AIDS malignancies</b>	31	96	137	32	43	38	41	39	39
<b>Cardiovascular disease</b>									
Myocardial infarction	14	32	54	13	7	5	10	11	7
Stroke	4	11	14	3	4	3	4	3	5
Other CVD	6	20	16	8	4	3	12	10	12
<i>Total</i>	24	63	84	24	15	11	26	24	24
<b>Non-AIDS infection</b>	24	44	31	4	7	6	10	6	12
<b>Liver disease</b>	17	30	62	8	9	10	11	6	5
<b>Lung disease</b>	4	12	33	7	4	9	5	14	12
<b>Non-natural death</b>									
Accident or violence	6	11	21	1	5	3	5	2	6
Suicide	13	26	11	7	7	3	5	8	5
Euthanasia	3	3	2	2	.	1	1	.	.
<i>Total</i>	22	40	34	10	12	7	11	10	11
<b>Alcohol and substance abuse</b>	10	14	19	1	4	4	4	2	3
<b>Other causes</b>	16	26	37	7	11	12	13	10	17
<b>Unknown</b>	28	62	55	17	18	19	18	19	19
<b>Total</b>	<b>400</b>	<b>635</b>	<b>722</b>	<b>151</b>	<b>155</b>	<b>149</b>	<b>165</b>	<b>159</b>	<b>159</b>

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

	Death			AIDS		
	RR (95% CI)	p- value	Overall p-value	RR (95% CI)	p- value	Overall p-value
<b>Risk factors</b>						
Male gender	1.43 (1.23-1.66)	<.001		1.01 (0.85-1.19)	0.920	
<b>Region of birth</b>						
Netherlands	1.00 (reference)		<.001	1.00 (reference)		0.112
Other	0.81 (0.73-0.89)	<.001		1.11 (0.99-1.26)	0.086	
<b>HIV-1 transmission route</b>						
Blood contact	0.77 (0.55-1.08)	0.132		0.92 (0.62-1.37)	0.684	
Heterosexual	1.08 (0.96-1.23)	0.213		0.91 (0.78-1.07)	0.243	
IDU	1.71 (1.40-2.08)	<.001		0.66 (0.50-0.87)	0.003	
MSM	1.00 (reference)		<.001	1.00 (reference)		0.010
Other	2.19 (1.66-2.89)	<.001		0.57 (0.39-0.84)	0.005	
<b>Age*</b>						
18-29	0.88 (0.65-1.21)	0.444	<.001	1.02 (0.83-1.27)	0.834	0.002
30-39	1.00 (reference)			1.00 (reference)		
40-49	1.44 (1.24-1.67)	<.001		1.12 (0.98-1.27)	0.109	
50-59	2.42 (2.08-2.80)	<.001		1.29 (1.11-1.51)	0.001	
60-69	4.22 (3.58-4.98)	<.001		1.37 (1.11-1.70)	0.003	
70+	9.23 (7.52-11.34)	<.001		1.81 (1.15-2.86)	0.011	
<b>CD4 cell count**</b>						
0-50	16.88 (14.13-20.15)	<.001	<.001	6.19 (4.95-7.74)	<.001	<.001
50-199	5.45 (4.72-6.29)	<.001		2.61 (2.19-3.11)	<.001	
200-349	2.16 (1.86-2.49)	<.001		1.52 (1.28-1.80)	<.001	
350-499	1.39 (1.20-1.62)	<.001		1.18 (0.98-1.41)	0.076	
500-749	1.00 (reference)			1.00 (reference)		
750+	0.89 (0.75-1.06)	0.198		1.05 (0.84-1.32)	0.665	
Per year longer on cART with HIV RNA >1,000 copies/ml	1.06 (1.04-1.08)	<.001	<.001	1.03 (1.00-1.05)	0.066	0.071
<b>Treatment status</b>						
Treatment-experienced at start cART	1.12 (1.01-1.24)	0.027		0.60 (0.53-0.69)	<.001	
Treatment-naïve at start	1.00 (reference)			1.00 (reference)		
<b>Prior AIDS event</b>						
Hepatitis B virus positive	1.85 (1.68-2.03)	<.001		1.00 (0.82-1.21)	0.998	
Hepatitis C virus positive	1.29 (1.11-1.49)	<.001		1.00 (0.82-1.21)	0.998	
Hepatitis C virus positive	1.42 (1.21-1.66)	<.001		1.29 (1.05-1.59)	0.016	

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	Death			AIDS		
	RR (95% CI)	p- value	Overall p-value	RR (95% CI)	p- value	Overall p-value
<b>Body mass index*</b>						
<18	2.62 (2.29-2.99)	<.001	<.001			
18-25	1.00 (reference)					
25-30	0.69 (0.61-0.77)	<.001				
30+	0.76 (0.62-0.93)	0.007				
<b>Smoking status</b>						
Current smoker	1.30 (1.14-1.49)	<.001	<.001	0.75 (0.66-0.86)	<.001	<.001
Never smoker	1.00 (reference)			1.00 (reference)		
Past smoker	1.54 (1.33-1.79)	<.001		0.95 (0.79-1.14)	0.575	
Early cART***	0.68 (0.48-0.97)	0.032		1.00 (0.77-1.30)	0.999	

\*Time-updated.

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

\*\*\*cART started within 12 months after last HIV-negative test.

Legend: cART=combination antiretroviral therapy; IDU=people who inject drugs; MSM=men who have sex with men; CI=confidence interval; RR=risk ratio.

*Appendix Table 3.4: Lost to follow up (no follow up after 31 December 2016) by region of origin and time-updated CD4 cell count.*

Last CD4 count	Total			Caribbean			Western Europe / North America		
	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)
<50	56	1,701	32.9 (24.9-42.8)	1	103	9.7 (0.2-54.2)	15	127	118.5 (66.4-195.5)
50-199	202	7,114	28.4 (24.6-32.6)	7	395	17.7 (7.1-36.5)	38	765	49.7 (35.1-68.2)
200-349	382	15,848	24.1 (21.7-26.6)	15	629	23.9 (13.3-39.3)	69	1,187	58.1 (45.2-73.6)
350-499	476	30,946	15.4 (14.0-16.8)	24	1,320	18.2 (11.6-27.0)	101	2,636	38.3 (31.2-46.6)
500-749	628	66,149	9.5 (8.8-10.3)	38	2,868	13.3 (9.4-18.2)	150	5,000	30.0 (25.4-35.2)
750+	357	66,309	5.4 (4.8-6.0)	21	2,773	7.6 (4.7-11.6)	112	5,759	19.4 (16.0-23.4)

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

Netherlands			Sub-Saharan Africa			South and South-East Asia		
n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)	n	PY	Incidence/ 1,000 PY (95% CI)
6	1,195	5.0 (1.8-10.9)	25	202	123.9 (80.2-183.0)	9	76	119.1 (54.5-226.1)
33	4,318	7.6 (5.3-10.7)	117	1,401	83.5 (69.0-100.1)	7	234	29.9 (12.0-61.6)
76	10,201	7.4 (5.9-9.3)	201	3,176	63.3 (54.8-72.7)	21	655	32.1 (19.8-49.0)
94	19,953	4.7 (3.8-5.8)	237	5,807	40.8 (35.8-46.4)	20	1,230	16.3 (9.9-25.1)
191	45,360	4.2 (3.6-4.9)	231	10,346	22.3 (19.5-25.4)	18	2,576	7.0 (4.1-11.0)
117	47,484	2.5 (2.0-3.0)	98	8,172	12.0 (9.7-14.6)	9	2,121	4.2 (1.9-8.1)

**Appendix Table 3.5: Absolute number of first AIDS events among HIV-1-positive individuals during the periods 1996–2000, 2001–2005, 2006–2010, and 2011–2016.**

CDC event	1996–	2001–	2006–	2011–	Total	
	2000	2005	2010	2016	n	%
AIDS dementia complex / HIV encephalopathy	45	52	56	47	200	3.38
CMV disease (other than lymph node, liver or spleen)	30	35	29	33	127	2.15
CMV retinitis	29	18	12	11	70	1.18
Candidiasis oesophageal	255	232	247	247	981	16.60
Candidiasis trachea, bronchi, lungs	7	13	7	7	34	0.58
Cervical cancer, invasive	3	4	7	3	17	0.29
Coccidioidomycosis, disseminated or extrapulmonary	.	.	1	.	1	0.02
Cryptococcosis extrapulmonary	21	32	32	12	97	1.64
Cryptosporidiosis, chronic intestinal (> 1 month)	21	12	10	10	53	0.90
Herpes simplex virus: chronic ulcer (> 1 month), bronchitis, pneumonitis, oesophagitis	32	42	60	39	173	2.93
Histoplasmosis, disseminated or extrapulmonary	9	12	10	7	38	0.64
Isosporiasis, chronic intestinal (> 1 month)	3	9	5	.	17	0.29
Kaposi's sarcoma	158	153	188	154	653	11.05
Leishmaniasis, visceral	.	1	2	3	6	0.10
Lymphoma, Burkitt's (or equivalent term) or immunoblastic (or equivalent term)	61	90	79	111	341	5.77
Lymphoma, primary, of brain	7	2	7	4	20	0.34
MAI / M. kansasii, disseminated or extrapulmonary	26	19	28	10	83	1.40
Microsporidiosis, chronic intestinal (> 1 month)	11	1	3	.	15	0.25
Mycobacterium, other species/unidentified (disseminated / extrapulmonary)	19	12	7	10	48	0.81
Other CDC C–event, specify	1	1	1	.	3	0.05
Penicilliosis	.	.	1	.	1	0.02
<i>Pneumocystis carinii</i> pneumonia	327	294	323	305	1,249	21.14
Pneumocystis, extrapulmonary	1	1	3	.	5	0.08
Pneumonia, recurrent (>1 one episode in a 1-year period)	47	65	66	94	272	4.60
Progressive multifocal leucoencephalopathy	18	23	35	23	99	1.68
Salmonella septicaemia, recurrent	2	.	.	.	2	0.03
Toxoplasmosis of the brain	68	99	55	47	269	4.55
Tuberculosis, extrapulmonary	78	109	81	50	318	5.38
Tuberculosis, pulmonary	101	165	110	74	450	7.62
Wasting syndrome due to HIV	47	56	77	87	267	4.52
<b>Total</b>	<b>1,427</b>	<b>1,552</b>	<b>1,542</b>	<b>1,388</b>	<b>5,909</b>	<b>100.00</b>

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

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

Age	Male			Female		
	n	PY	Incidence/1,000 PY (95% CI)	n	PY	Incidence/1,000 PY (95% CI)
18-29	6	9,950	0.6 (0.2-1.3)	24	6,049	4.0 (2.5-5.9)
30-39	79	36,202	2.2 (1.7-2.7)	65	14,154	4.6 (3.5-5.9)
40-49	256	59,613	4.3 (3.8-4.9)	88	12,690	6.9 (5.6-8.5)
50-59	273	39,582	6.9 (6.1-7.8)	47	5,337	8.8 (6.5-11.7)
60-69	175	14,266	12.3 (10.5-14.2)	18	1,765	10.2 (6.0-16.1)
70+	33	2,888	11.4 (7.9-16.0)	4	477	8.4 (2.3-21.5)

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

**Appendix Table 3.6B: 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.**

Age	Male			Female		
	n	PY	Incidence/1,000 PY (95% CI)	n	PY	Incidence/1,000 PY (95% CI)
18-29	6	9,934	0.6 (0.2-1.3)	5	6,032	0.8 (0.3-1.9)
30-39	76	36,109	2.1 (1.7-2.6)	24	14,090	1.7 (1.1-2.5)
40-49	416	58,971	7.1 (6.4-7.8)	87	12,539	6.9 (5.6-8.6)
50-59	638	38,299	16.7 (15.4-18.0)	42	5,243	8.0 (5.8-10.8)
60-69	422	13,251	31.8 (28.9-35.0)	41	1,707	24.0 (17.2-32.6)
70+	128	2,536	50.5 (42.1-60.0)	8	429	18.6 (8.1-36.7)

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

**Appendix Table 3.6C: Incidence of chronic kidney disease (an estimated glomerular filtration rate below 60 ml/min, estimated with the Cockcroft-Gault equation, and confirmed after 6 months or more) from 2008 onwards, according to gender and age.**

Age	Male			Female		
	n	PY	Incidence/1,000 PY (95% CI)	n	PY	Incidence/1,000 PY (95% CI)
18-29	41	6,804	6.0 (4.3-8.2)	11	3,077	3.6 (1.8-6.4)
30-39	89	20,629	4.3 (3.5-5.3)	21	8,217	2.6 (1.6-3.9)
40-49	160	39,070	4.1 (3.5-4.8)	62	9,092	6.8 (5.2-8.7)
50-59	243	30,012	8.1 (7.1-9.2)	90	4,213	21.4 (17.2-26.3)
60-69	310	11,405	27.2 (24.2-30.4)	75	1,172	64.0 (50.3-80.2)
70+	184	1,864	98.7 (84.9-114.0)	39	199	195.6 (139.1-267.4)

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

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**Appendix Table 3.6D: 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.**

Age	Male			Female		
	n	PY	Incidence/1,000 PY (95% CI)	n	PY	Incidence/1,000 PY (95% CI)
18-29	6	9,950	0.6 (0.2-1.3)	4	6,121	0.7 (0.2-1.7)
30-39	55	36,288	1.5 (1.1-2.0)	20	14,389	1.4 (0.8-2.1)
40-49	185	60,297	3.1 (2.6-3.5)	44	13,089	3.4 (2.4-4.5)
50-59	281	40,528	6.9 (6.1-7.8)	36	5,572	6.5 (4.5-8.9)
60-69	197	14,795	13.3 (11.5-15.3)	12	1,806	6.6 (3.4-11.6)
70+	72	2,863	25.2 (19.7-31.7)	8	502	15.9 (6.9-31.4)

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

**Appendix Table 3.6E: Incidence of myocardial infarction from 2000 onwards, according to gender and age.**

Age	Male			Female		
	n	PY	Incidence/1000 PY (95% CI)	n	PY	Incidence/1000 PY (95% CI)
18-29	1	9,961	0.1 (0.0-0.6)	2	6,127	0.3 (0.0-1.2)
30-39	24	36,372	0.7 (0.4-1.0)	6	14,413	0.4 (0.2-0.9)
40-49	171	60,188	2.8 (2.4-3.3)	24	13,135	1.8 (1.2-2.7)
50-59	212	40,209	5.3 (4.6-6.0)	11	5,645	1.9 (1.0-3.5)
60-69	138	14,627	9.4 (7.9-11.1)	9	1,822	4.9 (2.3-9.4)
70+	29	2,976	9.7 (6.5-14.0)	1	509	2.0 (0.0-10.9)

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

**Appendix Table 3.6F: Incidence of stroke from 2000 onwards, according to gender and age.**

Age	Male			Female		
	n	PY	Incidence/1000 PY (95% CI)	n	PY	Incidence/1000 PY (95% CI)
18-29	5	9,945	0.5 (0.2-1.2)	2	6,118	0.3 (0.0-1.2)
30-39	30	36,361	0.8 (0.6-1.2)	14	14,374	1.0 (0.5-1.6)
40-49	74	60,494	1.2 (1.0-1.5)	25	13,105	1.9 (1.2-2.8)
50-59	120	40,665	3.0 (2.4-3.5)	9	5,648	1.6 (0.7-3.0)
60-69	86	14,990	5.7 (4.6-7.1)	8	1,813	4.4 (1.9-8.7)
70+	35	3,022	11.6 (8.1-16.1)	6	509	11.8 (4.3-25.7)

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

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**Appendix Table 3.6G: Incidence of anal cancer in men from 2000 onwards, according to age.**

Age	Male		
	n	PY	Incidence/1000 PY (95% CI)
18-29	1	9,961	0.1 (0.0-0.6)
30-39	11	36,414	0.3 (0.2-0.5)
40-49	53	60,554	0.9 (0.7-1.1)
50-59	68	40,850	1.7 (1.3-2.1)
60-69	20	15,300	1.3 (0.8-2.0)
70+	3	3,187	0.9 (0.2-2.8)

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

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

Age	Male			Female		
	n	PY	Incidence/1,000 PY (95% CI)	n	PY	Incidence/1,000 PY (95% CI)
18-29	17	9,923	1.7 (1.0-2.7)	32	6,020	5.3 (3.6-7.5)
30-39	224	35,901	6.2 (5.4-7.1)	105	14,047	7.5 (6.1-9.0)
40-49	934	58,087	16.1 (15.1-17.1)	221	12,353	17.9 (15.6-20.4)
50-59	1,285	36,754	35.0 (33.1-36.9)	123	5,089	24.2 (20.1-28.8)
60-69	763	12,032	63.4 (59.0-68.1)	72	1,639	43.9 (34.4-55.3)
70+	204	2,085	97.9 (84.9-112.2)	16	372	43.0 (24.6-69.8)

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

Appendix Table 3.7: 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
<b>Male gender</b>	1.20 (1.06-1.35)	0.005	.	1.59 (1.27-1.98)	<.001	.
<b>Region of birth</b>						
Netherlands	1.00 (reference)	.	0.659	1.00 (reference)	.	0.018
Other	1.04 (0.95-1.13)	0.416	.	0.82 (0.71-0.95)	0.007	.
<b>HIV-1 transmission route</b>						
Other	1.50 (1.07-2.10)	0.017	.	1.66 (0.98-2.79)	0.058	.
MSM	1.00 (reference)	.	<.001	1.00 (reference)	.	0.012
Heterosexual	1.27 (1.14-1.41)	<.001	.	1.26 (1.07-1.49)	0.006	.
IDU	1.34 (1.08-1.67)	0.008	.	1.33 (0.93-1.89)	0.115	.
Blood contact	1.32 (1.00-1.74)	0.050	.	1.40 (0.91-2.14)	0.124	.
<b>Age*</b>						
18-29	0.60 (0.44-0.81)	<.001	<.001	0.48 (0.25-0.94)	0.031	<.001
30-39	1.00 (reference)	.	.	1.00 (reference)	.	.
40-49	1.95 (1.70-2.23)	<.001	.	2.57 (1.99-3.32)	<.001	.
50-59	3.77 (3.28-4.33)	<.001	.	5.48 (4.25-7.06)	<.001	.
60-69	6.55 (5.61-7.65)	<.001	.	9.72 (7.40-12.76)	<.001	.
70+	10.28 (8.31-12.71)	<.001	.	14.85 (10.57-20.87)	<.001	.
<b>CD4 cell count**</b>						
<50	5.23 (4.15-6.59)	<.001	<.001	3.61 (2.37-5.49)	<.001	<.001
50-199	1.93 (1.63-2.28)	<.001	.	1.63 (1.24-2.13)	<.001	.
200-349	1.30 (1.14-1.47)	<.001	.	1.25 (1.03-1.52)	0.024	.
350-499	1.09 (0.97-1.21)	0.142	.	1.06 (0.89-1.26)	0.524	.
500-749	1.00 (reference)	.	.	1.00 (reference)	.	.
≥750	1.10 (0.99-1.23)	0.081	.	1.24 (1.05-1.47)	0.013	.
<b>Per year longer with CD4 &lt;200 cells/mm<sup>3</sup></b>	0.98 (0.95-1.00)	0.082	.	1.00 (0.96-1.04)	0.950	.
<b>Per year longer on cART with HIV RNA &gt;10 copies/ml</b>	1.02 (1.00-1.04)	0.115	.	1.03 (0.99-1.07)	0.120	.
<b>Treatment status</b>						
Not or not yet started cART	1.39 (1.21-1.58)	<.001	<.001	1.06 (0.84-1.34)	0.637	0.089
Treatment-experienced at start cART	1.29 (1.16-1.43)	<.001	.	1.20 (1.02-1.42)	0.030	.
Treatment-naive at start	1.00 (reference)	.	.	1.00 (reference)	.	.
<b>Per year longer on cART</b>	1.01 (1.00-1.02)	0.072	.	1.00 (0.98-1.01)	0.682	.

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	Non-AIDS-defining malignancy			Diabetes mellitus			Chronic kidney disease		
	IRR (95% CI)	p- value	Overall p-value	IRR (95% CI)	p- value	Overall p-value	IRR (95% CI)	p- value	Overall p-value
	1.07 (0.86-1.35)	0.538	.	1.22 (1.01-1.46)	0.037	.	0.55 (0.46-0.65)	<.001	.
	1.00 (reference)	.	0.141	1.00 (reference)	.	<.001	1.00 (reference)	.	<.001
	0.86 (0.73-1.01)	0.058	.	1.40 (1.22-1.61)	<.001	.	1.39 (1.22-1.58)	<.001	.
	1.52 (0.88-2.61)	0.132	.	1.56 (0.87-2.78)	0.133	.	1.13 (0.68-1.87)	0.645	.
	1.00 (reference)	.	0.054	1.00 (reference)	.	<.001	1.00 (reference)	.	0.065
	1.06 (0.88-1.28)	0.556	.	1.52 (1.28-1.80)	<.001	.	0.98 (0.83-1.15)	0.798	.
	1.50 (1.06-2.12)	0.024	.	1.40 (0.96-2.04)	0.081	.	1.61 (1.17-2.21)	0.003	.
	1.69 (1.11-2.58)	0.015	.	1.43 (0.93-2.20)	0.101	.	1.14 (0.76-1.70)	0.532	.
	0.66 (0.37-1.18)	0.159	<.001	0.63 (0.43-0.94)	0.023	<.001	1.10 (0.77-1.57)	0.608	<.001
	1.00 (reference)	.	.	1.00 (reference)	.	.	1.00 (reference)	.	.
	2.13 (1.63-2.79)	<.001	.	1.51 (1.24-1.83)	<.001	.	1.47 (1.16-1.86)	0.002	.
	4.74 (3.63-6.20)	<.001	.	2.38 (1.94-2.93)	<.001	.	3.54 (2.81-4.45)	<.001	.
	8.89 (6.67-11.86)	<.001	.	4.40 (3.49-5.56)	<.001	.	12.46 (9.88-15.71)	<.001	.
	17.76 (12.59-25.07)	<.001	.	4.25 (2.89-6.24)	<.001	.	43.84 (33.93-56.65)	<.001	.
	2.87 (1.71-4.81)	<.001	<.001	9.25 (6.76-12.66)	<.001	<.001	2.23 (1.41-3.52)	<.001	<.001
	1.82 (1.35-2.44)	<.001	.	2.35 (1.81-3.05)	<.001	.	1.63 (1.27-2.09)	<.001	.
	1.42 (1.16-1.75)	<.001	.	1.14 (0.92-1.41)	0.221	.	1.24 (1.03-1.49)	0.020	.
	1.14 (0.94-1.37)	0.177	.	1.05 (0.87-1.26)	0.605	.	1.00 (0.85-1.17)	0.968	.
	1.00 (reference)	.	.	1.00 (reference)	.	.	1.00 (reference)	.	.
	0.87 (0.71-1.06)	0.156	.	1.18 (0.99-1.41)	0.063	.	1.06 (0.91-1.23)	0.471	.
	0.99 (0.95-1.03)	0.483	.	0.96 (0.92-1.00)	0.043	.	0.99 (0.96-1.03)	0.732	.
	0.99 (0.95-1.03)	0.585	.	1.01 (0.98-1.05)	0.447	.	0.99 (0.96-1.03)	0.586	.
	1.54 (1.22-1.95)	<.001	<.001	1.85 (1.50-2.27)	<.001	<.001	0.76 (0.59-0.97)	0.028	<.001
	1.18 (0.98-1.42)	0.074	.	1.38 (1.16-1.64)	<.001	.	1.37 (1.16-1.62)	<.001	.
	1.00 (reference)	.	.	1.00 (reference)	.	.	1.00 (reference)	.	.
	1.01 (0.99-1.03)	0.270	.	1.02 (1.01-1.04)	0.005	.	0.98 (0.96-0.99)	0.003	.

	Non-AIDS-defining disease			Cardiovascular disease		
	IRR (95% CI)	p- value	Overall p-value	IRR (95% CI)	p- value	Overall p-value
<b>Body mass index*</b>						
<18	1.45 (1.17-1.79)	<.001	<.001	1.27 (0.91-1.77)	0.164	0.010
18-25	1.00 (reference)	.	.	1.00 (reference)	.	.
25-30	1.19 (1.09-1.30)	<.001	.	0.99 (0.86-1.14)	0.853	.
>30	1.72 (1.51-1.96)	<.001	.	1.12 (0.89-1.41)	0.339	.
<b>Prior AIDS event</b>	1.25 (1.14-1.36)	<.001	.	1.15 (1.01-1.32)	0.036	.
<b>HBV-positive</b>	1.19 (1.03-1.37)	0.016	.	0.99 (0.78-1.26)	0.955	.
<b>HCV-positive</b>	1.13 (0.97-1.31)	0.117	.	0.97 (0.76-1.24)	0.805	.
<b>Hypertension</b>	1.19 (1.09-1.30)	<.001	.	1.26 (1.10-1.44)	<.001	.
<b>Smoking status</b>						
Current smoker	1.35 (1.22-1.50)	<.001	<.001	1.94 (1.64-2.30)	<.001	<.001
Never smoker	1.00 (reference)	.	.	1.00 (reference)	.	.
Past smoker	1.27 (1.12-1.43)	<.001	.	1.57 (1.29-1.91)	<.001	.
<b>Calendar year period</b>						
2000-2005	1.24 (1.10-1.39)	<.001	<.001	1.47 (1.22-1.77)	<.001	<.001
2006-2010	1.22 (1.11-1.34)	<.001	.	1.26 (1.08-1.46)	0.003	.
2011-2016	1.00 (reference)	.	.	1.00 (reference)	.	.
<b>Early cART within 12 months after last HIV-negative test</b>	1.03 (0.82-1.29)	0.790	.	1.10 (0.79-1.53)	0.576	.
<b>Per year longer on LOP/r</b>		.	.	1.01 (0.99-1.02)	0.435	.
<b>Per year longer on IDV</b>		.	.	1.02 (1.00-1.03)	0.072	.
<b>Recent use of ABC ***</b>		.	.	1.51 (1.31-1.74)	<.001	.
<b>Per year longer on ZDV</b>		.	.		.	.
<b>Per year longer on d4T</b>		.	.		.	.
<b>Per year longer on ddI</b>		.	.		.	.
<b>Per year longer on TDF</b>		.	.		.	.
<b>Prior cardiovascular event</b>		.	.		.	.
<b>Prior diabetes</b>		.	.		.	.

*Legend: ABC=abacavir; cART=combination antiretroviral therapy; d4T=stavudine; ddI=didanosine; IRR=incidence rate ratio; MSM=men who have sex with men; IDU=injecting drug users; IDV=indinavir; LOP/r=ritonavir-boosted lopinavir; TDF=tenofovir disoproxil fumarate; ZDV=zidovudine.*

	Non-AIDS-defining malignancy			Diabetes mellitus			Chronic kidney disease		
	IRR (95% CI)	p- value	Overall p-value	IRR (95% CI)	p- value	Overall p-value	IRR (95% CI)	p- value	Overall p-value
	1.76 (1.30-2.39)	<.001	<.001	1.39 (0.94-2.06)	0.099	<.001	5.15 (4.23-6.27)	<.001	<.001
	1.00 (reference)	.	.	1.00 (reference)	.	.	1.00 (reference)	.	.
	0.81 (0.69-0.96)	0.013	.	2.05 (1.77-2.38)	<.001	.	0.39 (0.33-0.46)	<.001	.
	0.87 (0.66-1.15)	0.327	.	3.93 (3.28-4.72)	<.001	.	0.25 (0.18-0.35)	<.001	.
	1.21 (1.05-1.40)	0.010	.	1.35 (1.18-1.55)	<.001	.	1.11 (0.98-1.25)	0.107	.
	1.58 (1.27-1.97)	<.001	.	1.11 (0.88-1.41)	0.385	.	1.37 (1.12-1.69)	0.003	.
	1.19 (0.93-1.53)	0.160	.	1.21 (0.94-1.54)	0.138	.	1.24 (1.01-1.53)	0.041	.
	1.02 (0.88-1.19)	0.752	.	1.19 (1.04-1.37)	0.014	.	0.99 (0.87-1.12)	0.885	.
	1.69 (1.40-2.03)	<.001	<.001	0.86 (0.73-1.01)	0.064	0.103	1.09 (0.94-1.26)	0.259	0.209
	1.00 (reference)	.	.	1.00 (reference)	.	.	1.00 (reference)	.	.
	1.47 (1.19-1.82)	<.001	.	1.06 (0.88-1.27)	0.533	.	1.05 (0.89-1.24)	0.540	.
	0.93 (0.75-1.15)	0.523	0.129	1.28 (1.06-1.55)	0.011	0.020		.	.
	1.13 (0.96-1.32)	0.147	.	1.19 (1.02-1.39)	0.024	.	0.81 (0.70-0.92)	0.002	0.002
	1.00 (reference)	.	.	1.00 (reference)	.	.	1.00 (reference)	.	.
	0.98 (0.66-1.45)	0.931	.	0.99 (0.66-1.49)	0.979	.	1.19 (0.91-1.54)	0.198	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.		.	.		.	.
		.	.	1.01 (1.00-1.01)	0.029	.		.	.
		.	.	1.01 (0.99-1.02)	0.309	.		.	.
		.	.	1.01 (1.00-1.03)	0.029	.		.	.
		.	.		.	.	0.99 (0.99-1.00)	0.054	.
		.	.		.	.	1.54 (1.27-1.88)	<.001	.
		.	.		.	.	1.64 (1.33-2.02)	<.001	.

Appendix Table 3.8: Specific CDC-B and CDC-C (AIDS) events occurring in individuals on cART with undetectable viral load between 2000 and 2016.

	CDC event	All events		0-49	
		n	%	n	%
CDC-B events	Bacillary angiomatosis	1	0.0	0	0.0
	Candidiasis, oropharyngeal	630	21.0	53	24.4
	Candidiasis, vulvovaginal	55	1.8	1	0.5
	Cervical dysplasia or carcinoma <i>in situ</i>	580	19.4	8	3.7
	Diarrhoea of unknown origin > 1 month	65	2.2	1	0.5
	Fever of unknown origin > 1 month	6	0.2	0	0.0
	Herpes simplex virus, mucocutaneous	18	0.6	2	0.9
	Herpes zoster, multidermatomal or 2+ episodes	211	7.0	9	4.1
	Myelopathy, HIV-related	9	0.3	0	0.0
	Neuropathy, peripheral, HIV-related	70	2.3	1	0.5
	Nocardiosis	1	0.0	1	0.5
	Oral hairy leukoplakia	52	1.7	1	0.5
	Pelvic inflammatory disease	3	0.1	0	0.0
	Thrombocytopenia, HIV-related	100	3.3	4	1.8
	Weight loss (> 10%) of unknown origin	35	1.2	2	0.9
	Other non C-category supposedly HIV-related	92	3.1	9	4.1
	<b>Subtotal</b>		<b>1,928</b>	<b>64.4</b>	<b>92</b>
CDC-C events	AIDS dementia complex / HIV encephalopathy	49	1.6	6	2.8
	Candidiasis, oesophageal	190	6.3	20	9.2
	Candidiasis trachea, bronchi, lungs	9	0.3	2	0.9
	Cervical cancer, invasive	8	0.3	1	0.5
	Cytomegalovirus disease (not lymph node, liver or spleen)	18	0.6	4	1.8
	Cytomegalovirus retinitis	14	0.5	3	1.4
	Coccidioidomycosis, disseminated/ extrapulmonary	1	0.0	0	0.0
	Cryptococcosis, extrapulmonary	14	0.5	7	3.2
	Cryptosporidiosis, chronic intestinal	9	0.3	3	1.4
	Herpes simplex virus: chronic bronchitis, pneumonitis, oesophagitis	56	1.9	7	3.2
	Histoplasmosis, disseminated or extrapulmonary	3	0.1	2	0.9
	Isosporiasis, chronic intestinal (> 1 month)	1	0.0	0	0.0
	Kaposi's sarcoma	78	2.6	3	1.4
	Leishmaniasis, visceral	5	0.2	1	0.5
	Lymphoma, non-Hodgkin	113	3.8	6	2.8

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CD4 category										
50-199		200-349		350-499		500-749		750+		
n	%	n	%	n	%	n	%	n	%	
1	0.2	0	0.0	0	0.0	0	0.0	0	0.0	
156	27.6	132	19.5	103	17.5	118	18.8	68	21.3	
5	0.9	10	1.5	17	2.9	17	2.7	5	1.6	
72	12.7	132	19.5	131	22.2	151	24.1	86	26.9	
5	0.9	17	2.5	11	1.9	22	3.5	9	2.8	
1	0.2	2	0.3	0	0.0	1	0.2	2	0.6	
3	0.5	2	0.3	4	0.7	4	0.6	3	0.9	
25	4.4	51	7.5	44	7.5	51	8.1	31	9.7	
4	0.7	2	0.3	0	0.0	0	0.0	3	0.9	
8	1.4	14	2.1	24	4.1	13	2.1	10	3.1	
0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
14	2.5	10	1.5	11	1.9	10	1.6	6	1.9	
0	0.0	1	0.1	1	0.2	1	0.2	0	0.0	
22	3.9	25	3.7	14	2.4	24	3.8	11	3.4	
5	0.9	8	1.2	6	1.0	9	1.4	5	1.6	
14	2.5	16	2.4	20	3.4	26	4.2	7	2.2	
<b>335</b>	<b>59.3</b>	<b>422</b>	<b>62.2</b>	<b>386</b>	<b>65.4</b>	<b>447</b>	<b>71.4</b>	<b>246</b>	<b>76.9</b>	
7	1.2	12	1.8	9	1.5	8	1.3	7	2.2	
49	8.7	48	7.1	29	4.9	25	4.0	19	5.9	
1	0.2	4	0.6	0	0.0	1	0.2	1	0.3	
2	0.4	1	0.1	1	0.2	3	0.5	0	0.0	
2	0.4	3	0.4	6	1.0	1	0.2	2	0.6	
4	0.7	2	0.3	4	0.7	1	0.2	0	0.0	
0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	
5	0.9	1	0.1	0	0.0	1	0.2	0	0.0	
0	0.0	1	0.1	3	0.5	1	0.2	1	0.3	
5	0.9	13	1.9	15	2.5	14	2.2	2	0.6	
0	0.0	0	0.0	0	0.0	1	0.2	0	0.0	
0	0.0	1	0.1	0	0.0	0	0.0	0	0.0	
9	1.6	21	3.1	16	2.7	21	3.4	8	2.5	
4	0.7	0	0.0	0	0.0	0	0.0	0	0.0	
30	5.3	27	4.0	23	3.9	23	3.7	4	1.3	

CDC event	All events		0-49	
	n	%	n	%
Lymphoma, primary, of brain	4	0.1	0	0.0
Microsporidiosis, chronic intestinal	3	0.1	1	0.5
MAI / <i>M. kansasii</i> , disseminated/extrapulmonary	22	0.7	5	2.3
Mycobacterium, other/unidentified (disseminated/extrapulmonary)	6	0.2	1	0.5
<i>Pneumocystis carinii</i> pneumonia	53	1.8	16	7.4
Pneumonia, recurrent (in a 1-year period)	262	8.7	13	6.0
Progressive multifocal leucoencephalopathy	16	0.5	4	1.8
Toxoplasmosis of the brain	16	0.5	6	2.8
Tuberculosis, extrapulmonary	37	1.2	3	1.4
Tuberculosis, pulmonary	61	2.0	4	1.8
Wasting syndrome due to HIV	15	0.5	7	3.2
Other CDC C-event, specify	5	0.2	0	0.0
<b>Subtotal</b>	<b>1,068</b>	<b>35.6</b>	<b>125</b>	<b>57.6</b>
<b>Total</b>	<b>2,996</b>	<b>100.0</b>	<b>217</b>	<b>100.0</b>

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

Appendix Table 5.1 Characteristics of 556 HIV-1 positive children in the Netherlands on combination antiretroviral therapy (cART).

Characteristic	Children with vertically-acquired HIV			Children with non-vertically-acquired HIV
	0-2 years	2-5 years	5-18 years	
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 <sup>3</sup> )*	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)	4.8 (4.0-5.3)

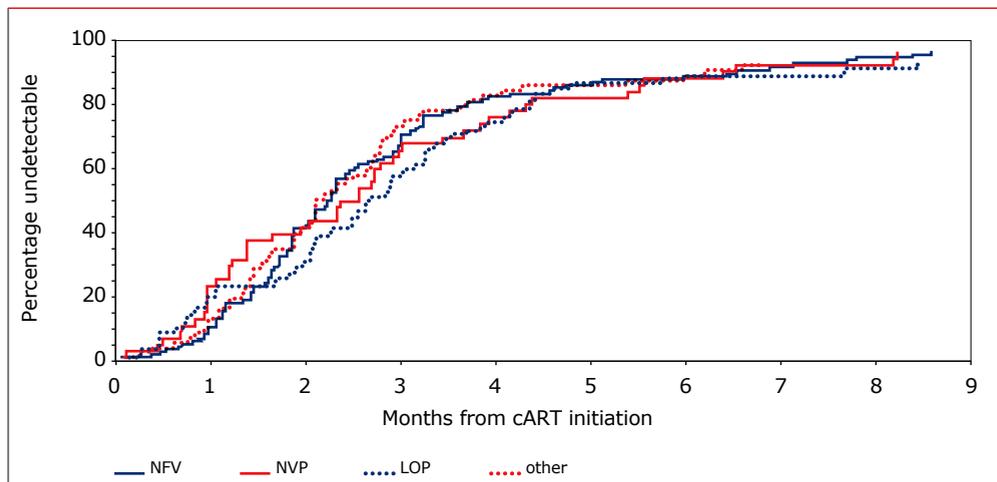
\*Median (IQR)

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

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CD4 category										
50-199		200-349		350-499		500-749		750+		
n	%	n	%	n	%	n	%	n	%	
1	0.2	2	0.3	1	0.2	0	0.0	0	0.0	
1	0.2	0	0.0	0	0.0	0	0.0	1	0.3	
7	1.2	5	0.7	2	0.3	2	0.3	1	0.3	
1	0.2	3	0.4	0	0.0	1	0.2	0	0.0	
19	3.4	6	0.9	6	1.0	5	0.8	1	0.3	
46	8.1	73	10.8	65	11.0	48	7.7	17	5.3	
6	1.1	2	0.3	2	0.3	2	0.3	0	0.0	
4	0.7	4	0.6	1	0.2	1	0.2	0	0.0	
8	1.4	7	1.0	4	0.7	10	1.6	5	1.6	
13	2.3	18	2.7	13	2.2	8	1.3	5	1.6	
4	0.7	1	0.1	2	0.3	1	0.2	0	0.0	
2	0.4	1	0.1	2	0.3	0	0.0	0	0.0	
<b>230</b>	<b>40.7</b>	<b>256</b>	<b>37.8</b>	<b>204</b>	<b>34.6</b>	<b>179</b>	<b>28.6</b>	<b>74</b>	<b>23.1</b>	
<b>565</b>	<b>100.0</b>	<b>678</b>	<b>100.0</b>	<b>590</b>	<b>100.0</b>	<b>626</b>	<b>100.0</b>	<b>320</b>	<b>100.0</b>	

**Appendix Figure 6.1:** Time to initial suppression of HIV RNA to <50 (or <500) copies/ml after the start of combination antiretroviral therapy among pregnant women, by third drug addition to the cART regimen.



**Legend:** cART=combination antiretroviral therapy; NFV=nelfinavir; NVP=nevirapine; LOP=lopinavir.

**Appendix Table 9.1:** Annual number of new HIV diagnoses, number of individuals entering care, and number of individuals starting combination antiretroviral treatment (cART). Note: Data collection for 2015 and 2016 had not yet been finalised at the time of writing.

Calendar year	Diagnosis	Entry into care	Start cART
≤2004	454	397	230
2005	42	54	44
2006	46	58	39
2007	39	43	44
2008	47	51	45
2009	50	54	49
2010	41	50	55
2011	54	55	46
2012	57	64	61
2013	69	62	80
2014	38	47	72
2015	41	47	49
2016	43	55	58
2017	2	5	10
Unknown	31	12	16
<b>Total</b>	<b>1,054</b>	<b>1,054</b>	<b>898</b>



# Acknowledgements

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*Data collection:* B.A.F.M. de Kruijf-van de Wiel, B. van der Ven.

*HIV clinical virologists/chemists:* A.G.M. Buiting, P.J. Kabel, D. Versteeg.

### Erasmus MC, Rotterdam

*HIV treating physicians:* M.E. van der Ende\*, H.I. Bax, E.C.M. van Gorp, J.L. Nouwen, B.J.A. Rijnders, C.A.M. Schurink, A. Verbon, T.E.M.S. de Vries-Sluijs, N.C. de Jong-Peltenburg.

*HIV nurse consultants:* N. Bassant, J.E.A. van Beek, M. Vriesde, L.M. van Zonneveld.

*Data collection:* H.J. van den Berg-Cameron, J. de Groot, M. de Zeeuw-de Man.

*HIV clinical virologists/chemists:* C.A.B. Boucher, M.P.G. Koopmans, J.J.A. van Kampen, S.D. Pas.

### Erasmus MC–Sophia, Rotterdam

*HIV treating physicians:* P.L.A. Fraaij, A.M.C. van Rossum, C.L. Vermont.

*HIV nurse consultants:* L.C. van der Knaap, E. Visser.

**Flevoziekenhuis, Almere**

*HIV treating physicians:* J. Branger\*,  
A. Rijkeboer-Mes.

*HIV nurse consultant:* C.J.H.M. Duijf-  
van de Ven.

**HagaZiekenhuis, Den Haag**

*HIV treating physicians:* E.F. Schippers\*,  
C. van Nieuwkoop.

*HIV nurse consultants:* J.M. van IJperen,  
J. Geilings.

*Data collection:* G. van der Hut.

*HIV clinical virologist/chemist:*  
N.D. van Burgel.

**HMC (Haaglanden Medisch Centrum),  
Den Haag**

*HIV treating physicians:* E.M.S. Leyten\*,  
L.B.S. Gelinck.

*HIV nurse consultants:*

A.Y. van Hartingsveld, C. Meerkerk,  
G.S. Wildenbeest.

*HIV clinical virologists/chemists:*  
E. Heikens.

**Isala, Zwolle**

*HIV treating physicians:* P.H.P.  
Groeneveld\*, J.W. Bouwhuis,  
A.J.J. Lammers.

*HIV nurse consultants:* S. Kraan,  
A.G.W. van Hulzen, M.S.M. Kruiper.

*Data collection:* G.L. van der Blik,  
P.C.J. Bor.

*HIV clinical virologists/chemists:*  
P. Bloembergen, M.J.H.M. Wolfhagen,  
G.J.H.M. Ruijs.

**Leids Universitair Medisch Centrum,  
Leiden**

*HIV treating physicians:* F.P. Kroon\*,  
M.G.J. de Boer, H. Scheper, H. Jolink,  
A.M. Vollaard.

*HIV nurse consultants:* W. Dorama,  
N. van Holten.

*HIV clinical virologists/chemists:*  
E.C.J. Claas, E. Wessels.

**Maasstad Ziekenhuis, Rotterdam**

*HIV treating physicians:* J.G. den  
Hollander\*, K. Pogany, A. Roukens.

*HIV nurse consultants:* M. Kastelijns,  
J.V. Smit, E. Smit, D. Struik-Kalkman,

C. Tearno. *Data collection:* T. van Niekerk.

*HIV clinical virologists/chemists:*  
O. Pontesilli.

**Maastricht UMC+, Maastricht**

*HIV treating physicians:* S.H. Lowe\*,  
A.M.L. Oude Lashof, D. Posthouwer.

*HIV nurse consultants:* R.P. Ackens,  
K. Burgers, J. Schippers.

*Data collection:* B. Weijenberg-Maes.

*HIV clinical virologists/chemists:*

I.H.M. van Loo, T.R.A. Havenith.

**MC Slotervaart, Amsterdam**

*HIV treating physicians:* J.W. Mulder\*,  
S.M.E. Vrouwenraets, F.N. Lauw.

*HIV nurse consultants:* M.C. van  
Broekhuizen, D.J. Vlasblom.

*HIV clinical virologists/chemists:*  
P.H.M. Smits.

**MC Zuiderzee, Lelystad**

*HIV treating physicians:* S. Weijer\*,  
R. El Moussaoui.

*HIV nurse consultant:* A.S. Bosma.

**Medisch Centrum Leeuwarden,  
Leeuwarden**

*HIV treating physicians:*  
M.G.A. van Vonderen\*, D.P.F. van Houte,  
L.M. Kampschreur.  
*HIV nurse consultants:* K. Dijkstra,  
S. Faber.  
*HIV clinical virologists/chemists:*  
J Weel.

**Medisch Spectrum Twente, Enschede**

*HIV treating physicians:* G.J. Kootstra\*,  
C.E. Delsing.  
*HIV nurse consultants:* M. van der  
Burg-van de Plas, H. Heins.  
*Data collection:* E. Lucas.

**Noordwest Ziekenhuisgroep, Alkmaar**

*HIV treating physicians:* W. Kortmann\*,  
G. van Twillert\*, R. Renckens.  
*HIV nurse consultant and data  
collection:* D. Ruiten-Pronk,  
F.A. van Truijen-Oud.  
*HIV clinical virologists/chemists:*  
J.W.T. Cohen Stuart, E.P. IJzerman,  
R. Jansen, W. Rozemeijer W. A. van der  
Reijden.

**OLVG, Amsterdam**

*HIV treating physicians:* K. Brinkman\*,  
G.E.L. van den Berk, W.L. Blok,  
P.H.J. Frissen, K.D. Lettinga,  
W.E.M. Schouten, J. Veenstra.  
*HIV nurse consultants:* C.J. Brouwer,  
G.F. Geerders, K. Hoeksema, M.J.  
Kleene, I.B. van der Meché, M.  
Spelbrink, A.J.M. Toonen, S. Wijnands.  
*HIV clinical virologists:* D. Kwa.  
*Data collection:* R. Regez (coordinator).

**Radboudumc, Nijmegen**

*HIV treating physicians:* R. van  
Crevel\*, M. Keuter, A.J.A.M. van der  
Ven, H.J.M. ter Hofstede, A.S.M.  
Dofferhoff, S.S.V. Henriët, M. van de  
Flier, K. van Aerde, J. Hoogerwerf.  
*HIV nurse consultants:* M. Albers,  
K.J.T. Grintjes-Huisman, M. de Haan,  
M. Marneef, A. Hairwassers.  
*HIV clinical virologists/chemists:*  
J. Rahamat-Langendoen, F.F. Stelma.  
*HIV clinical pharmacology  
consultant:* D. Burger.

**Rijnstate, Arnhem**

*HIV treating physicians:* E.H. Gisolf\*,  
R.J. Hassing, M. Claassen.  
*HIV nurse consultants:* G. ter Beest,  
P.H.M. van Bentum, N. Langebeek.  
*HIV clinical virologists/chemists:*  
R. Tiemessen, C.M.A. Swanink.

**Spaarne Gasthuis, Haarlem**

*HIV treating physicians:* S.F.L. van  
Lelyveld\*, R. Soetekouw.  
*HIV nurse consultants:* L.M.M. van der  
Prijt, J. van der Swaluw.  
*Data collection:* N. Bermon.  
*HIV clinical virologists/chemists:*  
W.A. van der Reijden, R. Jansen,  
B.L. Herpers, D. Veenendaal.  
*Medisch Centrum Jan van Goyen,  
Amsterdam*  
*HIV treating physicians:*  
D.W.M. Verhagen.  
*HIV nurse consultants:* M. van Wijk.

**Universitair Medisch Centrum  
Groningen, Groningen**

*HIV treating physicians:* W.F.W. Bierman\*, M. Bakker, J. Kleinnijenhuis, E. Kloeze, E.H. Scholvinck, Y. Stienstra, C.L. Vermont, K.R. Wilting, M. Wouthuyzen-Bakker.

*HIV nurse consultants:* A. Boonstra, H. de Groot-de Jonge, P.A. van der Meulen, D.A. de Weerd.

*HIV clinical virologists/chemists:* H.G.M. Niesters, C.C. van Leer-Buter, M. Knoester.

**UMC Utrecht, Utrecht**

*HIV treating physicians:* A.I.M. Hoepelman\*, J.E. Arends, R.E. Barth, A.H.W. Bruns, P.M. Ellerbroek, T. Mudrikova, J.J. Oosterheert, E.M. Schadd, M.W.M. Wassenberg, M.A.D. van Zoelen.

*HIV nurse consultants:* K. Aarsman, D.H.M. van Elst-Laurijssen, I. de Kroon, C.S.A.M. van Rooijen.

*Data collection:* M. van Berkel, C.S.A.M. van Rooijen.

*HIV clinical virologists/chemists:* R. Schuurman, F. Verduyn-Lunel, A.M.J. Wensing.

**VUmc, Amsterdam**

*HIV treating physicians:* E.J.G. Peters\*, M.A. van Agtmael, M. Bomers.

*HIV nurse consultants:* M. Heitmuller, L.M. Laan.

*HIV clinical virologists/chemists:* C.W. Ang, R. van Houdt, A.M. Pettersson, C.M.J.E. Vandenbroucke-Grauls.

**Wilhelmina Kinderziekenhuis, UMC  
Utrecht, Utrecht**

*HIV treating physicians:* L.J. Bont, S.P.M. Geelen, T.F.W. Wolfs.

*HIV nurse consultants:* N. Nauta.

**Sint Elisabeth Hospitaal, Willemstad,  
Curaçao**

*HIV treating physicians:* D. van de Wetering, J.F. Schattenkerk, F. Muskiet, R. Voigt.

*HIV nurse consultants:* I. van der Meer.

**Coordinating centre**

*Director:* P. Reiss.

*Deputy director:* S. Zaheri.

*Data analysis:* D.O. Bezemer, A.I. van Sighem, C. Smit, F.W.M.N. Wit, T.S. Boender.

*Data management and quality control:* M. Hillebregt, A. de Jong, T. Woudstra.

*Data monitoring:* D. Bergsma, S. Grivell, A. Jansen, R. Meijering, M. Raethke, T. Rutkens. *Data collection:* L. de Groot-Berndsen, M. van den Akker, Y. Bakker, M. Bezemer, E. Claessen, A. El Berkaoui, J. Geerlinks, J. Koops, E. Kruijne, C. Lodewijk, R. van der Meer,

L. Munjishvili, F. Paling, B. Peeck, C. Ree, R. Henstra-Regtop, Y. Ruijs-Tiggelman, M. Schoorl, A. Timmerman, E. Tuijn, L. Veenenberg-Benschop, S. van der Vliet, A. Wisse, E.C. Witte.

*Patient registration:* B. Tuk-Stuster.

# Composition of Stichting HIV Monitoring

## SHM Board

Name	Position	Representing	Affiliation
Dr F.P. Kroon	Chair	Nederlandse Vereniging van HIV Behandelaren (NVHB)	LUMC, Leiden
Y.T.H.P. van Duijnhoven	Secretary	GGD GHOR Nederland	GGD Amsterdam
Dr P.W.D. Venhoeven	Treasurer	Prinses Maxima Centre for Paediatric Oncology	
Prof. K. Stronks		AMC-UvA	AMC-UvA, Amsterdam
L.J.M. Elsenburg (until November 2016)		Hiv Vereniging	Hiv Focus Centrum
P. Brokx (as of November 2016)		Hiv Vereniging	Hiv Vereniging
Dr M.M.E. Schneider		Nederlandse Federatie Universitair Medische Centra (NFU)	UMC Utrecht
P.E. van der Meer		Nederlandse Vereniging van Ziekenhuizen (NVZ)	Albert Schweizer Ziekenhuis
J. Crasborn		Zorgverzekeraars Nederland	Achmea
Dr. M. van der Valk		Nederlandse Vereniging van HIV Behandelaren (NVHB)	AMC-UvA Amsterdam

## SHM Advisory Board

### Name

Prof. D.R. Kuritzkes (Chair)  
 Prof. Sir R.M. Anderson  
 (until December 2016)  
 Prof. M. Egger  
 Prof. C. Sabin  
 (as of December 2016)  
 Prof. B. Ledergerber  
 (as of December 2016)  
 Prof. T.B.H. Geijtenbeek  
 P.J. Smit  
 Dr M. van der Valk

### Affiliation

Brigham and Women's Hospital, MA, USA  
 Imperial College, London, UK  
  
 University of Bern, Switzerland  
 University College, London, UK  
  
 University Hospital Zurich, Switzerland  
  
 AMC-UvA, Amsterdam  
 Hiv Vereniging, Amsterdam  
 AMC-UvA, Amsterdam

## SHM working group

### Members

#### Name

Dr M.E. van der Ende (Chair)  
 Prof. C.A.B. Boucher  
 Dr F.C.M. van Leth

#### Affiliation

Erasmus MC, Rotterdam  
 Erasmus MC, Rotterdam  
 KNCV Tuberculosis Foundation, The Hague;  
 AIGHD Amsterdam

## Reviewers

### Name

Dr N.K.T. Back  
Prof. K. Brinkman  
Dr D.M. Burger  
(Pharmacology subgroup)  
Dr E.C.J. Claas  
Prof. G.J.J. Doornum (Emeritus)  
Dr S.P.M. Geelen  
Prof. A.I.M. Hoepelman  
Dr S. Jurriaans  
Prof. T.W. Kuijpers  
Dr W.J.G. Melchers  
Prof. J.M. Prins  
Prof. P.H.M. Savelkoul  
Dr R. Schuurman  
Dr H.G. Sprenger  
Dr A.M.J. Wensing

### Affiliation

AMC-UvA, Amsterdam  
OLVG, Amsterdam  
Radboudumc, Nijmegen  
  
LUMC, Leiden  
Erasmus MC, Rotterdam  
UMC Utrecht-WKZ, Utrecht  
UMC Utrecht, Utrecht  
AMC-UvA, Amsterdam  
AMC-UvA, Amsterdam  
Radboudumc, Nijmegen  
AMC-UvA, Amsterdam  
MUMC+, Maastricht  
UMC Utrecht, Utrecht  
UMCG, Groningen  
UMC Utrecht, Utrecht

## Hepatitis working group

### Name

Dr C. Richter  
(Chair until 1 November 2016)  
Dr J. Arends  
(Chair as of 1 November 2016)  
Prof. K. Brinkman  
Dr M.E. van der Ende  
(until May 2017)  
Prof. A.I.M. Hoepelman  
Dr J. van der Meer  
Dr. B. Rijnders  
(as of May 2017)  
Dr J. Schinkel  
Dr E.F. Schippers  
Dr C. Smit  
Dr M. van der Valk  
Dr T.E.M.S. de Vries-Sluis  
Dr A. Vollaard

### Affiliation

Rijnstate, Arnhem  
UMC Utrecht, Utrecht  
OLVG, Amsterdam  
Erasmus MC, Rotterdam  
UMC Utrecht, Utrecht  
AMC-UvA, Amsterdam  
Erasmus MC, Rotterdam  
AMC-UvA, Amsterdam  
HagaZiekenhuis, Den Haag  
Stichting HIV Monitoring, Amsterdam  
AMC-UvA, Amsterdam  
Erasmus MC, Rotterdam  
LUMC, Leiden

## SHM personnel

### Director

Prof. P. Reiss MD

### Deputy director

S. Zaheri MSc

## Data analysis, reporting & research unit

### Researchers

D.O. Bezemer PhD  
T.S. Boender PhD  
A.I. van Sighem PhD  
C. Smit PhD  
F.W.N.M. Wit PhD

<i>Data management</i>	M.M.J. Hillebregt MSc (coordinator) A.S. de Jong MSc T.J. Woudstra (as of 1 June 2017)
<i>QC &amp; protocol management</i>	S. Grivell MSc (protocol & helpdesk coordinator) A.M. Jansen MSc (data quality staff coordinator)
<i>Data quality staff</i>	D. Bergsma MSc A. de Lang PhD († 22 November 2016) R. Meijering MSc M.J.C. Rademaker MSc (until 30 November 2016) M.S. Raethke MSc S. Schnörr MSc (until 30 November 2016)
<i>Data protection officer</i>	M.M.B. Tuk-Stuster
<i>Patient registration &amp; data collection</i>	L.G.M. de Groot-Berndsen (coordinator) M.M.B. Tuk-Stuster (patient registration & quality management coordinator)

*Data collectors*

M. van den Akker  
 Y.M. Bakker  
 M. Bezemer-Goedhart (as of 1 December 2016)  
 E.J. Claessen (until 16 May 2017)  
 A. El Berkaoui  
 R. Henstra-Regtop  
 J. Koops  
 E.I. Kruijne  
 C.R.E. Lodewijk  
 L. Munjishvili MA  
 B.M. Peeck MSc  
 C.M.J. Ree  
 Y.M.C. Ruijs-Tiggelman  
 T. Rutkens  
 L. van de Sande MA (until 28 February 2017)  
 M.J.C. Schoorl MSc  
 A.G. Timmerman MSc (until 30 September 2017)  
 E.M. Tuijn-de Bruin  
 D.P. Veenenberg-Benschop  
 S. van der Vliet  
 S.J. Wisse MSc  
 T.J. Woudstra (until 30 May 2017)  
 F. Paling MSc (as of 1 April 2017)  
 J. Geerlinks (as of 1 April 2017)  
 R. van der Meer MA (as of 1 April 2017)  
 E.C.M. Witte (as of 1 May 2017)

**Communications unit**

C.J. Ester PhD (manager)  
 M.J. Sormani

**Human resources,  
 finance & administration**

I. Bartels (HR advisor)  
 A. J.P. van der Doelen (controller)  
 H.J.M. van Noort MSc (financial administrator)  
 M.M.T. Koenen (office manager)  
 Y. de Waart (office, HR & finance assistant)

## Expert clinical and public health advisors

<b>Name</b>	<b>Affiliation</b>
Dr. J. Arends	UMCU, Utrecht
Prof. K. Brinkman	OLVG, Amsterdam
Prof. S. Geerlings	AMC-UvA, Amsterdam
Prof. F. Kroon	LUMC, Leiden
Dr. L. van Leeuwen	AMC-UvA, Amsterdam
Dr. J. Nellen	AMC-UvA, Amsterdam
Dr. C. van Nieuwkoop	HagaZiekenhuis, The Hague
Dr. E. Op de Coul	RIVM, Bilthoven
Prof. J.M. Prins	AMC-UvA, Amsterdam
Dr. C. Richter	Rijnstate, Arnhem
Dr. A. van Rossum	Erasmus MC, Rotterdam
Dr. M. van der Valk	AMC-UvA, Amsterdam
Dr. A.M.J. Wensing	UMC Utrecht, Utrecht
Dr. T. Wolfs	Wilhelmina Kinderziekenhuis, Utrecht.

# Publications & presentations

The publications and presentations listed below are those available since the publication of the Monitoring Report 2016.

## Publications

**In-utero exposure to tenofovir is associated with impaired fetal and infant growth: need for follow-up studies in combination antiretroviral therapy/HIV-exposed infants**

Denneman L, Cohen S, Godfried MH, van Leeuwen E, Nellen JF, Kuijpers TW, Pajkrt D, van de Plas A, Smit C, Weijnsfeld AM, Scherpbier HJ, Bunders MJ.

*AIDS*. 2016 Aug 24;30(13):2135-7. doi: [10.1097/QAD.0000000000001156](https://doi.org/10.1097/QAD.0000000000001156)

**Kaposi sarcoma risk in HIV-infected children and adolescents on combination antiretroviral therapy from sub-Saharan Africa, Europe, and Asia**  
Pediatric AIDS-Defining Cancer Project Working Group for IeDEA Southern Africa, TAPHOD, and COHERE in EuroCoord.

*Clin Infect Dis*. 2016 Aug 30. pii: ciw519. [*Epub ahead of print*]

**Infection-related and -unrelated malignancies, HIV and the aging population**

Shepherd L, Borges Á, Ledergerber B, Domingo P, Castagna A, Rockstroh J, Knysz B, Tomazic J, Karpov I, Kirk O, Lundgren J, Mocroft A; EuroSIDA in EuroCOORD.

*HIV Med*. 2016 Sep;17(8):590-600. doi: [10.1111/hiv.12359](https://doi.org/10.1111/hiv.12359). Epub 2016 Feb 18

**Efavirenz versus boosted atazanavir-containing regimens and immunologic, virologic, and clinical outcomes: A prospective study of HIV-positive individuals**

Cain LE, Caniglia EC, Phillips A, Olson A, Muga R, Pérez-Hoyos S, Abgrall S, Costagliola D, Rubio R, Jarrín I, Bucher H, Fehr J, van Sighem A, Reiss P, Dabis F, Vandenhende MA, Logan R, Robins J, Sterne JA, Justice A, Tate J, Touloumi G, Pappas V, Esteve A, Casabona J, Seng R, Meyer L, Jose S, Sabin C, Hernán MA; HIV-CAUSAL Collaboration.

*Medicine (Baltimore)*. 2016 Oct;95(41):e5133. doi: [10.1097/MD.0000000000005133](https://doi.org/10.1097/MD.0000000000005133)

**The cardiovascular risk management for people living with HIV in Europe: how well are we doing?**

Shahmanesh M, Schultze A, Burns F, Kirk O, Lundgren J, Mussini C, Pedersen C, De Wit S, Kutsyna G, Mocroft A; EuroSIDA in EuroCOORD.

*AIDS*. 2016 Oct 23;30(16):2505-2518

**Chronic hepatitis B and C virus infection and risk for non-Hodgkin lymphoma in HIV-infected patients: A cohort study**

Wang Q, De Luca A, Smith C, Zangerle R, Sambatakou H, Bonnet F, Smit C, Schommers P, Thornton A, Berenguer J, Peters L, Spagnuolo V, Ammassari A, Antinori A, Roldan EQ, Mussini C, Miro JM, Konopnicki D, Fehr J, Campbell MA, Termote M, Bucher HC; Hepatitis Coinfection and Non Hodgkin Lymphoma project team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.

*Ann Intern Med.* 2016 Oct 18. doi: [10.7326/M16-0240](https://doi.org/10.7326/M16-0240). [Epub ahead of print]

**Prevalence and effect of pre-treatment drug resistance on the virological response to antiretroviral treatment initiated in HIV-infected children - a EuroCoord-CHAIN-EPPICC joint project**

Ngo-Giang-Huong N, Wittkop L, Judd A, Reiss P, Goetghebuer T, Duiculescu D, Noguera-Julian A, Marczyńska M, Giacchino C, Ene L, Ramos JT, Cellera C, Klimkait T, Brichard B, Valerius N, Sabin C, Teira R, Obel N, Stephan C, de Wit S, Thorne C, Gibb D, Schwimmer C, Campbell MA, Pillay D, Lallemand M; EuroCoord-CHAIN-EPPICC joint project study group.

*BMC Infect Dis.* 2016 Nov 8;16(1):654. doi:10.1186/s12879-016-1968-2

**Estimating HIV incidence and number of undiagnosed individuals living with HIV in the European Union/European Economic Area, 2015**

Pharris A, Quinten C, Noori T, Amato-Gauci AJ, van Sighem A, the ECDC HIV/AIDS Surveillance and Dublin Declaration Monitoring Networks.

*Eurosurveillance, Volume 21, Issue 48, 01 December 2016*

**Cigarette smoking and inflammation, monocyte activation, and coagulation in HIV-infected individuals receiving antiretroviral therapy, compared with uninfected individuals**

Kooij KW, Wit FW, Booiman T, van der Valk M, Schim van der Loeff MF, Kootstra N, Reiss P; AGEHIV Cohort Study Group.

*J Infect Dis.* 2016 Dec 15;214(12):1817-1821. doi: 10.1093/infdis/jiw459

**Suboptimal primary and secondary cardiovascular disease prevention in HIV-positive individuals on antiretroviral therapy**

van Zoest RA, van der Valk M, Wit FW, Vaartjes I, Kooij KW, Hovius JW, Prins M, Reiss P; AGEHIV Cohort Study Group.

*Eur J Prev Cardiol.* 2017 Jan 1:2047487317714350. doi: 10.1177/2047487317714350. [Epub ahead of print]

**Inequalities by educational level in response to combination antiretroviral treatment and survival in HIV-positive men and women in Europe**

Socio-economic Inequalities and HIV Working Group for Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord.

*AIDS*. 2017 Jan 14;31(2):253-262. doi: [10.1097/QAD.0000000000001270](https://doi.org/10.1097/QAD.0000000000001270)

**Reference curves for CD4<sup>+</sup> T cell count response to combination of antiretroviral treatment in HIV-1 infected naive patients**

Bouteloup V, Sabin C, Mocroft A, Gras L, Pantazis N, Le Moing V, d'Arminio Monforte A, Mary-Krause M, Roca B, Miro JM, Battegay M, Brockmeyer N, Berenguer J, Morlat P, Obel N, De Wit S, Fätkenheuer G, Zangerle R, Ghosn J, Pérez-Hoyos S, Campbell M, Prins M, Chêne G, Meyer L, Dorrucchi M, Torti C, Thiébaud R; Standard Reference Distribution of CD4 Response to HAART Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.

*HIV Med* 2017 Jan;18(1):33-44

**Factors associated with time to achieve an undetectable HIV RNA viral load after start of antiretroviral treatment in HIV-1-infected pregnant women**

van Snippenburg W, Nellen FJB, Smit C, Wensing AMJ, Godfried MH, Mudrikova T for the ATHENA cohort.

*Journal of Virus Eradication* 2017;3:34-39

**Timing of cART initiation in male and female migrants living with HIV in Western Europe: an observational cohort study (1997-2013)**

Migrant Health Working Group for the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord.

*AIDS*. 2017 Jan 21. doi: [10.1097/QAD.0000000000001411](https://doi.org/10.1097/QAD.0000000000001411). [Epub ahead of print]

**Cerebral blood flow and cognitive function in HIV-infected men with sustained suppressed viremia on combination antiretroviral therapy**

Su T, Mutsaerts HJ, Caan MW, Wit FW, Schouten J, Geurtsen GJ, Sharp DJ, Prins M, Richard E, Portegies P, Reiss P, Majoie CB; AGEHIV Cohort Study.

*AIDS*. 2017 Jan 24. doi: [10.1097/QAD.0000000000001414](https://doi.org/10.1097/QAD.0000000000001414). [Epub ahead of print]

**Plasma HIV-1 tropism and the risk of short-term clinical progression to AIDS or death**

Casadellà M, Cozzi-Lepri A, Phillips A, Noguera-Julian M, Bickel M, Sedlacek D, Zilmer K, Clotet B, Lundgren JD, Paredes R, on behalf of EuroSIDA in EuroCoord.

*PLoS One*. 2017 Jan 27;12(1):e0166613. doi: [10.1371/journal.pone.0166613](https://doi.org/10.1371/journal.pone.0166613). eCollection 2017

**An epidemiological modelling study to estimate the composition of HIV-positive populations including migrants from endemic settings**

Nakagawa F; Writing Group on HIV Epidemiologic Estimates in Countries With Migrant Populations From High Prevalence Areas.

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**Proactive HIV testing required [article in Dutch]**

Joore IK, Op de Coul ELM, Bom BCJ, van Sighem AI, Geerlings SE, Prins JM, van Bergen JEAM.

*Huisarts Wet* 2017;60(1):24-6

**Higher subcortical and white matter cerebral blood flow in perinatally HIV-infected children**

Blokhuis C, Mutsaerts HJ, Cohen S, Scherpbier HJ, Caan MW, Majoie CB, Kuijpers TW, Reiss P, Wit FW, Pakkrt D.

*Medicine (Baltimore)*. 2017 Feb;96(7):e5891. doi: [10.1097/MD.0000000000005891](https://doi.org/10.1097/MD.0000000000005891)

**Higher rates of triple-class virological failure in perinatally HIV-infected teenagers compared with heterosexually infected young adults in Europe**

Judd A, Lodwick R, Noguera-Julian A, Gibb DM, Butler K, Costagliola D, Sabin C, van Sighem A, Ledergerber B, Torti C, Mocroft A, Podzamczar D, Dorrucchi M, De Wit S, Obel N, Dabis F, Cozzi-Lepri A, García F, Brockmeyer NH, Warszawski J, Gonzalez-Tome MI, Mussini C, Touloumi G, Zangerle R, Ghosn J, Castagna A, Fätkenheuer G, Stephan C, Meyer L, Campbell MA, Chene G, Phillips A; Pursuing Later Treatment Options II (PLATO II) Project Team for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.

*HIV Med*. 2017 Mar;18(3):171-180. doi: [10.1111/hiv.12411](https://doi.org/10.1111/hiv.12411). Epub 2016 Sep 14

**Is response to anti-hepatitis C virus treatment predictive of mortality in hepatitis C virus/HIV-positive patients? Hepatitis C Working Group for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord.**

*AIDS*. 2017 Mar 13;31(5):661-668. doi: [10.1097/QAD.0000000000001378](https://doi.org/10.1097/QAD.0000000000001378)

**Predictors of eGFR progression, stabilisation or improvement after chronic renal impairment in HIV-positive individuals**

Ryom L, Mocroft A, Kirk O, Reiss P, Ross M, Smith C, Moranne O, Morlat P, Fux CA, Sabin C, Phillips A, Law M, Lundgren JD; D:A:D study group. *AIDS*. 2017 Mar 28. doi: 10.1097/QAD.0000000000001464. [Epub ahead of print]

**Increased brain-predicted ageing in treated HIV disease**

Cole JH, Underwood J, Caan MWA, De Francesco D, van Zoest RA, Leech R, Wit FWNM, Portegies P, Geurtsen GJ, Schmand B, Schim van der Loeff MF, Franceschi C, Sabin C, Majoie BLM, Winston A, Reiss P, Sharp DJ; COBRA collaboration. *Neurology*. 2017 Apr 4;88(14):1349-1357. doi: 10.1212/WNL.0000000000003790. Epub 2017 Mar 3

**Optimal timing of antiretroviral treatment initiation in HIV-positive children and adolescents: a multiregional analysis from Southern Africa, West Africa and Europe**

Schomaker M, Leroy V, Wolfs T, Technau KG, Renner L, Judd A, Sawry S, Amorissani-Folquet M, Noguera-Julian A, Tanser F, Eboua F, Navarro ML, Chimbete C, Amani-Bosse C, Warszawski J, Phiri S, N'Gbeche S, Cox V, Koueta F, Giddy J, Sygnaté-Sy H, Raben D, Chêne G, Davies MA; IeDEA West and Southern Africa regional collaborations and COHERE in EuroCoord. *Int J Epidemiol*. 2017 Apr 1;46(2):453-465. doi: 10.1093/ije/dyw097

**Phylogenetic evidence for underreporting of male-to-male sex among human immunodeficiency virus-infected donors in the Netherlands and Flanders**

van de Laar TJ, Bezemer D, van Laethem K, Vandewalle G, de Smet A, van Wijngaerden E, Claas EC, van Sighem AI, Vandamme AM, Compernelle V, Zaaijer HL. *Transfusion*. 2017 Apr 4. doi: 10.1111/trf.14097. [Epub ahead of print]

**Impact of CD4 and CD8 dynamics and viral rebounds on loss of virological control in HIV controllers**

Chereau F, Madec Y, Sabin C, Obel N, Ruiz-Mateos E, Chrysos G, Fidler S, Lehmann C, Zangerle R, Wittkop L, Reiss P, Hamouda O, Estrada Perez V, Leal M, Mocroft A, Garcia De Olalla P, Ammassari A, D'Arminio Monforte A, Mussini C, Segura F, Castagna A, Cavassini M, Grabar S, Morlat P, De Wit S, Lambotte O, Meyer L; HIV Controllers Project Working Group for the Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCOORD.

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**Grey and white matter abnormalities in treated HIV-disease and their relationship to cognitive function**

Underwood J, Cole JH, Caan M, De Francesco D, Leech R, van Zoest RA, Su T, Geurtsen GJ, Schmand BA, Portegies P, Prins M, Wit FW, Sabin CA, Majoie C, Reiss P, Winston A, Sharp DJ; Co-morBidity in Relation to Aids (COBRA) Collaboration.

*Clin Infect Dis.* 2017 Apr 6. doi: [10.1093/cid/cix301](https://doi.org/10.1093/cid/cix301). [*Epub ahead of print*]

**Comparison of dynamic monitoring strategies based on CD4 cell counts in virally suppressed, HIV-positive individuals on combination antiretroviral therapy in high-income countries: a prospective, observational study**

Caniglia EC, Cain LE, Sabin CA, Robins JM, Logan R, Abgrall S, Mugavero MJ, Hernández-Díaz S, Meyer L, Seng R, Drozd DR, Seage GR 3rd, Bonnet F, Dabis F, Moore RD, Reiss P, van Sighem A, Mathews WC, Del Amo J, Moreno S, Deeks SG, Muga R, Boswell SL, Ferrer E, Eron JJ, Napravnik S, Jose S, Phillips A, Justice AC, Tate JP, Gill J, Pacheco A, Veloso VG, Bucher HC, Egger M, Furrer H, Porter K, Touloumi G, Crane H, Miro JM, Sterne JA, Costagliola D, Saag M, Hernán MA; HIV-CAUSAL Collaboration.; Centers for AIDS Research Network of Integrated Clinical Systems.

*Lancet HIV.* 2017 Apr 11. pii: S2352-3018(17)30043-7. doi: [10.1016/S2352-3018\(17\)30043-7](https://doi.org/10.1016/S2352-3018(17)30043-7). [*Epub ahead of print*]

**Impact of co-morbidity and aging on health-related quality of life in HIV-positive and HIV-negative individuals**

Langebeek N, Kooij KW, Wit FW, Stolte IG, Sprangers MAG, Reiss P, Nieuwkerk PT; AGEHIV Cohort Study Group. *AIDS.* 2017 Apr 19. doi: [10.1097/QAD.0000000000001511](https://doi.org/10.1097/QAD.0000000000001511). [*Epub ahead of print*]

**Twenty years of combination antiretroviral therapy for HIV infection in the Netherlands: progression and new challenges [article in Dutch]**

Brinkman K, Boender TS, van der Valk M, van Sighem A, Reiss P, Kroon FP on behalf of the ATHENA observational HIV cohort.

*Ned Tijdschr Geneeskd.* 2017;161: D1123

**Survival of HIV-positive patients starting antiretroviral therapy between 1996 and 2013: a collaborative analysis of cohort studies**

The Antiretroviral Therapy Cohort Collaboration.

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**Antiretrovirals, fractures and osteonecrosis in a large international HIV cohort**

Borges ÁH, Hoy J, Florence E, Sedlacek D, Stellbrink HJ, Uzdaviniene V, Tomazic J, Gargalianos-Kakolyris P, Schmid P, Orkin C, Pedersen C, Leen C, Pradier C, Mulcahy F, Ridolfo AL, Staub T, Maltez F, Weber R, Flamholz L, Kyselyova G, Lungren JD, Mocroft A; for EuroSIDA.

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**High cellular monocyte activation in people living with human immunodeficiency virus on combination antiretroviral therapy and lifestyle-matched controls is associated with greater inflammation in cerebrospinal fluid**

Booiman T, Wit FW, Maurer I, De Francesco D, Sabin CA, Harskamp AM, Prins M, Garagnani P, Pirazzini C, Franceschi C, Fuchs D, Gisslén M, Winston A, Reiss P, Kootstra NA; Comorbidity in Relation to AIDS (COBRA) Collaboration.

*Open Forum Infect Dis.* 2017 May 25;4(3):ofx108. doi: 10.1093/ofid/ofx108. eCollection 2017 Summer

**Epidemiology of ageing with HIV: what can we learn from cohorts?**

Sabin CA, Reiss P.

*AIDS.* 2017 Jun 1;31 Suppl 2:S121-S128. doi: 10.1097/QAD.0000000000001374

**Cohort Profile: Collaboration of Observational HIV Epidemiological Research Europe (COHERE) in EuroCoord**

Chêne G, Phillips A, Costagliola D, Sterne JA, Furrer H, Del Amo J, Mocroft A, d'Arminio Monforte A, Dabis F, Miro JM, Barger D, Termote M, Schwimmer C, Salbøl Brandt R, Friis-Møller N, Raben D, Haerry D, Egger M, Weller I, De Wit S.

*Int J Epidemiol.* 2017 Jun 1;46(3):797-797n. doi:10.1093/ije/dyw211

**Predictors of estimated glomerular filtration rate progression, stabilization or improvement after chronic renal impairment in HIV-positive individuals**

Ryom L, Mocroft A, Kirk O, Reiss P, Ross M, Smith C, Moranne O, Morlat P, Fux CA, Sabin C, Phillips A, Law M, Lundgren JD; D:A:D study group. *AIDS*. 2017 Jun 1;31(9):1261-1270. doi: [10.1097/QAD.0000000000001464](https://doi.org/10.1097/QAD.0000000000001464)

**Comparison of Kaposi sarcoma risk in HIV-positive adults across five continents: a multiregional multicohort study**

Bohlius J; AIDS-defining Cancer Project Working Group for IeDEA and COHERE in EuroCoord. *Clin Infect Dis*. 2017 May 20. doi: [10.1093/cid/cix480](https://doi.org/10.1093/cid/cix480). [Epub ahead of print]

**Comparing viral load metrics and evaluating their use for HIV surveillance**

Bolijn R, Op de Coul ELM, van Sighem A, Blok WL, Kretzschmar ME, Heijne JCM; ATHENA National Observational HIV Cohort. *J Infect*. 2017 May 25. pii: S0163-4453(17)30144-5. doi: [10.1016/j.jinf.2017.05.010](https://doi.org/10.1016/j.jinf.2017.05.010). [Epub ahead of print]

**Viral genetic variation accounts for a third of variability in HIV-1 set-point viral load in Europe**

Blanquart F, Wymant C, Cornelissen M, Gall A, Bakker M, Bezemer D, Hall M, Hillebregt M, Ong SH, Albert J, Bannert N, Fellay J, Fransen K, Gourlay AJ, Grabowski MK, Günsenheimer-Bartmeyer B, Günthard HF, Kivelä P, Kouyos R, Laeyendecker O, Liitsola K, Meyer L, Porter K, Ristola M, van Sighem A, Vanham G, Berkhout B, Kellam P, Reiss P, Fraser C; BEEHIVE collaboration. *PLoS Biol*. 2017 Jun 12;15(6):e2001855. doi: [10.1371/journal.pbio.2001855](https://doi.org/10.1371/journal.pbio.2001855). eCollection 2017 Jun

**The human immunodeficiency virus continuum of care in European Union countries in 2013: data and challenges**

Gourlay A, Noori T, Pharris A, Axelsson M, Costagliola D, Cowan S, Croxford S, d'Arminio Monforte A, Del Amo J, Delpech V, Díaz A, Girardi E, Günsenheimer-Bartmeyer B, Hernando V, Jose S, Leierer G, Nikolopoulos G, Obel N, Op de Coul E, Paraskeva D, Reiss P, Sabin C, Sasse A, Schmid D, Sonnerborg A, Spina A, Suligoi B, Supervie V, Touloumi G, Van Beckhoven D, van Sighem A, Vourli G, Zangerle R, Porter K; European HIV Continuum of Care Working Group. *Clin Infect Dis*. 2017 Jun 15;64(12):1644-1656. doi: [10.1093/cid/cix212](https://doi.org/10.1093/cid/cix212)

**Immune reconstitution inflammatory syndrome associated with toxoplasmic encephalitis in HIV-infected patients**

van Bilsen WPH, van den Berg CHSB, Rijnders BJA, Brinkman K, Mulder JW, Gelinck LBS, Hoepelman AIM, Wit FWNM, van de Beek D, Prins JM.

*AIDS*. 2017 Jun 19;31(10):1415-1424. doi: [10.1097/QAD.0000000000001492](https://doi.org/10.1097/QAD.0000000000001492)

**High need to switch cART or co-medication with the initiation of DAAs in elderly HIV/HCV co-infected patients**

Smolders EJ, Smit C, Tmm De Kanter C, Dofferhoff A, Arends JE, Brinkman K, Rijnders B, Van Der Valk M, Reiss P, Burger DM.

*J Acquir Immune Defic Syndr*. 2017 Jun 22. doi: [10.1097/QAI.0000000000001488](https://doi.org/10.1097/QAI.0000000000001488). [Epub ahead of print]

**Mapping HIV prevalence in the Netherlands with geographic information systems [article in Dutch]**

Op de Coul ELM, Joore IK, van Sighem A, Bom BCJ, Hillebregt M, Prins JM, Geerlings SE, van Bergen JEAM.

*Ned Tijdschr Geneeskd*. 2017;161(0):D965

**Limited overlap between phylogenetic HIV and HCV clusters illustrates the dynamic sexual network structure of Dutch HIV-infected MSM**

Vanhommerig JW, Bezemer D, Molenkamp R, Van Sighem AI, Smit C, Arends JE, Lauw FN, Brinkman K, Rijnders BJ, Newsom AM, Bruisten SM, Prins M, Van Der Meer JT, Van De Laar TJ, Schinkel J; MOSAIC study and the ATHENA national observational cohort.

*AIDS*. 2017 Jul 7. doi: [10.1097/QAD.0000000000001592](https://doi.org/10.1097/QAD.0000000000001592). [Epub ahead of print]

**A survey of patients' perspectives on outpatient HIV care in the Netherlands**

Engelhard EAN, Smit C, Kroon FP, Nieuwkerk PT, Reiss P, Brinkman K, Geerlings SE.

*Infect Dis Ther*. 2017 Jul 4. doi: [10.1007/s40121-017-0164-z](https://doi.org/10.1007/s40121-017-0164-z). [Epub ahead of print]

**CD4 cell count response to first-line combination ART in HIV-2+ patients compared with HIV-1+ patients: a multinational, multicohort European study**

Wittkop L, Arsandaux J, Trevino A, Schim van der Loeff M, Anderson J, van Sighem A, Böni J, Brun-Vezinet F, Soriano V, Boufassa F, Brockmeyer N, et al. on behalf of the COHERE in EuroCoord and ACHIEV2e Study Group. *J Antimicrob Chemother*. 2017. dkk210, <https://doi.org/10.1093/jac/dkx210>

**Towards standardised definitions for monitoring the continuum of HIV care in Europe**

Gourlay AJ, Pharris AM, Noori T, Supervie V, Rosinska M, van Sighem A, Touloumi G, Porter K.

*AIDS*. 2017 Jul 18. doi: 10.1097/QAD.0000000000001597. [Epub ahead of print]

**Effect of immediate initiation of antiretroviral treatment in HIV-positive individuals aged 50 years or older**

Lodi S, Costagliola D, Sabin C, Amo JD, Logan R, Abgrall S, Reiss P, van Sighem A, Jose S, Blanco JR, Hernando V, Bucher HC, Kovari H, Segura F, Ambrosioni J, Gogos CA, Pantazis N, Dabis F, Vandenhende MA, Meyer L, Seng R, Gill J, Krentz H, Phillips A, Porter K, Grinsztejn B, Pacheco AG, Muga R, Tate J, Justice A, Hernán MA.

*J Acquir Immune Defic Syndr*. 2017 Jul 21. doi: 10.1097/QAI.0000000000001498. [Epub ahead of print]

**Immunological and virological response to antiretroviral treatment in migrant and native men and women in Western Europe; is benefit equal for all?**

Migrant Health Working Group for the Collaboration of Observational HIV Epidemiological Research in Europe (COHERE) in EuroCoord.

*HIV Med*. 2017 Jul 25. doi: 10.1111/hiv.12536. [Epub ahead of print]

**HIV testing week 2015: lowering barriers for HIV testing among high-risk groups in Amsterdam**

Bartelsman M, Joore IK, van Bergen JE, Hogewoning AA, Zuure FR, van Veen MG; HIV Transmission Elimination AMsterdam (H-TEAM) initiative.

*BMC Infect Dis*. 2017 Aug 1;17(1):529. doi: 10.1186/s12879-017-2617-0

**Hypertension in people living with HIV**

van Zoest RA, van den Born BH, Reiss P. *Curr Opin HIV AIDS*. 2017 Aug 4. doi: 10.1097/COH.0000000000000406. [Epub ahead of print]

**Terminal differentiation of T cells is strongly associated with CMV infection and increased in HIV-positive individuals on ART and lifestyle matched controls**

Booiman T, Wit FW, Girigorie AF, Maurer I, De Francesco D, Sabin CA, Harskamp AM, Prins M, Franceschi C, Deeks SG, Winston A, Reiss P, Kootstra NA; Co-morbidity in Relation to Aids (COBRA) Collaboration.

*PLoS One*. 2017 Aug 14;12(8):e0183357. doi: 10.1371/journal.pone.0183357. eCollection 2017

**Other publications**

**Sexually transmitted infections, including HIV, in the Netherlands in 2016**

Visser M, van Aar F, van Oeffelen AAM, van den Broek IVF, Op de Coul ELM, Hofstraat SHI, Heijne JCM, den Daas C, Hoenderboom BM, van Wees DA, Basten M, Woestenberg PJ, Götz HM, van Sighem AI, de Hoon S, van Benthem BHB *RIVM Rapport 2017-0003*

## Poster presentations

**Increasing ART coverage and viral suppression are associated with a substantial decline in new HIV infections in the Austrian Tyrol**

Leierer G, van Sighem A, Sarcletti M, Kitchen M, Gisinger M, Rappold M, Ledergerber B, Zangerle R

*HIV Glasgow, Glasgow, UK, 23-26 October 2016*

**Progression to liver-related complications in HIV/hepatitis B coinfecting patients in the era of potent combination antiretroviral therapy (cART) is not increased compared to hepatitis B mono-infection**

Lieveld F.

*AASLD (American Association for the study of Liver Diseases) Liver Meeting 2016, Boston USA, 11 November 2016*

**Despite a decreasing rate of virological failure in the treated Dutch HIV-infected population, transmitted HIV drug resistance in the Netherlands remains stable**

Hofstra LM, van Sighem A, Litsenburg M, Brinkman K, Bierman W, van der Ende ME, Hoepelman AIM, Van Kasteren M, Op de Coul E, Richter C, Boucher CAB, Wensing AMJ.

*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**Development and validation of the HCV-MOSAIC risk score to assist testing for acute HCV infection in HIV-infected MSM**

Newsum AM, Stolte IG, van der Meer JTM, Schinkel J, van der Valk M, Vanhommerig JW, Buvé A, Danta M, Hogewoning A, Prins M, on behalf of the MOSAIC study group.

*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**Effect of hepatitis C virus infection and its timing relative to HIV seroconversion on CD4 T-cell and HIV RNA trends among HIV-positive MSM**

van Santen D, van der Helm JJ, Touloumi GT, Pantazis NP, Muga RM, Bartmeyer BB, Gill JG, Sanders ES, Kelleher AK, Zangerle RZ, Porter KP, Prins MP, Geskus RG.

*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**Frequency of STI testing associated with sexual risk behavior and HIV serostatus among MSM in the Netherlands**

Reitsema M, Wallinga J, van Benthem BH, van Sighem AI, Schim van der Loeff MF, Xiridou M.

*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**Health related quality of life of HIV-infected patients in care in the Netherlands: A cross-sectional assessment of patient related factors, and comparison with other chronic diseases**

Nieuwkerk P, Engelhard EAN, Smit C.  
*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**HIV infection is independently associated with chronic kidney disease and mild glomerular hyperfiltration, particularly in those of African descent**

Kooij K, Vogt L, Wit FWNM, van der Valk M.  
*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**Increasing role of young MSM to HIV epidemic spread and renewal**

Ratmann O, Bezemer D, van Sighem A, Pettersson A, Bierman W, Reiss P, Fraser C, Boucher C.  
*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**Lack of compliance to hepatocellular carcinoma (HCC) screening guidelines in hepatitis B (HBV) or C (HCV) virus co-infected HIV patients with cirrhosis; COHERE in Eurocoord**

Smit C.  
*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**Several national HIV-1 non-B subtype sub-epidemics established in the Netherlands**

Bezemer D, Ratmann O, van Sighem A, Fraser C, Reiss P.  
*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

**The role of CMV and the need for appropriate HIV-uninfected controls to evaluate T-cell senescence in HIV-positive individuals on combination antiretroviral therapy**

Booiman T, Wit FW, Girigorie AG, de Francesco D, Sabin WCA, Harskamp AM, Prins M, de Franceschi C, Deeks SG, Winston A, Reiss P, Kootstra NA.  
*10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

### **Viral load metrics: an additional benefit for HIV surveillance?**

Heijne J, Bolijn R, Op de Coul E, van Sighem A, Blok WL, Kretzschmar ME. *10<sup>th</sup> Netherlands Conference on HIV Pathogenesis, Epidemiology, Prevention and Treatment, Amsterdam, the Netherlands, 22 November 2016*

### **Variation in ART-coverage and virological suppression among HIV key populations**

Laut K, on behalf of EuroSIDA *HepHIV 2017 Conference, St Julians, Malta, 31 January - 2 February 2017*

### **Central nervous system penetration of antiretroviral therapy in HIV-infected children**

Hof MV, Blokhuis C, Cohen S, Scherpbier HJ, Wit F, Pistorius M, Kootstra NA, Teunissen CE, Mathot R, Pajkrt D. *CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

### **Darunavir/r use and incident chronic kidney disease in HIV-positive persons**

Ryom L, Lundgren JD, Reiss P, Kirk O, Law M, Ross M, Morlat P, Fux CA, Mocroft A. *CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

### **Earlier diagnosis and treatment reduces HIV transmission in MSM in the Netherlands**

van Sighem A, Bezemer D, Op de Coul E, Branger J, de Boer M, Reiss P. *CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

### **First and recurrent venous thrombosis in HIV patients of the Dutch ATHENA cohort**

Rokx C, Borjas Howard J, Smit C, Wit F, Pieterman ED, Meijer K, Bierman W, Tichelaar V, Rijnders B. *CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

### **Integrase inhibitors are an independent risk factor for IRIS: an ATHENA cohort study**

Wijting I, Rokx C, Wit F, Postma A, Hoepelman A, van der Ende I, Reiss P, Rijnders B. *CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

### **Longitudinal analysis shows no evidence for accelerated brain ageing in treated HIV**

Cole JH, Caan MW, Underwood J, van Zoest R, De Francesco D, Winston A, Sabin C, Sharp DJ, Reiss P. *CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

**Stopping secondary TE prophylaxis in suppressed patients with CD4 100–200 is not safe**

Miro JM.

*CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

**Vascular health and cerebral blood flow in perinatally HIV-infected children**

Blokhuis C, Cohen S, Scherpbier HJ, Mutsaerts HJM, Meijers JC, Kootstra NA, Reiss P, Wit F, Teunissen CE, Pajkrt D.

*CROI 2017: Conference on Retroviruses and Opportunistic Infections, Seattle, USA, 13-16 February 2017*

**Durability of first-line combination antiretroviral therapy (cART) for HIV in the Netherlands**

Boender TS, Smit C, Wit F, Brinkman K, Prins J, Reiss P, on behalf of ATHENA. *21<sup>st</sup> International Workshop on HIV Observational Databases, Lisbon, Portugal, 30 March-1 April 2017*

**Initiation of cART: a nationwide overview of variation between HIV treatment centres**

Smit C.

*21<sup>st</sup> International Workshop on HIV Observational Databases, Lisbon, Portugal, 30 March-1 April 2017*

**Cardiovascular disease (CVD) and chronic kidney disease (CKD) event rates in HIV-positive persons at high predicted CVD and CKD risk: results from the D:A:D study**

Boyd MA, Mocroft A, Ryom L, d'Arminio Monforte A, Sabin C, El-Sadr W, Hatleberg CI, De Wit S, Weber R, Fontas E, Phillips A, Dabis F, Reiss P, Lundgren J, Law M, D:A:D Study Group. *IAS 2017, Paris, 23-26 July 2017*

**From HIV infection to HIV suppression: improvements in the time to reach successive stages in the HIV care continuum in the Netherlands**

van Sighem A, Op de Coul E, Boender TS, van Benthem B, Bouwhuis J, Brinkman K, Reiss P, on behalf of the ATHENA national HIV cohort. *IAS 2017, Paris, 23-26 July 2017*

**Initiation of cART: a nationwide overview of variation between HIV treatment centres in the Netherlands**

Boender TS, Smit C, Brinkman K, Prins JM, Kroon FP, Geerlings SE, Reiss P. *IAS 2017, Paris, 23-26 July 2017*

**People living with HIV and HIV-negative individuals with similar lifestyles show greater age advancement compared to healthy blood donors**

De Francesco D, Oehleke S, Bürkle A, Wit FW, Franceschi C, Kootstra NA, Libert C, Grune T, Weber D, Jansen EHJM, Reiss P, Sabin CA, for the Co-morBidity in Relation to Aids (COBRA) Collaboration. *IAS 2017, Paris, 23-26 July 2017*

**The application of artificial intelligence to predict response to different HIV therapies, without a genotype: new models for therapy optimisation in resource-limited settings**

Revell A, Hamers R, Morrow C, Wood R, Reiss P, van Sighem A, Johnson M, Ruiz L, Alvarez-Uria G, Sierra-Madero J, Montaner J, Lane HC, Larder B, RDI Data and Study Group.  
*IAS 2017, Paris, 23-26 July 2017*

**International trends in new HIV diagnoses among men who have sex with men in North America, Western Europe and Australia 2000-2014**

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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 CD<sub>4</sub> 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.

## **CD<sub>4</sub> (T<sub>4</sub>) cell**

CD<sub>4</sub><sup>+</sup> T-lymphocyte, or T<sub>4</sub> cell or T-helper cell. A white blood cell that plays a vital role within the immune system and can be infected by the HIV virus. In the course of the HIV infection the number of CD<sub>4</sub> cells may drop from normal levels (> 500 per mm<sup>3</sup>) to dangerously low levels (< 200 CD<sub>4</sub> cells per mm<sup>3</sup> blood).

**CDC**

US Centers for Disease Control and Prevention.

**Cib**

Centre for Infectious Disease Control Netherlands, National Institute for Public Health and Environment ([www.rivm.nl/cib](http://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.

**DAAs**

Direct-acting antivirals (DAAs) are new-generation drugs that treat hepatitis C by targeting specific steps in the hepatitis C virus life cycle. There are different classes of DAAs, defined by their mechanism of action and therapeutic target.

**DNA**

Deoxyribonucleic acid. A complex protein that carries genetic information. HIV can insert its own genetic material 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 affects the liver and 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**

Dutch HIV patients' association.

### **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.

### **Immunological failure**

A type of HIV treatment failure. There is no consensus on the definition of immunological failure. However, some experts define immunological failure as the failure to achieve and maintain adequate CD4 counts despite viral suppression.

### **Interferon**

Interferons are naturally-occurring proteins (cytokines) produced by immune cells in response to an antigen, usually a virus. Although they don't directly kill viral cells, they boost the immune response by signalling neighbouring cells into action and inhibiting the growth of malignant cells. There are three types of interferons: alpha, beta, and gamma. Laboratory-made interferons are used to treat certain cancers and opportunistic infections. Addition of polyethylene glycol to interferons prolongs the half-life of interferon. Pegylated interferon alpha is used to treat chronic hepatitis C infection.

### **Mono-infection**

When a person has only one infection.

**Mortality**

Mortality rate is a measure of the frequency of occurrence of death among a defined population during a specified time period.

**MSM**

Men who have sex with men.

**Nederlandse Federatie Universitair Medische Centra (NFU)**

Netherlands Federation of University Medical Centres.

**Non-AIDS events**

Diseases and clinical events that are not related to AIDS (i.e., that are not listed as being associated with AIDS by the Centers for Disease Control and Prevention) and include conditions such as malignancies, end-stage renal disease, liver failure, pancreatitis, cardiovascular disease.

**Non-Nucleoside Reverse Transcriptase Inhibitor (NNRTI)**

Antiretroviral HIV drug class. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) bind to and block HIV reverse transcriptase (an HIV enzyme). HIV uses reverse transcriptase to convert its RNA into DNA (reverse transcription). Blocking reverse transcriptase and reverse transcription prevents HIV from replicating.

**Nucleoside Reverse Transcriptase Inhibitor (NRTI)**

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**Nucleotide**

A building block of nucleic acids. DNA and RNA are nucleic acids.

**Nucleotide Reverse Transcriptase Inhibitor (NtRTI)**

A type of antiretroviral (ARV) HIV drug. Nucleotide reverse transcriptase inhibitors (NtRTIs) interfere with the HIV life cycle in the same way as NRTIs. Both block reverse transcription. NtRTIs are included in the NRTI drug class.

**NVHB**

Dutch Association of HIV-Treating Physicians (*Nederlandse Vereniging van HIV Behandelaren*).

**Person year**

A measure of time used in medical studies that combines the number of persons and their time contribution (e.g., in years) to the study. In the ATHENA cohort, 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 virologic response (SVR12 or SVR24)**

A measure of the response to hepatitis C virus (HCV) treatment. SVR12 or SVR24 indicates an undetectable level of HCV in blood 12 or 24 weeks, respectively, after completion of antiviral therapy for chronic 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.

**Virological failure**

A type of HIV treatment failure. Virological failure occurs when antiretroviral therapy (ART) fails to suppress and sustain a person's viral load to less than 200 copies/mL. Factors that can contribute to virologic failure include drug resistance, drug toxicity, and poor treatment adherence.

**Viral load**

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

**Viral suppression or virologic control**

When antiretroviral therapy (ART) reduces a person's viral load (HIV RNA) to an undetectable level. Viral suppression does not mean a person is cured; HIV still remains in the body.

**VWS**

Dutch Ministry of Health, Welfare and Sport.

*Some of the above definitions were taken from [www.aidsinfo.hiv.gov](http://www.aidsinfo.hiv.gov)*

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